# Hepatic disease and pregnancy: An overview of diagnosis and management

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***Objectives:*** **To provide a review of the current literature on hepatic disease in pregnancy, outlining the incidence, pathophysiology, diagnosis, and management of major diseases in this category.**

***Design:*** **A thorough review of expert analysis, case reports, and randomized clinical trials was used to assess current methods of managing the major diseases related to hepatic dysfunction in pregnancy. A review of bibliographies was also utilized.**

***Results:*** **Hepatic disease complicates nearly 3% of all pregnancies and is a significant cause of morbidity during the gravid state. However, several diseases, including HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), acute fatty liver of pregnancy, acute cholestasis of pregnancy, ruptured liver hematoma, and preeclampsia, can be managed with successful outcomes for both the mother and fetus if diagnosed in early stages. Astute clinical judgment and laboratory evaluation of the patient is vital in the appropriate diagnosis of hepatic disease in pregnancy.**

***Conclusions:*** **Early intervention and appropriate diagnosis can substantially reduce the morbidity and mortality associated with hepatic derangements of pregnancy. (Crit Care Med 2005; 33[Suppl.]:S332–S339)**

**Key Words: pregnancy; liver disease; jaundice**

Although isolated liver disease rarely occurs during pregnancy, hepatic disease during pregnancy poses a unique set of problems for both the obstetrician and the intensivist. It is estimated that liver disorders complicate up to 3% of all pregnancies (1), and the spectrum of diseases ranges from mild anomalies to gross derangements that can be detrimental to both the mother and the fetus. Hepatic disease during pregnancy can be divided into three main categories: hepatic disease peculiar to pregnancy, preexisting disease exacerbated by pregnancy, and coincidental acute liver or gall stone disease during pregnancy. Of vital importance to the treatment of these conditions is the accuracy of determination of gestational age and the timing of onset of the disease. Making the correct diagnosis as to the etiology of liver disease in pregnancy can be difficult but is vitally important, since failure to do so may result in an increase in morbidity and mortality for both mothers and fetuses. It is important to remember that most of the liver diseases not specific to pregnancy usually do not have a deleterious effect on the pregnancy itself (Table 1). This review summarizes common causes, epidemiology, and pathophysiology of acute hepatic failure associated with pregnancy, as well as current management strategies.

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## Normal Changes in Hepatic Function During Pregnancy

Physiologic changes that occur in every organ system during pregnancy cause alteration in normal laboratory values associated with hepatic function. Liver function tests are a panel of laboratory tests that profile discrete aspects of liver function. Liver cell injury or necrosis is measured by determining aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, whereas liver synthetic function (hepatitis, acute/chronic liver disease) is quantified by albumin levels and prothrombin time. Although some laboratory parameters appear abnormal during pregnancy in comparison with nonpregnancy because of an increase in blood volume, important markers of liver disease remain within normal limits, including ALT, AST, lactate dehydrogenase (LDH), bilirubin, γ-glutamyl transpeptidase, and prothrombin time. Serum albumin levels decrease during pregnancy secondary to a 50% increase in maternal plasma volume and reach a nadir toward the end of pregnancy. An increase in serum alkaline phosphatase secondary to fetal and placental production is observed in pregnancy, rendering it a poor means of diagnosing cholestasis during the third trimester of pregnancy. The elevation in aminotransferases or γ-glutamyl transpeptidase in pregnancy should signify pathology and should trigger a search for disease (Table 2). The liver, which is normally palpated 2 cm inferior to the right costal margin, may become more difficult to appreciate because of the expanding uterus within the abdominal cavity. Physical findings such as telangiectasia and palmar erythema, suggestive of liver disease in nonpregnant women, may appear in up to 60% of normal pregnancies because of the hyperestrogenic state of pregnancy, as the liver cannot metabolize quickly the large quantity of estrogen and progesterone produced by the placenta.

## HELLP Syndrome

*Incidence and Pathophysiology.* The syndrome of hemolysis, elevated liver function value, and low platelets (HELLP syndrome) is a well-recognized entity in obstetrics. Although originally thought to be simply a variant of preeclampsia and seen in only 4%–12% of these patients, recent studies suggest that this may be a

