Pregnancy-Related Liver Diseases

Calvin Pan, MD\textsuperscript{a,\,*}, Ponni V. Perumalswami, MD\textsuperscript{b}

Abnormal liver test results are obtained in 3% to 5% of pregnancies because of many potential causes, and the clinical outcomes range from self-limiting to rapidly fatal. There are 4 main conditions that cause abnormal liver tests in pregnant patients: physiologic changes in pregnancy, newly acquired liver disease, preexisting liver disease, and pregnancy-related liver disease. Abnormal liver function test results because of physiologic changes in a pregnant patient without liver dysfunction have a unique pattern and can be recognized when compared with the normal range of liver test results (Table 1).

Newly acquired liver disease in pregnant patients, include acute viral hepatitis, drug-induced liver injury, or gallstones, may cause abnormal liver test results. A third cause of abnormal liver test results includes preexisting chronic liver diseases such as cholestatic liver disease, autoimmune hepatitis, Wilson disease, and chronic viral hepatitis. Finally, pregnancy-related causes for liver disease are the most common reasons for abnormalities in liver test results in pregnancy. There are 5 distinct liver diseases unique to pregnancy including hyperemesis gravidarum (HG); intrahepatic cholestasis of pregnancy (ICP); preeclampsia; hemolysis, elevated liver enzymes, and low platelets with or without preeclampsia (HELLP syndrome); and acute fatty liver of pregnancy (AFLP). Unlike newly acquired or preexisting liver diseases, which may

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present at any time during pregnancy, pregnancy-related liver diseases have a unique timing of onset (Table 2).

This article focuses on the aforementioned causes of pregnancy-induced liver diseases.

**LIVER DISEASES RELATED TO PREGNANCY**

HG

Nausea with vomiting is common in pregnancy. HG is defined as intractable nausea and vomiting during the first trimester of pregnancy and is the most severe illness within the spectrum of nausea and vomiting in pregnancy.\(^1\) HG often leads to dehydration and electrolyte imbalance and occurs in about 0.3% of pregnancies but usually resolves by weeks 16 to 18 of gestation. In up to 10% of patients with HG, symptoms continue through pregnancy and resolve only with delivery of the fetus.\(^2,3\)

The mechanism for developing HG remains unclear. Proposed mechanisms include hormonal imbalance with increased levels of human chorionic gonadotropin (HCG) and estrogen and decreased levels of prolactin, coupled with overactivity of the hypothalamic-pituitary-adrenal axis.\(^4,5\) It is also proposed that the high level of HCG may stimulate the thyroid gland and upregulate the secretory processes of the upper gastrointestinal tract.\(^4\) Other studies speculate that cytokine, T cell–mediated immune reactivation, immunoglobulin, and complement play an important role in HG because high levels of tumor necrosis factor \(\alpha\), IgG, IgM, C3, C4, natural killer cells, and extrathymic T cells have been observed in patients with HG.\(^6,7\)

Risk factors for the development of HG include molar pregnancy, multiple pregnancies, preexisting diabetes or hyperthyroidism, and psychiatric disorders.\(^8\) An abnormal liver panel is seen in up to 50% of cases. Transaminases are usually elevated to between 2 and 10 times the upper limit of normal but rarely can be up to 20 times the normal with mild jaundice.\(^2\) The diagnosis of HG is clinical and based on exclusion of other underlying or newly acquired liver diseases, especially viral hepatitis.

<table>
<thead>
<tr>
<th>Disease Categories</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting Liver Diseases</td>
<td>Chronic hepatitis B or C, autoimmune hepatitis, primary sclerosing cholangitis, Wilson disease, primary biliary cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly Acquired Liver Diseases in Pregnancy</td>
<td>Viral hepatitis, gallstones, drugs, sepsis, Budd-Chiari syndrome (usually post partum)</td>
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</tr>
<tr>
<td>Diseases Related to Pregnancy</td>
<td>HG</td>
<td>ICP</td>
<td>HELLP syndrome, ICP, preeclampsia, AFLP</td>
</tr>
</tbody>
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Table 1

<table>
<thead>
<tr>
<th>Liver Test Results</th>
<th>Physiologic Changes Compared With Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>Alkaline phosphatase (2- to 4-fold), fibrinogen, fetoprotein, white blood cell, ceruloplasmin, cholesterol (2-fold), alpha or/and beta globulins, triglycerides</td>
</tr>
<tr>
<td>Unchanged</td>
<td>Aminotransferases, prothrombin time</td>
</tr>
<tr>
<td>Decreased</td>
<td>Bilirubin (or unchanged), (\gamma)-globulin, hemoglobin (third trimester)</td>
</tr>
</tbody>
</table>

