CHAPTER 99 ■ HEMORRHAGIC AND LIVER DISORDERS OF PREGNANCY
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IMMEDIATE CONCERNS

Major Problems

Maternal mortality is defined as deaths occurring during pregnancy or within 6 weeks postpartum, with the cause of death identified as complications related to pregnancy, delivery, or the puerperium (International Classification of Diseases, 9th Revision, codes 630–676). It has decreased significantly over the past century, falling from 850 deaths per 100,000 deliveries in 1900 to 7.5 deaths per 100,000 in 1982 (1). This rate has remained stable at approximately 7.5 per 100,000 deliveries between 1982 and 1996. Hemorrhage and hypertensive disorders are the major contributors to maternal death rates (2). Hemorrhagic disorders can become life threatening and quickly challenge the obstetrician. Appropriate care requires an efficient plan with the understanding of the special complications associated with pregnancy and the gravid uterus. There are two main subtopics in this chapter that the reader needs to consider; these include placental complications (abruption and previa) and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)/disseminated intravascular coagulation (DIC).

As hepatic disorders in pregnancy can be devastating to both fetus and the pregnant patient, this chapter will address liver disorders related to pregnancy, specifically hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, and acute fatty liver of pregnancy.

Stress Points

1. The physician must be aware of the potential hemorrhagic complications to which pregnancy predisposes the patient and fetus, and the physiologic and pathologic risk factors. Rapid diagnosis and treatment are critical to patient safety.
2. Liver disorders can vary from irritating and relatively minor, to life threatening with significant morbidity and mortality.

HEMORRHAGIC CONCERNS

Significant bleeding in pregnancy can be quantified by total amount, or by amount and time period over which the bleeding occurred (3,4). 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.

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 a normal pregnancy.

The reader is asked to refer to Chapter 49 for more detailed description of essential physiologic concerns related to coagulation and Chapter 170 for coagulation disorders.

PLACENTAL COMPLICATIONS

Placental Abruption

Placental abruption (abruptio 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 (secondhand) smoking, parity, prior caesarean delivery, and African American ethnicity (5,6). 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 for two previous episodes (7). 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. Ultrasound has limited usefulness as it reveals a retroplacental blood clot in only 15% of cases, thus giving a high false-negative rate (5).

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. Traditionally, placenta previa was referenced
The topic of preeclampsia/eclampsia is discussed in Chapter 98. 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 (10). The clinical entity was first noted by Prichard et al. in 1954 (11). 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 (12) noting 13 cases of HELLP in a population of 4,188 patients with preeclampsia (310 per 100,000 patients). Although much speculated, the true cause is unclear. Older theories dealt with long-chain 1-hydroxycyclo-CoA (LCHAD) and other fatty acid oxidation defects. However, these have not been proven to be major risk factors in HELLP (13,14). Current research has found associations with genetic mutations of the Fas gene and regulation of the immune system (15,16). There are also studies regarding the prognostic values of hyaluronic acid (17) and serotonin (18) to evaluate liver function and platelet activation, respectively. Risk factors have been shown to include African Americans (19) and a history of prior pregnancy with HELLP. The recurrence rate has been reported as 14% (20).

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% (21). 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 (22). Additionally, case reports of hepatic rupture (23–26) 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 (27).

The clinical features and laboratory evaluation of HELLP have not been clearly 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 (22). Elevated liver enzymes, primarily aspartate transaminases (AST), alanine transferase (ALT) and/or bilirubin, are present; however, there is no strict definition of the degree of elevation. There is also great variability in establishing the criteria for low platelets, varying from 130,000 to less than 50,000 cells/μL. Patients with HELLP also have altered vascular reactivity (28), and methods of prediction of HELLP by Doppler ultrasound have been examined, revealing a decrease in dual hepatic blood supply preceding the onset of HELLP (29,30). Objective parameters for DIC include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), elevated fibrinogen degradation products, and elevated D-dimers; as fibrinogen is increased in a normal pregnancy, the value in DIC may decrease to “normal” (nonpregnant) values, so 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 multigorgan dysfunction, DIC, liver infarction or hemorrhage, renal failure, suspected placental abruption, or a nonreassuring fetal status (22).

There is more controversy regarding the recommendations if the pregnancy is less than 34 weeks’ gestation and there are only mild to moderate laboratory abnormalities. Generally,
Physiologic Changes Associated with Pregnancy

Pregnancy-related hormones and fetal enzymes significantly affect the maternal liver. Known changes in the liver profile result in increased serum albumin 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 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 (40).

One of the main hormones causing alterations in hepatic physiology is estrogen. Estrogen produces an increase in the hepatic rough endoplasmic reticulum, which increases 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 (41). 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 an increased lithogenicity (42).

Progestosterone, 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 (43).