Table 1. Signs and symptoms of liver diseases in pregnancy

| Symptom or Sign | Diseases Associated with Pregnancy (Trimester) | Diseases Unrelated to Pregnancy |
|---|---|---|
| Itching | Intrahepatic cholestasis of pregnancy (2 or 3) | Primary biliary cirrhosis<br>Drug hepatotoxicity |
| Jaundice | Hyperemesis gravidarum (1) | Choledocholithiasis |
| | Intrahepatic cholestasis of pregnancy (2 or 3) | Acute viral hepatitis |
| | Dubin-Johnson syndrome (2 or 3) | Drug hepatotoxicity |
| | Acute fatty liver of pregnancy (3) | Exacerbation of underlying liver disease: chronic hepatitis, autoimmune disease, Wilson's disease, primary biliary cirrhosis |
| | Preeclampsia or eclampsia (2 or 3) | |
| | HELLP syndrome (2 or 3) | |
| Upper abdominal pain (epigastric or right upper quadrant) | Acute fatty liver of pregnancy (3) | Biliary tract disease |
| | Preeclampsia or eclampsia (2 or 3) | Gastroesophageal reflux |
| | HELLP syndrome (2 or 3) | Acute viral hepatitis |
| | Acute hepatic rupture (3) | Peptic ulcer disease |
| | Budd-Chiari syndrome (3) | |
| Nausea or vomiting | Hyperemesis gravidarum (1) | Biliary tract disease |
| | Acute fatty liver of pregnancy (3) | Acute viral hepatitis |
| | Preeclampsia or eclampsia (2 or 3) | Drug hepatotoxicity |
| | HELLP syndrome (2 or 3) | Viral syndrome |
| Thrombocytopenia with or without disseminated intravascular coagulation | Acute fatty liver of pregnancy (3) | Fulminant hepatitis |
| | Preeclampsia or eclampsia (2 or 3) | Cirrhosis |
| | HELLP syndrome (2 or 3) | Thrombotic thrombocytopenic purpura<br>Hemolytic-uremic syndrome |

*The numbers in parentheses indicate the trimesters in which a disease commonly presents. Diseases occurring in the third trimester may also present immediately post partum. Liver and gastroesophageal diseases unrelated to pregnancy may present at any time during gestation.



Table 2. Abnormalities of liver function in pregnancy

- Cholestasis
  - Drug-induced liver disease
  - Intrahepatic cholestasis of pregnancy
  - Cholelithiasis with common duct obstruction
  - Dubin-Johnson syndrome
  - Hyperemesis gravidarum
- Increased transaminase levels
  - Mild
    - Preeclampsia/eclampsia
    - HELLP syndrome
    - Drug-induced liver disease
    - Hyperemesis gravidarum
    - Budd-Chiari syndrome
    - Intrahepatic cholestasis of pregnancy
    - Acute hepatic rupture
    - AFLP
  - Severe
    - Toxemia with liver infarction
    - Budd-Chiari syndrome with portal vein thrombosis
    - Acute hepatic rupture
    - Shock
    - Drug-induced liver disease

HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy.

unique entity unto itself. The incidence of HELLP syndrome has been placed at about 1 in 1000 pregnancies, with most cases (>70%) occurring antenatally (2). The pathogenesis of this derangement has not been fully understood, although mechanisms similar to preeclampsia have been proposed. As in preeclampsia, the mechanism may be attributed to activation of the complement and coagulation cascades, increased vascular tone, platelet aggregation, and alteration of the thromboxane:prostacyclin ratio, leading to systemic endothelial and microvascular injury and causing microangiopathic hemolytic anemia, periportal hepatic necrosis, and thrombocytopenia. An association with a defect in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) has also been described, which would liken the syndrome to acute fatty liver of pregnancy (AFLP) rather than preeclampsia (3).

*Clinical Presentation and Laboratory Diagnosis.* Laboratory abnormalities in HELLP syndrome include hemolysis with increased bilirubin levels and LDH levels >600 IU/L, moderately elevated transaminase levels (AST and ALT, 200–700 IU/L), and a platelet count <100,000/mL. In general, women may complain of pain in the right-upper quadrant of the abdomen, accompanied by nausea and vomiting. Significant weight gain or edema is also observed. Patients may also initially present with the stigmata of preeclampsia, showing elevated blood pressure and proteinuria. Sibai et al. (4), however, found that in up to 20% of women, no antecedent hypertension or proteinuria was documented, a circumstance elucidating that preeclampsia may not be a harbinger of this syndrome in some patients. In a study of 427 women at the University of Tennessee–Memphis, late findings of HELLP syndrome were noted to be disseminated intravascular coagulation (23%), pulmonary edema (6%), placental abruption (16%), and retinal detachment (.9%) (2). No correlation has been shown between degree of liver function abnormalities, extent of hypertension, and liver biopsy findings (i.e., periportal hemorrhage and periportal or focal parenchymal necrosis with hyaline deposits). Hepatic infarction and rupture have been reported to occur in HEELP syndrome, however.It is of utmost importance that both the intensivist and obstetrician recognize this disease and not diagnose other conditions that may present similarly, such as hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, systemic lupus, hepatitis, pancreatitis, and appendicitis. Conversely, HELLP syndrome may be given as the initial diagnosis when another medical condition is the etiology. Goodlin et al. (5) studied 11 cases in 1991 of women whose initial diagnosis was HELLP syndrome but who were found to have other serious conditions, including cardiomy-

opathy, biliary disease, and lupus. Maternal mortality rate ranges from 1% to 3% and is attributable to disseminated intravascular coagulation and spontaneous or postpartum hemorrhage. The perinatal mortality rate is approximately 30%; more than one-third of fetuses are born prematurely or exhibit intrauterine growth retardation. Prompt delivery is the primary treatment for HELLP syndrome.