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Table 2

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The clinical management of HG is primarily supportive. Patients should be instructed to maintain oral hydration and a high-carbohydrate, low-fat diet. In addition, patients who can tolerate oral intake of food are counseled to take small portioned meals. In patients who cannot maintain their body weight because of intractable vomiting, enteral nutrition and intravenous rehydration may be required. In most patients, HG resolves with the replacement of electrolytes and glucose, rehydration, and nutritional support. Parenteral hydrocortisone may lead to rapid resolution in severe cases, with slow improvement. Rarely, serious complications may occur, which include malnutrition, spontaneous esophageal rupture, hyperthyroidism, or even Wernicke encephalopathy caused by vitamin B₁₂ deficiency.

ICP

ICP is defined as pruritus and elevated bile acid (BA) levels during the late second or third trimester of pregnancy, with resolution after delivery. ICP is the most common pregnancy-related liver disorder, with a prevalence of about 1 in 1000 to 1 in 10000. ICP is common in South Asia, South America, and Scandinavian countries and has the highest incidence in Chile and Bolivia (5%–15%). However, in North America, the incidence is less than 1%, with a trend of increase in recent reports. Risk factors for the development of ICP include multiparity, advancing maternal age, twin pregnancies, and a history of cholestasis due to oral contraceptive use.

While the cause of ICP is not clearly known, it is likely multifactorial, involving genetic, hormonal, and exogenous factors. Studies have demonstrated that sex hormones have known cholestatic effects through inhibition of the hepatocellular bile salt export pump (Bsep). In addition, increased levels of sex hormones in pregnancy have been associated with an abnormal metabolic response with impaired sulfation, which has been a proposed cause for ICP. The hepatic transport systems for biliary excretion can also be affected and saturated by the large amount of sulfated progesterone metabolites. Genetic studies to date suggest that at least 10 different multidrug resistance–associated protein (MDR) 3 mutations have been identified in progressive familial intrahepatic cholestasis. MDR3 is the transporter of phospholipids across the canalicular membrane, and mutations (ABCB4/abcb4) may result in loss of function and raised BA levels as a secondary effect. A recent study in Italy identified 5 genes that are expressed differentially in patients with ICP compared with controls. These genes are involved in hepatobiliary transport and cholesterol metabolism (ABCC4 [MRP4 protein] and NR1H3 [LXR-α protein]), protein trafficking and cytoskeleton construction (HAX1 and TTLL5), as well as pathophysiology of pruritus (GABRR1 [GABA receptor type A rho1]). Other studies have suggested the Bsep ABCB11 and the MRP2 ABCC2 as the other candidate proteins that may be involved in ICP. Finally, Reyes and colleagues have reported that exogenous factors associated with ICP increase intestinal permeability suggesting that there may be enhanced absorption of bacterial endotoxin. Still other studies from Chile have proposed a role for dietary factors (selenium deficiency), seasonal variability, and geographic variations in ICP.

Patients with ICP typically present with generalized pruritus, predominately on the palms and the soles of the feet, and the condition is worse at night. Pruritus usually starts during weeks 25 to 32 of pregnancy and resolves after delivery. While skin lesions specific to the disorder are absent, excoriations caused by scratching are often noted on physical examination. In general, serum abnormalities present 4 weeks after the onset of pruritus. The most early and specific abnormality in laboratory findings in ICP is the elevation of serum total bilirubin acid level, and it is usually less than 5 mg/dL. Jaundice occurs in approximately 10% to 25% of patients, and some may have diarrhea.
or steatorrhea as a complication of cholestasis. Aminotransferase levels vary from 2 to 15 times the upper limit of normal. Elevation of alkaline phosphatase levels is not diagnostically helpful because of it is produced by both placenta and bone in pregnancy. The serum γ-glutamyl transferase level is usually normal or modestly elevated. A prolonged prothrombin time (PT) may be noted, which is most often caused by vitamin K deficiency because of the subclinical steatorrhea from cholestasis.

