A Systematic Approach to Pregnancy-Specific Liver Disorders

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Abstract: Consultation for liver disease during pregnancy is challenging for both the hepatologist and gynecologist, as normal physiologic changes during pregnancy can mimic chronic liver disease. Pregnancy-specific liver disorders are leading causes of abnormal liver function tests during pregnancy. Moreover, up to 3% of all pregnant women in developed countries experience liver diseases nonspecific to pregnancy. When severe, pregnancy-specific liver disorders are associated with significant morbidity and mortality for both the mother and the fetus. The main factors that determine maternal prognosis are the type of liver disease; degree of impaired synthetic, metabolic, and excretory liver function; and timing of delivery. This article focuses on a systematic approach to diagnosing and managing pregnancy-specific liver disorders, which includes understanding normal findings in pregnancy, excluding liver diseases nonspecific to pregnancy, factoring in trimester status, and using clinical clues to make a diagnosis and provide treatment in a timely fashion.

Keywords
Liver disease, pregnancy, hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, preeclampsia, eclampsia, acute fatty liver of pregnancy

Liver disease affects 3% of all pregnancies and can lead to serious complications to the mother and the fetus.[1-4] Liver diseases during pregnancy can be divided into 2 main categories: those unique to pregnancy and those unrelated to pregnancy. Liver diseases unrelated to pregnancy affect the general population and include viral hepatitis, cirrhosis and portal hypertension, autoimmune liver diseases, Wilson disease, and nonalcoholic fatty liver disease, which is associated with gestational diabetes. Pregnancy-unrelated liver disorders can occur at any time during pregnancy and should be in the differential diagnosis when working up abnormal liver tests during pregnancy. Pregnancy-specific liver disorders include hyperemesis gravidarum (HG); intrahepatic cholestasis of pregnancy (IHCP); preeclampsia (PE)/eclampsia; hemolysis, elevated liver tests, and low platelets (HELLP) syndrome; and acute fatty liver of pregnancy (AFLP) (Figure 1). Before considering the diagnosis of pregnancy-specific liver disorders, liver disorders that are not related to

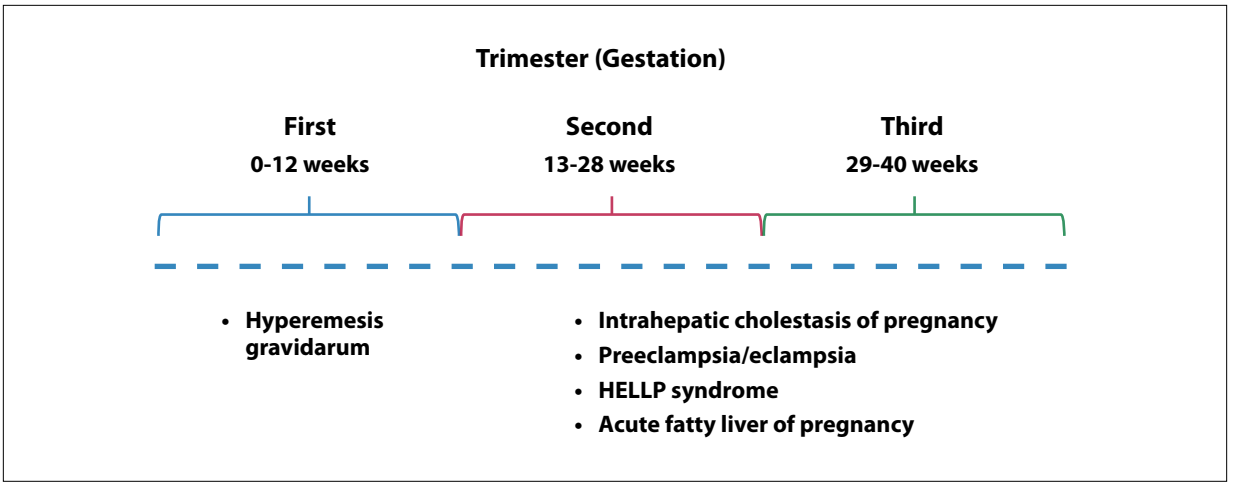

Figure 1. Timeline of pregnancy-specific liver disorders.
HELLP, hemolysis, elevated liver tests, and low platelets.

pregnancy must be excluded. The aim of this article is to provide a systematic approach to pregnancy-specific liver disorders.