The laboratory findings associated with HELLP syndrome help differentiate it from other diseases with similar presentation. The standard workup includes a complete blood cell count with differential and platelet counts, a liver panel (specifically, determination of AST, ALT, and bilirubin values), serum LDH determination, and peripheral smear. Elevated serum uric acid (>6.0), blood urea nitrogen, and serum creatinine values should also be noted, as they may indicate renal impairment associated with this entity. There is controversy, however, about exactly what laboratory values constitute a definition of HELLP syndrome. Sibai et al. (2), in a large-scale study of 442 women, noted that overt evidence of hemolysis (schistocytes on peripheral smear, increase in serum indirect bilirubin value, etc.), a platelet count <100,000, an AST value >70 IU/L, and a serum LDH value >600 IU/L in the setting of preeclampsia are together diagnostic of HELLP syndrome (2).

*Management and Prognosis.* The overriding consensus in the treatment of HELLP syndrome is delivery of the fetus. Imperative to this decision is the stability of the mother and fetal well-being. Signs and symptoms of maternal hypotension (tachycardia, decreasing blood pressure, dyspnea) or fetal distress (decreased fetal heart rate) are indications for emergent delivery. Patients who are stable and have only mild to moderate aberrations in laboratory values should also consider induction of labor or elective cesarean section, as this syndrome can proceed to a severe state rapidly, especially if the gestational age is >34–35 wks. Fetuses less than this gestational age are managed more conservatively if the mother is stable, with only mild anomalies in laboratory values.

Corticosteroids are very useful in therapy for HEELP syndrome. When administered before 32 wks, corticosteroids promote fetal lung maturity, and such treatment is associated with better postnatal outcomes. As many patients with HELLP syndrome suffer concomitant preeclampsia, the use of antihypertensives is indicated, including administration of methyldopa (in mild cases) or hydralazine or labetalol (in more severe cases) (6). Prophylactic magnesium sulfate should be used to prevent seizures, with close monitoring of respiratory rate and reflexes to prevent magnesium toxicity.

Caesarian section is not an absolute requirement for women with HELLP syndrome, and standard rubrics for determining vaginal vs. operative delivery should be used. Of note is the necessity to monitor liver function, complete blood cell count, and platelet levels postpartum for up to 48 hrs, because some patients' conditions may actually worsen after delivery (7). In a study of 147 women, Martin et al. (8) found that most continued to have worsening thrombocytopenia and increasing LDH levels up to 48 hrs postpartum but usually recovered normal platelet levels by day 6 postpartum.

## Acute Fatty Liver of Pregnancy

*Incidence and Pathophysiology.* AFLP is a rare and potentially fatal disease (18% maternal mortality, 23% fetal mortality) that occurs in the third trimester of pregnancy. Hepatic histopathology reveals microvesicular fatty infiltration of hepatocytes in the absence of significant inflammation or necrosis. The incidence of AFLP has been difficult to determine because few large-scale trials have been performed to study this disease. The most recent study by Castro et al. (9) in Boston, of 200,000 births over a 15-yr period, places the incidence at 1 in 6,659 births. Other earlier studies, by Pockros et al. in Baltimore, showed the incidence to be lower, at about 1 in 13,000 deliveries in a predominantly Hispanic population (10). The pathophysiology of this disease presents the remarkable relationship between mother and fetus. As the fetus continues to grow, fatty acid oxidation is used as a means of producing metabolic energy. An association between AFLP and a deficiency of the enzyme LCHAD may be implicated in the pathogenesis of this disease. Deficiency of this enzyme increases levels of long-chain fatty acids. Such defects in fatty acid oxidation are reflected by elevations in urinary organic acid levels and in plasma carnitine and acylcarnitine levels, detected after an overnight fast. Sims et al. (11) offered the first molecular explanation of this disease, elucidating that a single point mutation of a guanine to cytosine at base pair 1528 (G1528C) caused the derangement. Fetuses with a deficiency of this enzyme accumulate long-chain fatty acids that have not undergone oxidation. These fatty acids enter the maternal serum and are hepatotoxic. Furthermore, the placenta itself may produce excess fatty acids (during steroidogenesis) and may further elevate maternal free fatty acids. Mothers who are heterozygous for deficiency of LCHAD have a greater risk of developing this disease. In a study of 12 women in Connecticut with a history of AFLP, eight were found to be heterozygous for the LCHAD deficiency. Among those women, eight subsequent pregnancies were complicated by AFLP (12).

It is important to note that not all women with LCHAD deficiencies develop fatty liver of pregnancy. The exact reason why some women with LCHAD are spared is currently unknown at the moment. In addition, because other enzyme deficiencies of fatty acid oxidation can occur, LCHAD is not a distinct cause of AFLP. Several case reports have been published in which other enzyme deficiencies involved in β-oxidation have been described as causing symptoms of liver failure similar to AFLP. In one such report, a deficiency of carnitine palmitoyltransferase was implicated in the development of maternal illness, illustrating that LCHAD, while the most common enzyme deficiency, is not a unique derangement causing AFLP (13). Chorionic villous sampling or amniocentesis can assist in prenatal identification of fetuses with LCHAD deficiency.

