CHAPTER 79

Hemorrhagic and Liver Disorders of Pregnancy

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INTRODUCTION

Maternal mortality is defined as “The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes” (Internal Classification of Diseases, 10th Revision, code O95). During the past century, the maternal mortality ratio in the United States significantly fell from 850 deaths per 100,000 deliveries in 1900, to 7.5 deaths per 100,000 in 1982, and then increased to 17.8 deaths per 100,000 live births in 2009 (1); unfortunately, this ratio has continued increasing. The National Center for Health Statistics has reported that the maternal mortality ratio increased by 62% between 1990 and 2006, from 8.2 to 13.3 per 100,000 (2). There are currently renewed efforts focusing on hospital safety, early warning signs, and improved training for perinatologists to address maternal mortality and morbidity (3–5).

Hemorrhage and hypertensive disorders are the major contributors to maternal death rates (6). Placental abruption, placenta previa, and accreta/increta/percreta disorders can become life threatening, and quickly pose a challenge for even an experienced obstetrician. Preeclampsia with severe features, including HELLP, can cause multorgan failure including widespread coagulopathy. Appropriate care requires an efficient plan with the understanding of the unique complications associated with pregnancy and the gravid uterus. This chapter will focus on these conditions as well as imitators that are frequently equally morbid such as thrombotic thrombocytopenia purpura (TTP), atypical hemolytic uremic syndrome (aHUS), and acute fatty liver of pregnancy.

BACKGROUND PHYSIOLOGY CHANGES

Coagulation Changes

In pregnancy, if factors are measured, one will note an increase in factors I (fibrinogen), VII, VIII, IX, and X. Functional tests, such as the prothrombin time (PT), partial thromboplastin time (PTT), and bleeding times (BT) should not change in normal pregnancy. There is a relatively common disorder in pregnancy, gestational thrombocytopenia, that elicits an asymptomatic low platelet count. Most of these women have platelet values greater than 70,000 cells/μL, and two-thirds of them fall between 130,000 and 150,000 cells/μL (7). This diagnosis is used for women with no previous history of thrombocytopenia with occurrence during the third trimester. There is no fetal thrombocytopenia seen, and the disorder spontaneously resolves after delivery.

The reader is referred to Chapter 143 for a detailed description on coagulation disorders.

Liver Changes

Pregnancy-related hormones and fetal enzymes significantly affect the maternal liver. Known changes in the liver profile reveal a decrease in serum albumin, which is secondary to the dilutional effect of a 50% increase in maternal plasma volume. There is also an increase in serum alkaline phosphatase due to placental/fetal production. Markers of liver injury, such as aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase, will not change in normal pregnancy. Bilirubin and gamma-glutamyl transpeptidase are both significantly lowered (8).

One of the main hormones causing alterations in the hepatic physiology is estrogen, which produces an increase in the hepatic rough endoplasmic reticulum, thereby increasing the production of proteins. The approximate sevenfold increase in estradiol—related to multiple factors, from changes in the binding hormones, to changes in metabolism and production—in the first trimester and a further fivefold increase by term, stimulates an approximate sixfold increase in the production of the sex hormone–binding globulin (9). Estrogen also has an inverse relationship with bile salt production and bile flow. There is a change in both composition of the bile and in the rate of cholesterol and phospholipid production; these changes produce increase in lithogenicity (10).

Progesterone, another hormone known to cause significant hepatic changes, mainly affects an increase of smooth endoplasmic reticulum and an increase in cytochrome P-450. Additionally, there is notable smooth muscle relaxation of the gallbladder and biliary ductal system. Progesterone can also produce slow-wave dysrhythmia in the gastrointestinal tract (11).

It is now thought that there are genetic influences specifically related to MDR3 gene mutations in liver diseases in pregnancy. Refer to Chapter 17 for more detailed description of essential physiologic concerns related to the liver.

Hemorrhagic Concerns

Significant bleeding in the pregnancy can be quantified by the total amount or by amount and time period over which the bleeding occurred (12,13). Generally, postpartum hemorrhage—defined by the total estimated blood loss—is established when there is greater than 500 mL for vaginal deliveries and more than 1 L for cesarean deliveries. Additionally, clinical symptoms and signs with respect to the blood loss are considered in the management. Postpartum hemorrhage...
can quickly become an emergent situation. There are many hospital systems that utilize a massive transfusion protocol; the main objective of these is to administer blood products early in the resuscitation process. These protocols involve a series of blood products and serum tests, which are automatically supplied based on the initiation of the protocol, without waiting for lab results. There are nuances seen, but many centers focus on a ratio of 1:1:1 for packed red blood cells, fresh frozen plasma, and platelets (14).