Physiologic Changes During Pregnancy

Pregnancy is associated with physiologic changes that can mimic chronic liver disease, thus making a diagnosis of liver disease in pregnancy challenging. It is common to see maternal tachycardia, increased cardiac output, and a fall in blood pressure during pregnancy.[5] Plasma volume expansion is also common.[6] Because of the elevated levels of estrogen during pregnancy, physical findings may include telangiectasias, spider angiomas, and palmar erythema, all of which can be seen in chronic liver disease.[7,8]

Owing to plasma volume expansion and hemodilution, there is a moderate decrease in hematocrit and albumin during pregnancy; hence, anemia and hypoalbuminemia are common laboratory findings.[9,10] Although alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and prothrombin time are unchanged in pregnancy, alkaline phosphatase (ALP) and alpha-fetoprotein are usually elevated owing to placental and fetal yolk sac production, respectively (Table 1).[11-13]

Approach to Abnormal Liver Tests in Pregnancy

The initial steps for assessing the cause of abnormal liver tests in a pregnant patient should be the same as when approaching a nonpregnant patient. Evaluation should start with history and physical examination, review of potential problematic medications, and relevant serologic workup depending on history and physical examination findings.[14] Before initiating a workup, clinicians should be familiar with the normal biochemical changes seen in pregnancy (Table 1). In addition, the source of elevated ALP should be confirmed by obtaining ALP isoenzyme and gamma-glutamyl transferase if the total ALP is elevated.[15,16] Because serum albumin levels are low during pregnancy, liver function can be assessed by measuring international normalized ratio (INR).[17] Although most pregnant patients are screened for hepatitis B and hepatitis C, it is prudent to assess all patients for viral hepatitis and initiate appropriate management.[18-20]

Table 1. Changes in Liver-Associated Tests During Pregnancy[11-13]

Laboratory Test	Change From Prepregnancy State
White cell count	No change
Hemoglobin	Decreased
Platelets	No change
Aminotransferase[a]	No change
Total bilirubin	No change
Alkaline phosphatase	Elevated
Gamma-glutamyl transferase	No change
Albumin	Decreased
International normalized ratio	No change
Alpha-fetoprotein	Elevated

[a]Alanine aminotransferase and/or aspartate aminotransferase.

In general, serologic workup for abnormal liver tests should include hepatitis A antibody immunoglobulin M (IgM), hepatitis B surface antigen, hepatitis B core antibodies IgM and immunoglobulin G (IgG), hepatitis C antibody, antinuclear antibody, antismooth muscle antibody, total serum IgG, serum ferritin, transferrin saturation percentage, alpha-1-antitrypsin, and ceruloplasmin. Hepatitis E IgM and IgG should be obtained in select cases in which the etiology of hepatitis remains unclear. Antimitochondrial antibody and ultrasound imaging should be ordered in patients with elevated ALP from a hepatic source to assess for primary biliary cholangitis and biliary obstruction, respectively.[14] More formal studies for primary sclerosing cholangitis may be needed after delivery.

Imaging

Depending on the clinical scenario, imaging of the hepatic parenchyma, biliary system, or hepatic vasculature may be needed in the systematic approach to liver disorders in pregnancy. Ultrasonography with or without Doppler uses sound waves, not radiation; therefore, it is safe for mother and child[21] and is recommended as the first-line imaging modality for assessing abnormal liver tests.[12] Magnetic resonance imaging (MRI) without contrast does not use ionizing radiation and is also considered safe in pregnancy.[22] Gadolinium, the contrast most commonly used for MRI, crosses the placenta and has been shown to cause fetal morbidity; hence, it should be avoided during pregnancy.[22,23] Large doses of ionizing radiation have been linked to teratogenicity (eg, growth restriction, microcephaly, severe intellectual disability), with the greatest risk of exposure at 8 to 15 weeks of gestation.[24] The risk of fetal abnormality is considered negligible at 5 rads or less.[25] Most computed tomography (CT) scans use 1.3 to 3.5 rads (less than 5 rads) of ionizing radiation; therefore, CT is not associated with fetal harm. Although CT is safe in pregnancy, the American College of Obstetricians and Gynecologists recommends that, if accessible in a timely manner, MRI is a safer alternative to CT in cases where the 2 modalities are equivalent for the diagnosis in question.[22] Although liver biopsy is usually not required for the diagnosis of pregnancy-specific liver disorders, it may be performed in select cases in which the cause of the injury is unknown and there is progressive liver disease.