*Clinical Presentation and Laboratory Diagnosis.* The presentation of this disease is varied, but most women complain of vague abdominal pain, fatigue, nausea, and vomiting. Since many patients are subclinical, these symptoms may be dismissed as being associated with normal pregnancy. It is important to distinguish this entity from HELLP syndrome and preeclampsia. Important to note is that slowly developing jaundice may be the presenting sign as further infiltration of the liver parenchyma ensues. As liver failure continues, some women may present with altered mentation and hepatic encephalopathy. Many patients will begin to experience moderate to severe hypoglycemia as well. Up to 60% of patients may develop renal failure, further causing deterioration of their condition (14). Laboratory abnormalities in AFLP include AST and ALT elevations to <1000 IU/L, prolongation of prothrombin time and partial thromboplastin time, decreased fibrinogen,

renal failure, severe hypoglycemia, and bilirubin levels of 1–10 ng/dL. Laboratory assessment shows elevated levels of liver transaminases; three studies showed varied levels. Usta et al. (15) surveyed women in 1994 with AFLP and found a mean AST level of 1067 U/L, but Castro et al. (16), surveying 28 patients in 1996, found the mean AST was only 210 U/L. This discrepancy illustrates that even only mildly elevated levels of liver transaminases can still indicate AFLP. Castro and Fasset et al. (17) studied the same phenomenon again in 1998 and found that the mean AST was again around 200 U/L.

As the disease progresses, three noteworthy complications occur. Hypofibrinogenemia and increased prothrombin time and activated thromboplastin times are also noted in this illness. Reduction of antithrombin III in patients with AFLP is a common finding. In a study of 23 patients at the University of Southern California, 100% of participants with AFLP had significant depression of antithrombin III levels (16). This can be an ominous sign, as disseminated intravascular coagulation may ensue, further contributing to morbidity in this condition. Diabetes insipidus may also be found in the peripartum and postpartum period, although the exact mechanism of this development remains poorly delineated.

*Management and Prognosis.* Although definitive diagnosis of AFLP is made by liver biopsy, liver biopsy is not necessary for diagnosis. Fifty percent of patients will have signs of preeclampsia, and HELLP syndrome may present with similar symptomatology. The discriminating feature between the two is that the microvesicular infiltration in AFLP substantially decreases the metabolic activity of the liver, thus causing increases in serum bilirubin levels. Some centers advocate the use of ultrasonography to assist in the diagnosis of liver disease in pregnancy, such as HELLP (16). However, Usta et al. (15) found that these tests offer poor specificity and perhaps are not necessary to make an appropriate diagnosis.

Resolution of nearly all symptoms of the disease occurs after expeditious delivery by stopping the overload on the mother's hepatic fatty-acid oxidation system. If pregnancy is not terminated promptly, fulminant maternal hepatic failure may ensue. Many of the laboratory abnormalities linger after delivery and may even become worse in the initial postpartum period. Individual symptoms of hypoglycemia and acidosis secondary to hepatic failure should be treated with appropriate intravenous fluids (dextrose) and ventilation/electrolytes, respectively. Should patients develop renal failure, dialysis is indicated to remove ammonia and other toxins that have accumulated because of both kidney and liver failure. Coagulopathies may be corrected with antithrombin III infusion and platelet transfusion when disseminated intravascular coagulation ensues, although Castro et al. (16) reported a similar outcome for patients who received antithrombin III and those who did not.

The route of delivery requires sound clinical judgments on the part of the clinician. Vaginal delivery may place undue stress on the mother, whereas cesarean section in the presence of severe coagulopathy can contribute to significant postoperative complications such as wound dehiscence, subfascial hematoma, and hemorrhage. The surgical theater should be ready with appropriate blood products should these issues arise (cryoprecipitate, fresh frozen plasma, etc.). The postpartum course of the disease is generally complete resolution of symptoms, with normal liver histology returning after delivery. The morbidity and mortality of this disease are generally associated with late diagnosis and poor management of the complications noted.

## Ruptured Liver Hematoma

*Incidence and Pathophysiology.* Hepatic rupture and infarction are rare complications of preeclampsia and occur in the third trimester of pregnancy. Older, multigravida mothers with preeclampsia are at higher risk. Less frequently, rupture may complicate growth of an hepatic adenoma or other masses of pregnancy. Diagnosis is defined by employing computed tomography or magnetic resonance imaging. This event generally occurs in the setting of HELLP syndrome or severe preeclampsia, with an incidence of approximately 1 in 45,000 live births (18). The mortality of this condition, as studied by Masas et al. (19), can be as high as 30%. As this entity is rare, few large studies analyzing this phenomenon have been completed. Most of the literature has been compilations of case reports.