PLACENTAL COMPLICATIONS

Placental Abruption

Placental abruption (abruption placentae) is a condition in which the placenta separates from the implantation site of the uterus prior to the delivery of the fetus. The area of hemorrhage along the decidua basalis expands as the bleeding progresses. This hematoma may be concealed or present clinically with vaginal bleeding. The underlying mechanism may be related to vascular damage caused by preeclampsia, trauma, cocaine/alcohol use, or chorioamnionitis. Risk factors for abruption include either maternal or paternal (second-hand) smoking, multiparity, prior cesarean delivery, and African-American ethnicity (15,16). The incidence ranges between 0.4% and 0.8%, and there is a 15% recurrence rate for a subsequent pregnancy and a 20% recurrence rate after two previous episodes (17). Morbidity and mortality of both the mother and fetus can be significant with this process if the hemorrhage is significant.

Classic clinical manifestations include vaginal bleeding, abdominal pain/uterine irritability, and fetal heart rate abnormalities or fetal distress; of note, however, is that none or all of these symptoms may be present. It is important to have a high index of suspicion, because ultrasound has limited usefulness for diagnosis. It reveals a retroplacental blood clot in only 15% of cases, thus giving a high false-negative rate (15).

Treatment with fluid resuscitation, adequate oxygenation, and close fetal monitoring is critical. With evidence of significant hemorrhage or fetal distress, delivery must be expedited. It is critical to anticipate additional postpartum complications, such as uterine atony, to limit further hemorrhage.

Placenta Previa

Placental previa occurs with improper implantation of the placenta such that it overlies the internal os of the cervix during the third trimester. The incidence of placenta previa is noted to be approximately 0.5% (18). Risk factors include prior placenta previa, a history of cesarean delivery, or African-American ethnicity (15,16). The incidence ranges between 0.4% and 0.8%, and there is a 15% recurrence rate for a subsequent pregnancy and a 20% recurrence rate after two previous episodes (17). Morbidity and mortality of both the mother and fetus can be significant with this process if the hemorrhage is significant.

Clinical symptoms include painless vaginal bleeding, abdominal pain/uterine irritability, and fetal heart rate abnormalities or fetal distress; of note, however, is that none or all of these symptoms may be present. It is important to have a high index of suspicion, because ultrasound has limited usefulness for diagnosis. It reveals a retroplacental blood clot in only 15% of cases, thus giving a high false-negative rate (15).

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Placenta Accreta, Increta, Percreta

The issue of abnormal placentation can involve not only the specific location, but also how it is attached to the endometrial layer. Placenta accreta is a term for implantation in which there is abnormally firm adherence to the uterus. This is caused by abnormalities in the decidua basalis and Nitabuch layer (19). More specifically, placenta accreta, involves direct attachment between the placental villi and myometrium. Whereas placenta increta describes the villi invading the myometrium, percreta refers to a complete penetration through the myometrium, and may invade surrounding organs.

The overall incidences of the above placental problems has increased. This is thought to be due to the increasing rates of cesarean deliveries (20). Often, after a surgical procedure involving the lower uterine segment, the healing surgical site becomes an abnormal placentation attachment area. There is a noted significant increased risk with increasing cesarean deliveries, especially when considered at the time of a placenta previa. Early suspicion and detection are crucial for preventing significant morbidity and mortality. Antenatal diagnosis
using ultrasound in conjunction with Doppler imaging may be helpful (21).

Abnormal placental attachment is an emergent issue facing clinicians today. There are more women presenting with increasing numbers of repeat cesarean sections, and many clinicians are not adequately prepared for the possible emergency at hand. Oftentimes, a placenta accreta/increta/percreta requires a cesarean hysterectomy; without proper antenatal diagnosis and preparation, this can become a dire situation. When diagnosed antenatally, there is the necessary time to plan for multidisciplinary management inputs. These may include uterine artery balloon occlusion by interventional radiology, urologic stent placement, additional surgical expertise from gynecologic oncology or general surgery, and early activation of massive transfusion protocols. While studies often do not show a significant difference in mortality or even total amount of blood products transfused for urologic stents or balloon occlusion of iliac arteries, many tertiary and quaternary centers nevertheless include these preparatory steps in their approach (22–24).