Pregnancy-Specific Liver Disorders

Pregnancy-specific liver disorders include HG, IHCP, PE/eclampsia, HELLP syndrome, and AFLP (Figure 1). The pattern of liver test abnormality in each of these diseases is summarized in Table 2.[26-29] Given the variability of ALP levels during pregnancy, they should not be used in the diagnosis of any pregnancy-specific liver disorders.

Table 2. Degree of Liver-Associated Test Abnormalities With Pregnancy-Related Liver Disorders[26-29]

Condition	Aminotransferase[a]	Total Bilirubin
Hyperemesis gravidarum	1-3×[b]	<4 mg/dL
Intrahepatic cholestasis of pregnancy	1-5×[b]	<5 mg/dL
Preeclampsia/eclampsia	≥2×	<5 mg/dL
HELLP syndrome	≥2×	<5 mg/dL
Acute fatty liver of pregnancy	5-10×	<10 mg/dL

[a]Alanine aminotransferase and/or aspartate aminotransferase.
[b]Can be up to 1000 IU/L.
HELLP, hemolysis, elevated liver tests, and low platelets.

Hyperemesis Gravidarum

The hallmark symptoms of HG are severe nausea and vomiting, resulting in dehydration, ketoacidosis, and loss of 5% or more of prepregnancy body weight. HG occurs in 0.3% to 2.0% of pregnancies and usually arises early in the first trimester with symptoms usually abating by 20 weeks of gestation.[30] The severe nausea and vomiting associated with HG can be quantified using the Pregnancy-Unique Quantification of Emesis Score, which includes questions on the number of daily episodes of vomiting, retching, and the length of nausea episodes. Patients with HG usually have a score of at least 13, which denotes severe symptoms.[31,32]

Mild elevations in ALT and AST (1-3 times the upper limit of normal) are seen in up to 50% of cases until 16 weeks of pregnancy, although higher levels have been reported (Table 2).[26,27] HG should be suspected when a pregnant patient presents with abnormal liver tests in conjunction with severe nausea and vomiting (Figure 2). Because HG is a diagnosis of exclusion, other causes of elevated liver tests, such as viral hepatitis, autoimmune diseases, biliary disease, pancreatic disease, urinary tract infection, and gastrointestinal infections, should be excluded before making the diagnosis.[33] Abdominal pain is rare in HG, and its presence should indicate another diagnosis.

Risk factors for HG include multiple or molar pregnancies, increased body mass index, history of diabetes or thyroid disease, and previous pregnancy with HG.[27]