The pathophysiology of this disease remains largely unknown. Immunofluorescence staining of the liver in women who develop this condition has shown fibrin deposition in the intrahepatic sinusoids (specifically in association with preeclampsia and eclampsia) (20) Neutrophilic infiltrates are also noted in biopsy specimens from these patients. It is theorized that as fibrinogen is deposited, the obstruction causes liver distention and ultimately rupture, resulting in a massive extravasation of blood between the liver proper and Glisson's capsule. Fibrin deposition also causes stimulation of platelets, formation of thrombi, and ultimately necrosis of hepatic tissue (21). As blood accumulates, the capsule itself may rupture, causing hemoperitoneum. The surgeon should be immediately aware of this upon entering the peritoneum when operating on a preeclamptic patient or a patient with HELLP syndrome.

*Clinical Presentation and Laboratory Diagnosis.* The clinical presentation and laboratory findings of this disease may be somewhat ambiguous and must be distinguished from other conditions such as cocaine abuse, liver abscess, AFLP, and trauma. Clinical presentation consists of nonspecific gastrointestinal symptoms, followed by an acute phase of arterial rupture. Liver hematoma and rupture should be suspected in a preeclamptic/HELLP patient who presents with right-upper-quadrant pain and hypotension. In all cases, intraparenchymal hemorrhage precedes the rupture, in contrast to hepatic rupture secondary to trauma. The pathophysiology of liver rupture remains unclear but includes desensitization of the reticuloendothelial system in the liver during prior pregnancies, leading to accumulation of fibrin deposits, blockade of sinusoids, cellular necrosis, hemorrhage, and rupture. Laboratory anomalies of elevated AST and ALT values may be noted as well as thrombocytopenia. These symptoms and laboratory findings necessitate imaging of the liver. In a study of 33 patients, Barton and Sibai found that nearly half of patients whose laboratory findings at presentation were consistent with HELLP syndrome and who had shoulder pain, hypotension, or neck pain were found to have subcapsular liver hematomas (22). It is therefore highly recommended that women who have the aforesaid symptoms and for whom laboratory findings are consistent with HELLP syndrome undergo imaging of the liver (abdominal computed tomography, magnetic resonance imaging, or right-upper-quadrant ultrasonography.)

*Management and Prognosis.* Once a subcapsular hematoma is diagnosed,

careful evaluation of the patient is of utmost importance for proper management. Contained hematomas that have not ruptured in a normotensive patient and are not associated with signs of severe blood loss may be managed conservatively with intravenous fluids and appropriate blood products. Barton and Sibai (23) recommend conservative management of patients who are hemodynamically stable, with judicious monitoring of coagulation study findings, appropriate imaging of the abdomen, and treatment of the underlying condition that led to the formation of the hematoma (preeclampsia, eclampsia, and HELLP syndrome). Unstable patients who develop peritoneal signs and symptoms of shock should be referred for emergent surgical intervention. Transcatheter embolization may also be used in large hematomas, with intervention by a trauma surgeon if rupture occurs (24).

Recent studies have pointed out the possible use of recombinant factor VIIa in the treatment of spontaneous subcapsular hematoma. Factor VII stimulates the formation of hemostatic plugs at points of hemorrhage. Merchant et al. (21) used this treatment for three patients who developed hemodynamic instability after the formation of a subcapsular liver hematoma. Two patients responded well to the treatment: hemostatic stability was achieved and appropriate increases in hematocrit occurred after treatment. The other patient responded hemostatically to treatment but later died of anoxic brain injury secondary to cardiac arrest, although hemodynamic control of the hematoma was established and documented before her death. Recombinant factor VIIa has not been used extensively because of the fear of thrombosis and possible pulmonary embolism. Also, because many patients with HELLP syndrome may develop disseminated intravascular coagulation, use of this agent can exacerbate this condition. Merchant et al. do not report the development of consumptive coagulopathy in their patients and cite Hedner and Erhardsten's study (25) of >170,000 uses of recombinant factor VIIa with only five thromboembolic events, six myocardial infarctions, and four cerebrovascular accidents. Large-scale studies have yet to be completed on this intervention, and its use merits further investigation.

## Intrahepatic Cholestasis of Pregnancy

*Incidence and Pathophysiology.* Intrahepatic cholestasis of pregnancy (ICP), or icterus gravidarum, is a rare and serious medical condition seen in the third trimester, with fetal mortality rates of 11% to 20% when untreated and prevalence rates estimated at 1/1,000 to 1/10,000 pregnancies. The disease is seen more frequently in older, multiparous women and in the winter months. ICP clusters in families and is more common in women with a history of cholestasis who are taking oral contraceptives. Both racial and genetic predispositions for ICP have been observed, complicating 0.01 to 0.02% of pregnancies in North America, 1% to 1.5% in Sweden, and 5% to 20% in Chile. Perhaps the most striking aspect of this derangement is the high incidence of complications. A study done in Britain of 337 women with ICP showed that 38% of fetuses were born prematurely and that 7% of women experienced an intrauterine fetal demise (26). The high incidence of perinatal morbidity and mortality makes this entity one of the most concerning to the obstetrician and critical care specialist.