Several atypical presentations of ICP can occur, most notably with variations in the disease course. Some patients can have an early onset of pruritus in the first trimester. In addition, pruritus can resolve spontaneously before delivery with or without an improvement in serum liver test results. Patients can develop pruritus without the usual serum abnormalities. In patients with serum test abnormalities, these laboratory findings may last up to 1 to 2 months after delivery. Finally, rarely, patients may develop abdominal pain or have pruritus and serum abnormality that is exacerbated postpartum with no signs of liver failure. The diagnosis of ICP is based on the clinical feature of pruritus, which is unique to ICP compared with HELLP and AFLP. The differential diagnosis of any pregnant patient with pruritus includes newly acquired viral hepatitis, preexisting liver diseases including primary biliary cirrhosis, choledocholithiasis, or chronic viral hepatitis. Choledocholithiasis can be ruled out with an abdominal sonogram.

A variety of treatment options have been previously studied for ICP. Antihistamines, benzodiazepines, phenobarbital, and epomediol have not shown any significant benefit. Other studies have demonstrated some clinical improvement in ICP with the administration of cholestyramine, dexamethasone, and S-adenosyl-L-methionine. However, these treatments have been proven to be less effective than ursodeoxycholic acid (UDCA) in relieving pruritus and improving liver test result abnormalities, especially aminotransferases and BA levels. Therefore, UDCA is the treatment of choice for ICP. It is unclear how UDCA works, but several studies suggest that UDCA can reduce BA levels by increasing the expression of placental BA transporters and facilitating the placental transport of BAs from the fetal to the maternal compartment. Another hypothesis suggests that UDCA promotes BA clearance by facilitating the insertion of transporter proteins such as Bsep (ABCB11) or MRP2 (ABCC2) into the canalicular membranes. UDCA, 10 to 15 mg/kg bodyweight, (up to 2.0 g/d) is usually well tolerated and safe to the fetus without teratogenicity.

Although maternal effects are mild, ICP is associated with a high frequency of fetal distress (20%–40%), with occasional antenatal sudden fetal death and premature labor (60%). Fetal complications are probably caused by elevated fetal levels of BA because of the increased flux of BAs from the mother to the fetus or the impairment of fetal BA transported across the placental membrane to the maternal circulation on top of the immaturity of fetal BA transport systems; high maternal levels of BA correlate with fetal morbidity and mortality. Glantz and colleagues have suggested using maternal BA levels of 40 µmol/L as a threshold for early delivery. Close monitoring and early delivery after confirming fetal lung maturity may be the best way to prevent sudden antenatal death. When delivery is not advisable, treatment with UDCA improves maternal pruritus and aminotransferase levels, which may benefit the fetus, because fetal morbidity and mortality are correlated with maternal BA levels. Counseling should be provided to women with a history of ICP because recurrence of cholestasis is common (40%–60%) with future pregnancies or hormonotherapy.

Liver Dysfunction Related to Preeclampsia

Affecting 5% to 10% of pregnancies, preeclampsia is a syndrome of hypertension (blood pressure [BP] ≥140/90), edema, and new onset of proteinuria during the late second (≥20 weeks of gestation) or third trimester. Proteinuria is defined as more than 300 mg protein
per 24-h urine collection or 1+ or greater protein on urine dipstick testing of 2 random urine samples collected at least 4 to 6 hours apart. While the cause is unknown, several factors play a role in the pathogenesis, including abnormal vascular response to placentation, increased systematic vascular resistance, enhanced platelet aggregation, activation of the coagulation system, trophoblast invasion of the spiral arteries, abnormal trophoblast differentiation, and endothelial dysfunction.

Clinically, patients can present with symptoms including severe headache, fatigue, epigastric/right upper quadrant abdominal pain, vomiting, changes in vision, and swelling of the face and extremities. Physical exam findings include hypertension, seizures, focal neurologic signs, hyperreflexia, oliguria, oligohydramnios, and intrauterine growth retardation. In addition to proteinuria, patients may have increased serum uric acid levels, liver transaminase level elevation up to 20 times the upper limit of normal, and hyperbilirubinemia. Although there is no specific treatment of hepatic involvement in preeclampsia, these changes may indicate the development of severe preeclampsia, which requires immediate delivery of the fetus. The main complication of preeclampsia is development of eclampsia, which is characterized by intractable seizures. Hepatic complications of preeclampsia include subcapsular hemorrhage and capsular rupture with life-threatening intra-abdominal bleeding. Obstetric complications include placental abruption, fetal demise, and fetal syndrome characterized by fetal growth retardation, reduced amniotic fluid, and abnormal oxygenation.