OTHER CONDITIONS ASSOCIATED WITH DISSEMINATED INTRAVASCULAR COAGULATION IN PREGNANCY

HELLP Syndrome

The topic of preeclampsia and eclampsia is discussed in Chapter 78, Cardiac Disease and Hypertensive Disorders in Pregnancy.

The acronym HELLP, for the syndrome consisting of hemolysis, elevated liver enzymes, and low platelets, was first used by Weinstein in 1982 (25). It is currently thought to be a distinct variant, rather than a progression, of the preeclampsia/eclampsia continuum. The incidence is rare, with Bhattacharya and Campbell (26) noting 13 cases of HELLP in a population of 4,188 patients with preeclampsia (310 cases/100,000 patients). Although much speculated, the true cause is unclear. Currently there are numerous genes thought to play a role in the development of HELLP syndrome, each of which seem to also interact in a complicated mechanism. In current research, near 200 genes have been identified in relation to preeclampsia or HELLP syndrome (27). We have also seen that the Fas receptor, Vascular Endothelial Growth Factor gene, and Factor V Leiden mutation are associated with an increased risk of HELLP when compared to healthy women (28). Although hundreds of possibilities have been discussed, there is no practical application for this information yet. Risk factors for this syndrome have been shown to include African Americans (29) and a history of prior pregnancies with HELLP. The recurrence rate has been reported at 14% (30).

HELLP is a disease with significant morbidity and mortality, both maternal and perinatal. In a prospective study of 442 pregnancies with HELLP, the risk of maternal death was found to be 1.1% (31). Significant maternal morbidity included DIC (21%), placental abruption (16%), acute renal failure (7.7%), pulmonary edema (6%), and rare occurrences of subcapsular liver hematoma and retinal detachment (32). Additionally, case reports of hepatic rupture (33–36) have been documented. Fetal outcome is typically related to the necessity to proceed with preterm delivery. Neonatal outcomes include risk of intensive care requirements, mechanical ventilation, sepsis, and intraventricular hemorrhage (37).

The clinical features and laboratory evaluation of HELLP have not been firmly defined. Generally, the findings reflect the disease process on the vascular supply of the maternal liver. The hemolysis can be noted by an abnormal peripheral smear, elevated serum bilirubin, low serum haptoglobin levels, elevated lactate dehydrogenase (LDH) of subtypes LDH1/LDH2, or a fall in the hemoglobin (32). Elevated liver enzymes, generally aspartate transaminases (AST), alanine transferase (ALT), and/or bilirubin are present; however, there is no strict definition of the degree of elevation, although many use a value roughly twice the upper limit of normal. There is also great variability in establishing the criteria for low platelets, varying from 150,000 to less than 50,000 cells/µL. Patients with HELLP will also have altered vascular reactivity (38), and methods of prediction by Doppler ultrasound have been examined, revealing a decrease in dual hepatic blood supply preceding the onset of HELLP (39,40). Objective parameters for disseminated intravascular coagulation (DIC) include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), elevated fibrinogen degradation products, and elevated D-dimers. It is important to note fibrinogen is increased in a normal pregnancy, so the value indicative of DIC may decrease to “normal” (nonpregnant) values; thus it is not used as an objective parameter.

Treatment of HELLP includes supportive care in a facility suited for such high-level care. Prompt delivery of the fetus is indicated if the patient is beyond 34 gestational weeks or sooner if the disease has progressed to multiorgan dysfunction, DIC, liver infarction or hemorrhage, renal failure, suspected placental abruption, or a nonreassuring fetal status (32). There has been debate regarding the management of a patient diagnosed with HELLP under 34 weeks gestation. There was a randomized controlled trial exploring expectant management for severe preeclamptic patients between 28 and 32 weeks, which had some positive outcomes; however, they excluded any patient with abnormal lab values (41), which is a diagnostic factor for HELLP. When making the decision to continue with pregnancy or expedite delivery, maternal morbidity/mortality is weighed against the risk of fetal prematurity and its associated morbidities. Many clinicians recommend treating with antenatal steroids for fetal lung maturity with subsequent delivery 24 to 48 hours later, if the patient is stable enough to delay delivery (31,42).