The pathophysiology of this disease is thought to be associated with endocrine, environmental, and hereditary factors, although the exact etiology of this disease is still unknown. From an endocrine standpoint, it is thought that increasing estrogen levels throughout the course of the pregnancy contribute to the development of ICP (27). This is supported by the fact that women with multiple gestations have an increased risk of having the disorder (multiple gestations cause a proportional increase in the estrodiol levels in maternal circulation). Estrodiol acts on the basolateral side of the hepatocyte to decrease membrane permeability and fluidity. This in turn leads to a decrease in the $Na^+/K^+$-ATPase pump, a decreased sodium gradient, and ultimately a failure of sodium-dependent bile acid uptake by hepatocytes (28). Progesterone also has been thought to play an important role in the pathophysiology of the disease because it inhibits glucuronyltransferase, which in turn inhibits the clearance of estrogens by the liver, thus amplifying their effects (28). Women with a family history have an increased risk of developing ICP (29), and the risk is even greater if they have had the disease previously. Since a broad presentation of the disease exists, it has been thought that the genetic basis of ICP is complex (27). A heterozygous mutation in the MDR3 gene has been theorized as a possible genetic etiology for ICP (21). This gene codes a phospholipid secreting channel in the bile canaliculus, and the mutation produces malfunctioning protein. This was found in a study of only three women in one consanguineous family; large trials of the gene mutation have yet to be completed. There is also an environmental component, as more women are found to develop ICP in the winter, for unknown reasons (30).

*Clinical Manifestations and Laboratory Diagnosis.* Patients usually present in the third trimester, by the 30th week of pregnancy, with reports of moderate to severe pruritis. Eighty percent of patients have pruritus alone, whereas pruritus and jaundice develop in 20% of patients. An interesting feature of the disease is that the pruritis begins on the palms and soles of the feet and grows in an ascending pattern, although this is not a requirement for diagnosis. The pruritis may become so severe that the patient presents with gross excoriations on the body. It is generally believed that the pruritis presents before overt laboratory anomalies are noted (31). In later stages, jaundice may develop in up to 20% of women. A key diagnostic feature lies in the laboratory values, namely, a marked elevation in serum bile acid levels. Both chenodeoxycholic acid and cholic acid are between 10 and 100 times the normal levels of healthy pregnant women (32). Laboratory data show bilirubin levels that rarely exceed 6 mg/dL, alkaline phosphatase levels ranging from normal to four times normal, and transaminase levels that may be significantly elevated. A liver biopsy, although not recommended for diagnosis, will show normal hepatic parenchyma and widening of the bile canaliculi (under electron microscopy) with cholestasis (32).

*Management and Prognosis.* ICP is associated with preterm delivery, increased perinatal mortality, and meconium staining. ICP is a significant risk factor for both fetal morbidity and mortality. Glatz et al. studied 690 women over a 3-yr period in Sweden who had a clinical diagnosis of ICP. They found that 4.3% of women proceeded to preterm labor, 7.1% of fetuses had asphyxia events, and meconium staining of the amniotic fluid occurred in nearly 25% of deliveries (33). The authors also found a correlation between the serum bile acid levels and the

incidence of fetal complications that occurred during the pregnancies. Women with serum bile acid levels >40 μmol/L had a significantly higher rate of complications than did women with lower bile acid levels (33). Treatment of the pruritis is usually accomplished with ursodeoxycholic acid, which has been shown to significantly reduce itching and serum bile acids. Ursodeoxycholic acid alters the overall distribution of bile acids from the fetal circulation. The optimal treatment of ICP is delivery of the fetus; in most women, cholestasis and the ensuing pruritis resolve within a few days postpartum, although in a few cases these may last for a few weeks. Delivery is usually delayed until 38 wks of gestation to enable fetal maturation but should not be delayed if the patient or fetus exhibits signs of instability. Maternal outcomes are favorable, with both laboratory values and symptoms resolving within 1–2 wks postpartum. Up to 60% of women with ICP will have a recurrence in subsequent pregnancies.

## Hepatitis B and C Infections

*Incidence and Pathophysiology.* Viral hepatitis is the most common cause of jaundice in pregnancy, and the course of most hepatitis infections is unaltered by pregnancy. A more severe course of viral hepatitis has been noted in patients with hepatitis E. Among pregnant women with hepatitis E infection the fatality rate is about 10%–20%. The two most common types of viral hepatitis infection are hepatitis B and hepatitis C.