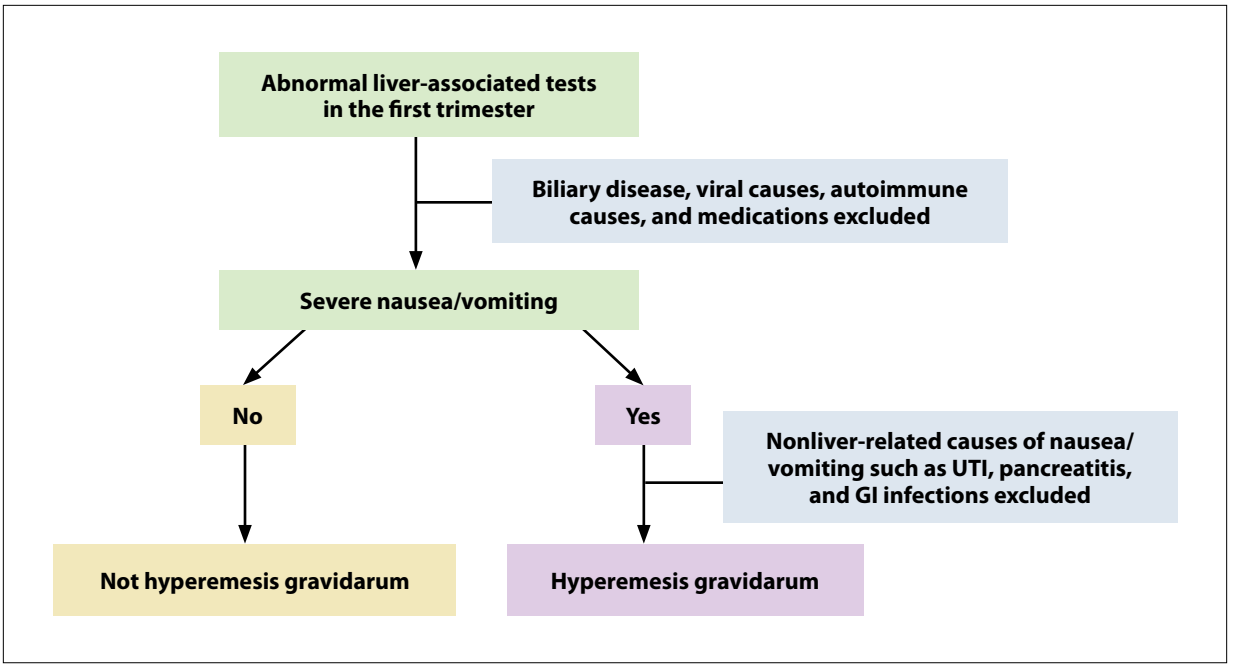

Figure 2. Evaluation of a patient suspected of having hyperemesis gravidarum.

GI, gastrointestinal; UTI, urinary tract infection.

Complications from HG are related to excessive vomiting and decreased oral intake, and include electrolyte imbalance and dehydration resulting in kidney injury and ketonuria. Thiamine deficiency occurs rarely with prolonged duration of vomiting and results in Wernicke encephalopathy.[34]

Treatment for HG is supportive, focusing on hydration, electrolyte repletion, and controlling symptoms.[35] Owing to the potential concern for thiamine deficiency, dextrose-containing solutions should be avoided.[34] Intravenous infusion of sodium chloride 0.9% is the preferred solution for hydration.[33] Antiemetic therapy is the cornerstone treatment for HG. HG is usually not associated with any major adverse maternal or fetal outcomes.[25-27]

Intrahepatic Cholestasis of Pregnancy

IHCP is typically seen in the second or third trimester and should be suspected when a pregnant patient has intense pruritus (mainly on the palms and soles) and abnormal liver tests in a cholestatic pattern (greater increase from normal values of ALP when compared with ALT) (Figure 3).[36] IHCP is the most common pregnancy-specific liver disorder and second only to viral hepatitis as the most common cause of jaundice in pregnancy.[37] The incidence of IHCP is 0.2% to 2.0%, but varies widely with ethnicity and geographic location, with Northern Europe and South America being the most common sites. Some studies have estimated the incidence of IHCP in Chile to

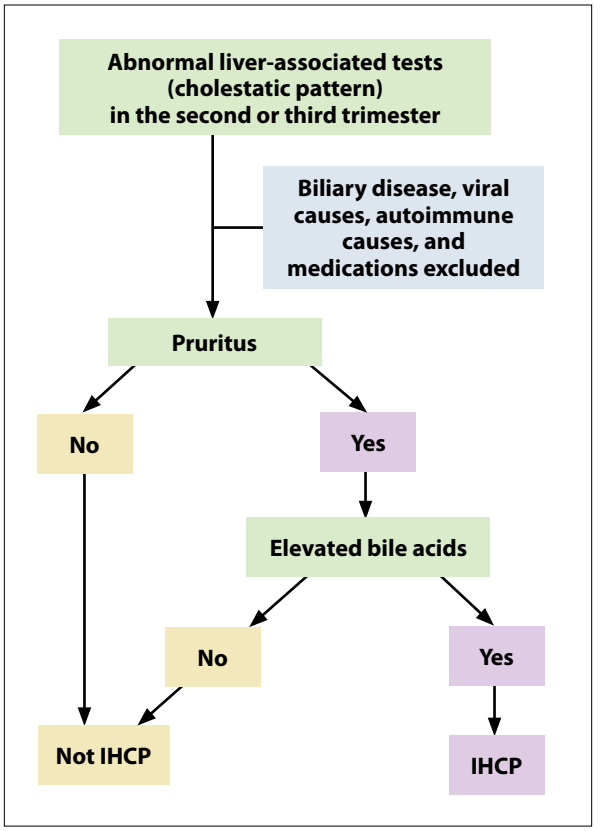

Figure 3. Evaluation of a patient suspected of having intrahepatic cholestasis of pregnancy (IHCP).

be as high as 4%.[38-40] The pruritus tends to worsen with progression of pregnancy, but symptoms usually resolve within 48 hours of delivery.[41] Jaundice can occur; however, it is less common than pruritus, usually affecting less than 25% of patients.[27,42] Like pruritus, jaundice usually improves after delivery, and alternative etiologies should be pursued if the cholestasis fails to resolve after delivery.