There is significant debate over the use of steroids for the treatment of the laboratory abnormalities of HELLP. Some studies have shown clinical benefit (32,33); whereas others (34) found insufficient evidence of beneficial effect. In 1990, a study performed at the University of Mississippi Medical Center found the use of glucocorticoids, antenatally or postpartum, demonstrated disease stabilization and accelerated recovery (43,44). Additionally, Eculizumab, a targeted inhibitor of complement protein C5, was utilized in a case report for the treatment of preeclampsia and HELLP syndrome. This resulted in a normalization of laboratory parameters and delayed delivery for 17 days, thus reducing neonatal morbidity (45). Although there are several promising possibilities for treatment, when HELLP syndrome progresses, management of DIC must address the underlying cause (46); transfusion of both packed red cells and component therapy as indicated, as well as fluid replacement and oxygenation, are critical.
Thrombotic Thrombocytopenic Purpura

When faced with thrombocytopenia in pregnancy, it is crucial to differentiate the cause so that the correct treatment may be utilized. Thrombotic thrombocytopenic purpura (TTP) is associated with low platelets and the formation of platelet thrombi in the microvasculature. Oftentimes, these are the only two signs present. However, the classic pentad includes microangiopathic hemolytic anemia, thrombocytopenic purpura, renal disease, neurologic abnormalities, and fever. It is often difficult to differentiate TTP from HELLP syndrome but, in general, with TTP the platelet counts will be lower and the LDH will be higher (47). The cause of TTP is a deficiency of ADAMTS13, a plasma metalloprotease, whose job is to cleave large von Willebrand factor multimers into smaller, more compact ones. There are a variety of reasons as to why plasma ADAMTS13 concentrations may be decreased in a pregnant patient, including genetic deficiency, autoimmune disorders, infection, DIC, pancreatitis, and pregnancy itself (48).

It is often necessary to make a presumptive diagnosis of TTP, based upon presentation and initial laboratory testing. Initial testing should include a CBC (thrombocytopenia), peripheral blood smear, complete metabolic profile (creatinine may be normal or increased), LDH (markedly elevated), bilirubin (elevated), haptoglobin level, coagulation testing (usually normal), Coombs test (negative), and ADAMTS13 activity and inhibitor. ADAMTS13 testing is only performed at specialized laboratories; therefore, treatment should be initiated when TTP suspected, even without confirmatory results. The mainstay treatment is plasma exchange therapy with glucocorticoids. With TTP, platelet transfusions are contraindicated, unless they are addressing an immediate life-threatening bleed (47). Platelet transfusion may actually worsen the condition by providing more material that will accumulate, then thrombose in the microvasculature (49). Because of this major difference in treatment, it is extremely important to differentiate between TTP and HELLP syndrome.

Atypical Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is defined as microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. aHUS, also referred to as complement-mediated HUS, is due to gene mutations on complement factors (48,49). aHUS is a rare condition, quoted to occur one-third to one-half as frequent as TTP; however, TTP and aHUS can be difficult to differentiate. There are clinical features which may help distinguish between the two, such as focal defects in TTP, and abdominal symptoms such as nausea, vomiting, and pain are more frequently seen with aHUS (48). Treatment for aHUS often involves supportive care along with plasma exchange; there has been promising research and outcomes with the addition of the drug Eculizumab (48).

LIVER CONCERNS

Hyperemesis Gravidarum

Hyperemesis gravidarum (HG) is a condition characterized by serious and persistent vomiting that limits fluid intake and adequate nutrition. Clinical manifestations include weight loss greater than 5% of prepregnancy weight, weakness, dehydration, ketosis, and muscle wasting. HG occurs in approximately 0.3% to 2.0% of pregnancies, seems to affect a diverse population with multiple risk factors, and can be associated with a range of outcomes. Studies have associated HG to various hormone levels, including those of human chorionic gonadotropin, estrogen (59), prolactin (60), thyroxine (61), androgens (61), cortisol (62), and maternal prostaglandins (63). Other factors identified include a prior history of HG with previous pregnancies (64), female fetal gender (65,66), maternal age, maternal weight (67), and smoking (68). Helicobacter pylori may (69–71) or may not (72) have a role. Chronic medical conditions such as history of gastritis, allergies, and gallbladder disease (62) contribute to the risk. Additionally,
the interpregnancy interval and paternity (65) have been examined; although the cause cannot be established, the relationship is being studied.

A complete differential diagnosis includes multiple systems. Obstetric and gynecologic conditions such as a molar pregnancy, degenerating uterine leiomyoma, or ovarian torsion should be considered. Gastrointestinal causes could include gastroenteritis, gastroparesis, achalasia, biliary tract disease, hepatitis, intestinal obstruction, peptic ulcer disease, pancreatitis, and appendicitis. The patient needs to be evaluated for urinary tract conditions, including pyelonephritis, uremia, and kidney stones. Metabolic diseases, including hyperthyroidism, diabetic ketoacidosis, porphyria, and Addison disease, should be ruled out. Neurologic disorders, drug reactions, and psychiatric conditions are other considerations.