*Hepatitis B.* Hepatitis B is thought to infect nearly 35,000,000 people worldwide, making it one of the most prevalent diseases in the world. It is most commonly found in developing countries, with a high incidence reported in China, Southeast Asia, and sub-Saharan Africa, where seropositivity of the general population can approach between 50% and 90% (34). Hepatitis B infection during pregnancy poses unique dangers to both the fetus and the mother. With the introduction of the hepatitis B vaccine in the West, the incidence of this disease is relatively small in comparison with that in the developing world. Euler et al. (35) conducted the most recent long-term study of the prevalence of hepatitis B seropositivity among pregnant women in the United States. They found that of 10,523 women in four urban centers, 0.97% of blacks, 0.6% of whites, 0.14% of Hispanics, and 5.79% of Asian-Americans were seropositive for the hepatitis virus (35). Specifically, patients were all found to be positive for the hepatitis B surface antigen.

The three main modes of transmission from the mother to the infant are *in utero* infection, direct inoculation during delivery, and postnatal transmission during breast-feeding. *In utero* infection of the fetus is considered unusual except in the setting of acute hepatitis B infection during the third trimester, secondary to infection of placental capillaries (36). Direct inoculation of the fetus during delivery represents the most common mode of transmission. As the fetus passes through the vaginal canal, blood present there is swallowed by the fetus. Up to 95% of infants born to mothers who are hepatitis B antigen–positive have the antigen in their gastric fluid (35). The time of maternal infection also dictates the risk posed to the fetus with regard to transmission. Euler et al. (35) report that a mother who is positive for hepatitis B surface antigen and hepatitis B e-antigen (indicating high infectivity) has a risk of up to 90% of infecting the fetus. This has been confirmed in previous studies by Gao et al. (37) in China, who found a transmission rate of nearly 100% among women who were positive for both hepatitis B surface antigen and hepatitis B e-antigen.

*Clinical Manifestations of Laboratory Diagnosis.* Acute hepatitis B infection usually presents as a subclinical, mild illness, and most patients do not report any discernable symptoms. Up to 30% of patients will develop scleral icterus, nausea and vomiting, and right-upper-quadrant tenderness (38). Laboratory values will include elevated serum transaminase (AST and ALT) value, in the thousands. Most patients will have resolution of symptoms in a few weeks with supportive care, and only a small percentage (0.5%–1.5%) will develop fulminant hepatic failure (39). Because the presentation of acute hepatitis B infection is similar to that of HELLP syndrome and AFLP, it is imperative that the clinician order the appropriate laboratory tests, perform a diligent physical examination, and monitor vital signs. HELLP syndrome can be differentiated from acute hepatitis B infection in that in the former there is a substantial elevation of blood pressure from baseline and jaundice is generally not present.

Several studies have focused on the use of pharmacologic agents to prevent transmission of the hepatitis B virus from mother to infant. Lamivudine is a cytosine analog that acts as a nucleoside reverse transcriptase inhibitor and has been used to treat hepatitis B infection during pregnancy. Van Zonneveld et al. (40) studied a group of eight highly viremic patients in Holland and treated them with lamivudine to help prevent transmission of the virus to the fetus. They concluded that all but one infant became uninfected with the virus, proving that there was a substantial reduction in the perinatal transmission rates with lamivudine therapy (40). The study was replicated by Guan-Guan et al. (41) in China; they found that in a group of 38 chronically infected hepatitis B patients, lamivudine therapy during pregnancy substantially decreased perinatal transmission and delayed active hepatitis in mothers.

Hepatitis C infection also presents unique problems for the gravid female. The clinical course of hepatitis C infection remains largely unchanged in the gravid state, but implications for the fetus are many. It is estimated that 1% to 4.3% of pregnant women are infected with the virus, and nearly 30% to 40% of patents will go on to develop overt liver cirrhosis (42, 43). It has been noted, however, that maternally acquired hepatitis C infection in neonates does have a slower, more indolent course. Perinatal transmission has been shown to be the leading cause of hepatitis C infection amongst infants and children (44). Gibb et al. (44a), in a study of 441 women in Britain, found that 6.7% of infants born to mothers who were hepatitis C–positive were also infected and that the rate was nearly three times that for mothers coinfected with HIV.

No large-scale studies have examined the efficacy of pharmacologic intervention in preventing transmission to the fetus. Lamivudine use has been established as a modality to prevent the transmission of hepatitis B to neonates, but no such trial has been examined on a large scale for hepatitis C. Maternal viral load is an important predictor of vertical transmission, as higher viral loads have been associated with a greater risk of transmission. Yeung et al. (45) performed a meta-analysis of over 77 studies done between 1992 and 2000 and found that other important risk factors for transmission included coinfection with HIV (the most significant), modality of delivery, and whether or not the infant was breast-fed. Of interest in the same analysis was that the rate of transmission with cesarean

section and vaginal delivery was nearly identical: 6.8% and 6.7%, respectively. The use of ribavirin, an antiviral agent common in the treatment of hepatitis C infection, is contraindicated for pregnant women because several studies have shown it to be a potent teratogen. Women who are breast-feeding are also advised not to take ribavirin during pregnancy.