After excluding viral hepatitis, autoimmune disease, and biliary disease, the diagnosis of IHCP is made when pruritus is present and the fasting bile acid concentration is elevated (typically >10 µmol/L). Importantly, other causes of liver disease do not typically raise bile acid levels. In IHCP, aminotransferase levels may also be elevated (1-5 times the upper limit of normal), with total bilirubin levels usually less than 5 mg/dL.[27,43] Risk factors for IHCP include prior history of cholestasis secondary to oral contraceptive use, prior pregnancy complicated by IHCP, or a family history of IHCP.[11]

First-line treatment for IHCP is initiation of ursodeoxycholic acid (UDCA) at 10 to 15 mg/kg maternal body weight. UDCA relieves pruritus, improves liver tests, and is safe and well tolerated by the mother and fetus.[44,45] Maternal outcomes in IHCP are favorable; however, elevated bile acid levels are associated with unfavorable fetal outcomes such as preterm labor, prematurity, and perinatal death.[46] Fetal distress correlates with rising bile acid concentrations and is more prevalent when bile acid levels exceed 40 µmol/L.[47,48] Levels greater than 100 µmol/L are associated with stillbirth.[49] Given the increased risk of fetal distress and negative outcomes, early delivery at 37 weeks is recommended, as intrauterine death is more common the last few weeks of pregnancy.[12]

Preeclampsia and Eclampsia

The hallmark findings of PE include a systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg and proteinuria (≥300 mg/24-hr urine specimen) occurring after 20 weeks of gestation in a previously normotensive woman.[50] PE affects 5% to 8% of all pregnancies and is associated with renal insufficiency and liver injury.[51] Eclampsia is considered when a pregnant woman with PE develops generalized tonic-clonic seizures or coma with no other explanation.

PE is a serious condition and is the leading cause of maternal death, severe maternal morbidity, maternal intensive care admissions, cesarean section, and prematurity.[52] Clinical features include right upper quadrant pain, headache, nausea, and vomiting. Abnormalities in liver tests can occur and are because of vasoconstriction leading to reduced hepatic blood flow and eventual ischemia.

Abnormal liver tests in the second or third trimester along with hypertension and proteinuria are highly suggestive of PE (Figure 4). Aminotransferase levels are abnormal in 20% to 30% of cases (≥2 times the upper limit of normal) (Table 2).[11] Conjugated bilirubin, albumin, and INR values are usually normal.

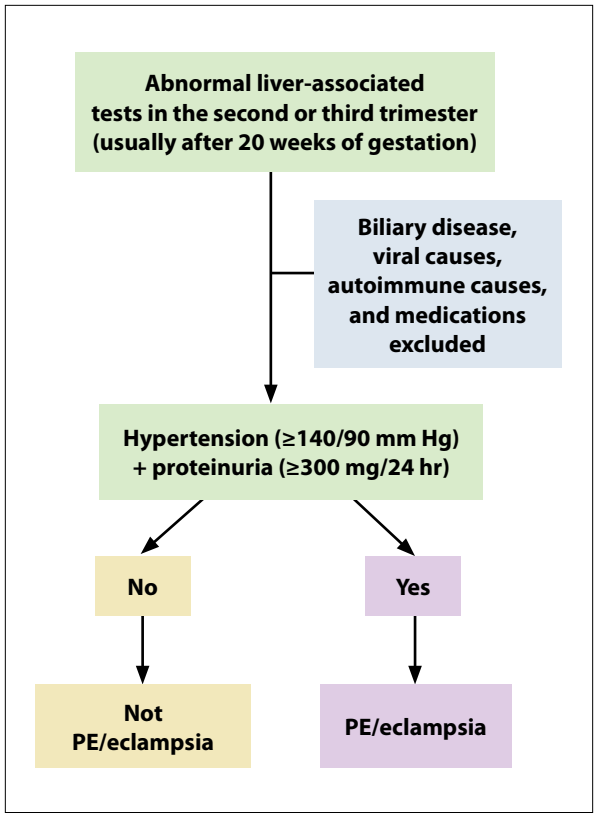

Figure 4. Evaluation of a patient suspected of having preeclampsia (PE). Eclampsia is defined as the occurrence of generalized tonic-clonic seizures or coma in a woman with PE.