Definitive therapy for preeclampsia is delivery of the fetus. Patients with severe preeclampsia should be hospitalized. Patients who are at or before their 32nd week of gestation with uncomplicated or moderate preeclampsia (urinary protein excretion ≤1 g/24 h, systolic BP ≤160 mm Hg) may be managed as outpatients with close follow-up. The use of antihypertensive agents has not been shown to alter the course of maternal disease or decrease perinatal morbidity or mortality. Post partum, hypertension and proteinuria subside within 12 weeks after delivery. In a minority of patients, long-term antihypertensive therapy is required.

In general, maternal and perinatal outcomes are favorable in women with mild preeclampsia developing beyond 34 weeks’ gestation but could be worse if preeclampsia occurs before 33 weeks’ gestation, in those with preexisting medical conditions, and in those living in developing countries. Women who develop preeclampsia are also at an increased risk of developing cardiovascular disease later in life.

**HELLP Syndrome**

HELLP syndrome is a multisystem disorder characterized by hemolysis, elevated levels of liver enzymes, and low platelet counts with or without preeclampsia. HELLP syndrome is a potentially life-threatening complication of pregnancy. The prevalence of HELLP syndrome is estimated to be 0.6% of deliveries. Risk factors for the development of HELLP syndrome include advanced maternal age, Whites and multiparity. The pathogenesis of HELLP syndrome is not known. However, in two-thirds of the patients, the condition occurs in the third trimester, and microangiopathic hemolytic anemia is the hallmark of the syndrome but is not specific to this entity. It is thought that the microangiopathic hemolytic anemia is associated with vascular endothelial injury, fibrin deposition in blood vessels, and platelet activation with platelet consumption. Histopathologically, HELLP syndrome is characterized by periportal or focal parenchymal necrosis with hyaline deposition of fibrin material in the sinusoids.

Clinical symptoms of the syndrome include epigastric or right upper quadrant pain, malaise, headache, nausea, and vomiting. On physical examination, hypertension, generalized edema, and weight gain are common signs. Laboratory findings revolve around presence of 3 laboratory criteria: thrombocytopenia, elevated
aminotransferase levels, and hemolysis. Several different classifications have been proposed. Generally, platelet count less than 100,000/mm³, aspartate aminotransferase levels greater than 70 U/L, and L-lactate dehydrogenase (LDH) levels greater than or equal to 600 U/L are helpful to make the diagnosis. The Mississippi classification is based on the degree of thrombocytopenia and the elevation of transaminase and LDH levels, which has been proposed for assessing the severity of the pathologic process (Table 3).

Risk factors for preeclampsia include antiphospholipid antibody syndrome, chronic hypertension, chronic renal disease, elevated body mass index, maternal age greater than 40 years, multiple gestation, nulliparity, preeclampsia in a previous pregnancy (particularly if severe or before 32 weeks of gestation), pregestational diabetes mellitus, connective tissue disorders, protein C and S deficiencies, factor V Leiden mutation, and hyperhomocysteinemia.

Serious maternal complications are common in HELLP syndrome. A high index of suspicion and an early diagnosis are key to the management of patients with HELLP syndrome. The most frequent complications are disseminated intravascular coagulopathy (30%), abruptio placenta (16%), acute kidney injury (7.7%), aspiration pneumonia (7%), pulmonary edema (6%), acute respiratory distress syndrome, cardiopulmonary arrest (4%), cerebral hemorrhage (1.2%), and retinal detachment (0.9%). Rarely, severe ascites, subcapsular hematoma, hepatic failure, and hepatic rupture can occur (0.015%). 38,39 Disseminated intravascular coagulation (DIC) may be a late complication, and patients can have a prolonged PT and increased International Normalized Ratio. Proteinuria is a common finding but not required to make the diagnosis. Computed tomography (CT) may show subcapsular hematomas, intraparenchymal hemorrhage, hepatic rupture, or infarction.

Management of the woman with HELLP syndrome begins with hospitalization for stabilization of hypertension and DIC, seizure prophylaxis, and fetal monitoring followed by prompt delivery of the fetus. Transfer to a tertiary care center is advocated, if possible. CT or magnetic resonance image of the liver should be obtained. If the pregnant woman is at or beyond 34 weeks' gestation or if there is any evidence of multiorgan dysfunction or severe complication, immediate induction of labor is recommended. If the gestational age is between 24 to 34 weeks, corticosteroids are administered to accelerate fetal lung maturity in preparation for delivery 48 hours later. After delivery, close monitoring of the mother should continue because studies have shown worsening thrombocytopenia and increasing LDH levels up to 48 hours postpartum. Most laboratory values normalize in 48 hours after delivery of the fetus.