Some studies have found HG to be protective against adverse outcomes (73), whereas more recent studies have failed to prove this relationship (74). Current research shows a relationship between HG and low birth weight that is mostly attributed to poor maternal weight gain (75–77). In addition to potentially compromised fetal outcomes, a worsened maternal morbidity and mortality are also noted. Cases of Wernicke encephalopathy (78–81), central pontine myelinolysis (82–84), severe liver injury (85), splenic avulsion (86) pneumomediastinum following esophageal rupture (87), and acute renal failure (88) have been reported.

Treatment for HG is primarily supportive, with antiemetics, fluid therapy, and electrolyte replacement. Natural remedies such as pyridoxine (vitamin B6) and ginger (89) have been shown to be effective. Additionally, behavior modification with avoidance of strong odors/scents and adjustment of diet may be tried. However, if these measures are inadequate, hospitalization and treatment with steroids (90–92) and parenteral nutrition may be necessary.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP) is the most frequent of the pregnancy-related liver diseases (93), occurring in approximately 1% of pregnancies (94). It is a condition characterized by the progressive pruritus of cholestasis, with elevated fasting bile salts—specifically chenodeoxycholic acid, deoxycholic acid, and cholic acid elevations more than 10 µmol/L—and elevated aminotransferases. Clinical manifestations begin in the late second or third trimester and most often will resolve spontaneously within 2 to 3 weeks postpartum. Although the direct cause is unknown, research has shown a strong familial component. Nonetheless, ICP affects specific populations at different rates. For example, ICP occurs in less than 0.2% of pregnancies in women of North American and Central/Western European descent, whereas Scandinavian and Baltic populations show a rate of 1% to 2%, and Chilean and Bolivian populations have shown rates of 5% to 15% (94). The severe form of ICP—bile acid levels above 40 µmol/L—in the Swedish population is associated with a frame shift mutations in the gene coding for the ATP-binding cassette transporter, specifically the ABCB4_5 gene variant (formerly known as multidrug resistance gene 3, MDR3) (95–97). Mutations in the bile salt export pump (BSEP) can also predispose a patient to ICP (98).

Other possible causes relate to “leaky gut” theories (99). This theory is based on the increased absorption of bacterial endotoxins and the enterohepatic circulation of cholestatic metabolites of sex hormones and bile salts. Research has also shown an association with low maternal serum estrogen (100,101).

Fetal complication rates are directly related to maternal serum bile acids (102). Bile acid levels greater than 40 µmol/L are associated with perterm delivery, fetal asphyxia events, and meconium staining (103). Additionally, case reports of neonatal respiratory distress syndrome (103) and fetal death (104) are noted; on the other hand, maternal morbidity and mortality are low.

Supportive measures for pruritus with antihistamine are inadequate, as this agent has limited effectiveness and fails to address the bile acid elevation and fetal concerns. Cholestyramine, S-adenosylmethionine, and dexamethasone were the treatments of choice (105). However, newer research is advocating the use of ursodeoxycholic acid, which is a tertiary bile acid. Initial use of ursodeoxycholic acid was with bear bile in traditional Chinese medicine for the treatment of liver disease (106). Recent research has shown ursodeoxycholic acid to be more effective in reducing bile acids and bilirubin (107–110). Fetal risks are decreased, but not eliminated. Because of this, careful fetal monitoring and delivery at 36 to 37 weeks should be considered (111). Earlier delivery at fetal lung maturity has also been advocated (105).

Key Points

- Maternal mortality has been increasing in the United States over the last decade due to a lapse in attention and training regarding critical conditions in pregnancy.
- Placenta previa and accreta are disorders which require multidisciplinary teamwork involving interventional radiology, urology, gynecology oncology, and blood bank.
- HELLP syndrome requires prompt delivery, with delay reserved for administration of antenatal steroids, and supportive therapy in a critical care setting.
- TTP and atypical HUS are imitators of HELLP syndrome. Diagnosis should include assessment of ADAMTS13 levels for TTP and complement levels for aHUS.
- Fetal death is associated with cholestasis of pregnancy. It is infrequent but unpredictable, and earlier delivery is advocated due to this.

References