### Budd Chiari Syndrome

Budd Chiari syndrome refers to hepatic venous obstruction secondary to thrombosis of the hepatic vein or suprahepatic inferior vena cava. The most common causes of hepatic venous thrombosis include myeloproliferative disorders such as hereditary thrombophilias, polycythemia vera, and myelodysplastic syndrome. In a study of 237 patients in the Netherlands who were diagnosed with Budd-Chiari syndrome, up to 23% were found to have an associated myeloproliferative disease (46). Hypercoagulability associated with protein C and protein S deficiency, antithrombin III deficit, and pregnancy also poses risk factors for the development of this disease. Oral contraceptive use also has been documented as a risk factor for the development of Budd Chiari syndrome (47). Pregnancy can exacerbate this condition as it is a hypercoagulable state.

Budd Chiari syndrome in an acute setting may present similarly to other hepatic derangements of pregnancy with right-upper-quadrant pain and jaundice. It is important to rule out life-threatening diseases such as severe HELLP syndrome and ruptured liver hematoma, which require emergent surgical intervention. One of the key differentiating features in the disease is the presence of ascites, which may develop rapidly if the obstruction is large. Chronic thrombosis may present in a more indolent fashion, with dull discomfort and abdominal pain. Workup of this disease includes Doppler ultrasonography of the right-upper quadrant of the abdomen, followed by abdominal computed tomographic scanning. Venography is the "gold standard" for diagnosis because it will show occlusion of the hepatic vein. Treatment of this disease in pregnancy is controversial because a balance between maternal health and fetal outcome may be difficult to achieve. Unless contraindicated by bleeding disorders, anticoagulation is advocated for indolent or chronic disease (48). Because the use of coumadin is contraindicated in pregnancy, heparin is the choice pharmacologic treatment to prevent further thrombosis. Acute treatment with associated liver failure is best treated with surgical intervention to decompress the liver or with transjugular intrahepatic portosystemic shunt placement (TIPS). This procedure may be technically difficult in a late-term pregnancy because the gravid uterus may obstruct the placement of the shunt. Ultimately, some patients may require liver transplantation, which has been shown to be effective in up to 88% of patients in combination with anticoagulation (49). Large-scale studies of this intervention in pregnancy have not been performed, but one case report has shown that the procedure can be tolerated, with normal fetal development (although in that case the mother died 15 months later) (50).

### Wilson's Disease

Hepatolenticular degeneration secondary to reduced copper excretion, or Wilson's disease, also affects pregnancy. The disease has been linked to a defect in a hepatic copper transport protein that allows copper to be secreted into the bile and excreted with the feces. The specific protein defect of the ATP7B transport protein has been studied and found to be the derangement responsible for Wilson's disease (51). As copper builds up within the hepatocytes, copper ions will spill into the serum and be deposited in various tissues such as the brain, kidney, and eyes. The hepatitis that ensues from the destruction of the hepatic parenchyma will cause patients to present with jaundice and elevated liver enzyme (AST and ALT) values. As serum copper levels continue to rise, patients may develop the neuropsychiatric stigmata of the disease, secondary to deposition of copper in the basal ganglia. Oder et al. studied a group of 47 patients with Wilson's disease who exhibited neuropsychiatric phenomena and found that they included a Parkinson's-like triad (bradykinesia, cogwheel rigidity, and impaired cognition), ataxia from cerebellar degeneration, and dyskinesia. The hallmark ocular lesions of the disease are Keyser-Fleisher rings in the iris, which illustrate extensive extravasation of copper into the serum.

Fertility is generally affected in women with Wilson's disease because they may experience amenorrhea and frequent miscarriages (52). These are due to hormone fluctuations and copper ions inhibiting follicular aromatase (53). The long-term effects on infants born to women with both treated and untreated Wilson's disease have yet to be studied in a large clinical trial, but a few studies have examined the disease's effects on pregnancy. Treatment of this disease during pregnancy is similar to that during nonpregnancy. Brewer et al. (54) studied 19 women and 26 pregnancies and found that treatment with zinc throughout the pregnancy resulted in 24 normal infants and two infants afflicted with heart defects and microcephaly. The use of other chelating agents that help bind copper, including penicillamine and trientine, has also been studied. In a brief review of the literature over the past 25 yrs, Sternlieb advises use of the aforesaid chelating agents to successfully manage the disease during pregnancy, with positive outcomes for both mother and infant, and states that the risk of teratogenicity is low (52).

## CONCLUSIONS

Liver disease in pregnancy may present in a subtle or dramatic fashion. Prognostic determinations should be based on the patterns of liver function abnormalities, time of gestation, and symptomatology. Diagnosis may be confirmed by serologic assays; evaluations with ultrasonographic, computed tomographic, or magnetic resonance imaging of the hepatobiliary system; or liver biopsy. The results can effect management by delaying or accelerating treatment delivery. Advances in our understanding of the molecular biology of these hepatic diseases in pregnancy will eventually lead to development of novel adjunctive approaches to treating these diseases.

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