The most frequent severe maternal complications including mortality have been observed in patients with Mississippi class I HELLP syndrome. The perinatal mortality is estimated to be 7% to 22%, with a maternal mortality of 1%. 40 Causes of perinatal mortality include premature detachment of the placenta, intrapartum asphyxia, and prematurity. Subsequent pregnancies in patients with HELLP syndrome carry a high risk of complications including recurrent HELLP. 38,41

<table>
<thead>
<tr>
<th>Class</th>
<th>Platelets (Cells/μL)</th>
<th>Transaminases (IU/L)</th>
<th>LDH (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;50,000</td>
<td>≥70</td>
<td>&gt;600</td>
</tr>
<tr>
<td>II</td>
<td>50,000–100,000</td>
<td>≥70</td>
<td>&gt;600</td>
</tr>
<tr>
<td>III</td>
<td>100,000–150,000</td>
<td>≥40</td>
<td>≥600</td>
</tr>
</tbody>
</table>

Pan & Perumalswami
AFLP is a rare condition that is estimated to affect 1 in 7000 to 16000 pregnancies.\textsuperscript{42,43} AFLP is associated with microvesicular fatty infiltration of the liver, hepatic failure, and encephalopathy. Most commonly occurring in the third trimester of pregnancy, AFLP carries significant perinatal and maternal mortality.

Recent data suggest that deficiencies of the enzymes of mitochondrial fatty acid beta oxidation (FAO) may play a role in the development of AFLP. The most commonly reported enzyme deficiency in this disorder is a long-chain 2-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. The defect is in the alpha subunit of the mitochondrial protein is associated with G1528C or E474Q mutations.\textsuperscript{44,45} Most recently, studies by Natarajan and colleagues\textsuperscript{46} demonstrated that placental mitochondrial function is compromised in AFLP, which may lead to free radical production and accumulation of fatty acids in the placenta, resulting in maternal hepatocyte stress and mitochondrial dysfunction leading to acute liver failure.

AFLP has unique clinical features. About 40% to 50% of patients with AFLP are nulliparous with an increased incidence in twin pregnancies.\textsuperscript{47} Patients often present with nonspecific symptoms including anorexia, nausea, emesis, malaise, fatigue, and headache. On physical examination, the patient may have jaundice, hypertension, edema, and hepatic encephalopathy. Laboratory findings include serum aminotransferase levels varying from normal to 1000 U/L, but are usually about 300 to 500 U/L. The total bilirubin concentration is typically less than 5 mg/dL. Other laboratory abnormalities include anemia, leukocytosis, normal or low platelet counts, coagulopathy with or without DIC, hypoalbuminemia, hypoglycemia, and acute kidney injury.

The diagnosis and management of AFLP is a medical and obstetric emergency, and therefore, early diagnosis is the key to improving survival. Management includes hospitalization for stabilization of hypertension and DIC, seizure prophylaxis, and fetal monitoring followed by immediate delivery of the fetus or termination of the pregnancy along with intensive support. The aminotransferase levels and encephalopathy improve within 72 hours of delivery, but continued intensive support may be required to help manage the complications of liver failure. Most patients recover in 1 to 4 weeks post partum.

Maternal mortality in AFLP is 3% to 12% and fetal mortality is 15% to 66%.\textsuperscript{48–50} The strong association of AFLP with LCHAD deficiency in the fetus suggests a necessity of neonatal testing for enzymatic defects of FAO. Women who are carriers of the LCHAD mutation have an increased risk of recurrence of AFLP in 20% to 70% of pregnancies.\textsuperscript{44,51}

**SUMMARY**

Liver dysfunction in pregnancy is frequently encountered in clinical practice. Liver disease related to preeclampsia and ICP are common and can affect fetal mortality. Even less common, HELLP syndrome and AFLP may cause severe liver dysfunction, hemorrhage, liver failure, and maternal death. Whereas mechanisms are poorly defined for all causes of pregnancy-related liver disease, recent advances have elucidated new possible mechanisms of disease; genetic defects are detected only in a minority of patients, but further study is needed. Genes expressed differentially in patients with ICP have been further explored. Challenges remain in differentiating liver disease related to pregnancy from other acute liver diseases. Early delivery and advances in supportive management are the only available options for improving the prognosis in liver diseases associated with preeclampsia, which includes liver dysfunction related to preeclampsia, HELLP, and AFLP.
REFERENCES