It is now thought that there are genetic influences specifically related to MDR3 gene mutations in liver diseases in pregnancy. Refer to Chapter 48 for more detailed description of essential physiologic concerns related to the liver.

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 with various hormone levels, including those of human chorionic gonadotropin, estrogen (44), prolactin (45), thyroxine (46), an-drogens (46), cortisol (47), and maternal prostaglandins (48). Other factors identified included prior history of HG with previous pregnancies (49), female fetal gender (50,51), maternal age, maternal weight (52), and smoking (53). Helicobacter pylori may (54-56) or may not (57) have a role. Chronic medical conditions such as history of gastritis, allergies, and gallbladder disease (58) contribute to the risk. Additionally, the interpregnancy interval and parity (50) 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 ketosacidosis, poikilothermia, 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 (59), whereas more recent studies have failed to prove this relationship (60). Current research shows a relationship between HG and low birth weight that is mostly attributed to poor maternal weight gain (61-63). In addition to potentially compromised fetal outcomes, a worsened maternal morbidity and mortality are also noted. Cases of Wernicke encephalopathy (64-67), central pontine myelinolysis (68-70), severe liver injury (71), splenic avulsion (72), pneumomediastinum following esophageal rupture (73), and acute renal failure (74) 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 (75) 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 (76-78) 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 (79), occurring in approximately 1% of pregnancies (80). 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 (81). 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 11% (80). The severe form of ICP—bile acid levels more than 40 μmol/L—in the Swedish population is associated with a frame shift mutation in the gene coding for the ATP binding cassette transporter, specifically the ABCB4 gene variant (formally known as multidrug resistance gene 3, MDR3) (82–84). Mutations in the bile salt export pump (BSEP) can also predispose a patient to ICP (85). Other possible causes relate to “leaky gut” theories (86). 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 (87,88).

Fetal complication rates are directly related to maternal serum bile acids (89). Bile acid levels greater than 40 μmol/L are associated with preterm delivery, fetal asphyxial events, and meconium staining (90). Additionally, cases of neonatal respiratory distress syndrome (90) and fetal death (91) are noted; on the other hand, maternal morbidity and mortality are low.

Supportive measures for pruritus with antihistamine is inadequate, as it has limited effectiveness and fails to address the bile acid elevation and fetal concerns. Cholestyramine, ursodeoxycholic acid/deoxycholic acid, which is a tertiary bile acid. Initial use of UDCA was with bear bile in traditional Chinese medicine for the treatment of liver disease (93). Recent research has shown UDCA to be more effective in reducing bile acids and bilirubin (94–97). Fetal risks are decreased, but not eliminated. Because of this, careful fetal monitoring and delivery at fetal lung maturity should be considered (92). Ondansetron is also being evaluated as a treatment for pruritus; however, no data are noted on fetal benefits of that antiemetic (98).

**Acute Fatty Liver Disease of Pregnancy**

Acute fatty liver disease of pregnancy (AFLP) is a rare but potentially fatal disease that occurs in the third trimester. Gestational ages vary between 34.5 weeks’ (99,100) and 37 weeks’ gestation (101). Incidence has been documented as 1 in 6,659 births (102) to 1 in 13,900 births (102). It is characterized by significant malaise, nausea/vomiting, anorexia, abdominal pain, and jaundice (103). Clinical signs include hypertension, jaundice, elevated serum transaminases, coagulopathies, thrombocytopenia, and hypoglycemia. A high index of suspicion should be maintained if evidence of these signs and symptoms are noted (104). Imaging studies are often performed but have limited usefulness in making the diagnosis; ultrasound may show nonspecific changes (104). Computerized tomography (CT) has a high false-negative rate (100). Liver biopsy is the gold standard in confirming the diagnosis; however, it is rarely necessary and carries significant maternal risk in the setting of disseminated intravascular coagulation (DIC).

This disease is noted to have significant risks with respect to morbidity and mortality. Older research reported maternal and perinatal mortality rates as high as 75% and 85%, respectively (104). Although the maternal mortality rate has fallen significantly, fetal mortality has remained as high as 66% (101). Maternal morbidity includes coagulopathies (specifically DIC) (105), hepatic encephalopathy (100), respiratory compromise (pulmonary edema or respiratory acidosis) (100,106), and renal insufficiency (102). Current research has found an associated genetic component with mitochondrial trifunctional protein mutations (106,107).

Treatment of this disease is supportive, with management in a higher-level setting, specifically an ICU. Delivery is recommended as efficiently as possible. Debates regarding prolonged inductions and surgical risks of cesarean are common. The decision should be individualized, and should include the patient and her family. Hypoglycemia should be treated with dextrose-containing solutions. Elevated ammonia levels can be decreased with neomycin. Blood transfusions and replacement of clotting factors should be considered as appropriate; AFLP generally resolves within 2 to 3 days postpartum; however, cases of fulminant hepatic failure requiring liver transplantation have been reported (108).

**References**