Maternal and fetal morbidity are associated with elevated liver function tests. Obstetric complications from PE include placental abruption, preterm delivery, intrauterine growth restriction, and fetal demise.[27] Liver disease in PE does not require specific treatment, and the cornerstone of therapy is blood pressure control and prompt treatment of seizures, if present. An expectant approach is advised up to 34 weeks of gestation to limit fetal morbidity.[53] Delivery is recommended at 36 to 37 weeks; however, if there is fetal or maternal worsening, delivery should be considered at 24 to 34 weeks.[27]

Hemolysis, Elevated Liver Tests, and Low Platelets Syndrome

HELLP syndrome affects 0.5% to 0.9% of pregnancies.[54] Similar to PE, HELLP syndrome typically arises in the second or third trimester, usually between 28 and 36 weeks of gestation; however, there have been reports of HELLP syndrome in the postpartum setting.[55] It is debatable if HELLP syndrome is a complication of severe PE

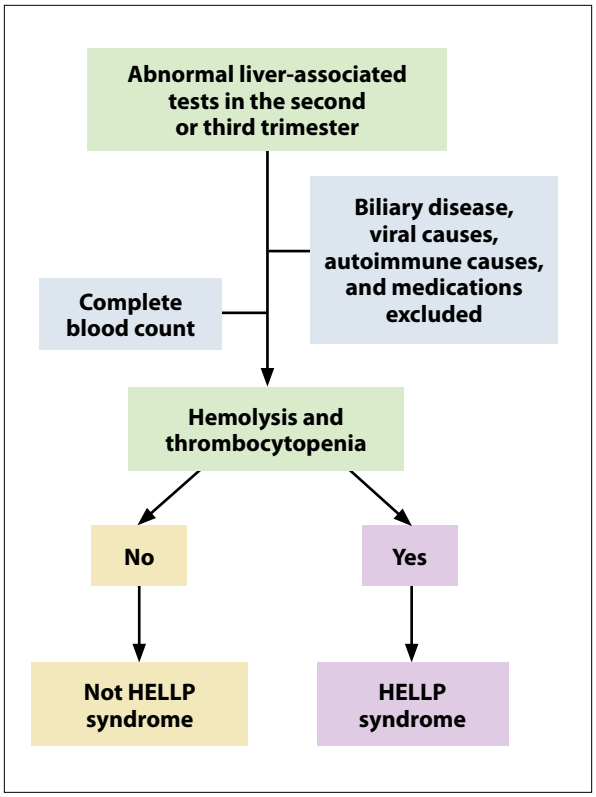

Figure 5. Evaluation of a patient suspected of having hemolysis, elevated liver tests, and low platelets (HELLP) syndrome.

or a separate disorder. It has been reported that as many as 15% to 20% of patients with HELLP syndrome do not have hypertension or proteinuria, suggesting that it is a unique disorder of pregnancy.[56-58] Conversely, it has also been reported that 10% of women who have severe PE develop HELLP syndrome, suggesting that it is a complication of PE.[59]

Although there are no pathognomonic clinical signs in a patient with HELLP syndrome, typical presentation includes signs of hemolytic anemia and thrombocytopenia, with platelets usually less than 100,000 cells/mL and elevated AST and ALT (≥2 times the upper limit of normal), as well as elevated unconjugated bilirubin and lactate dehydrogenase as a result of hemolysis (Table 2).[60] Similar to PE, common symptoms include malaise, headache, nausea, vomiting, and right upper quadrant pain. Hypertension and proteinuria are found in 80% of patients.

HELLP syndrome should be part of the differential diagnosis when assessing a pregnant patient with abnormal liver tests in the second or third trimester. After excluding biliary pathology and viral and autoimmune etiologies, a diagnosis of HELLP syndrome should be strongly considered if hemolysis and thrombocytopenia are present, especially if the patient has a history of PE (Figure 5).

Maternal complications that are associated with HELLP syndrome, such as hepatic infarction (especially when liver tests are in the thousands accompanied by severe abdominal pain), subcapsular hematoma, hepatic rupture and hemorrhage, abruptio placentae, and disseminated intravascular coagulation, can be severe. The maternal mortality rate is 1% to 5%.[28,61,62] Patients with HELLP syndrome and severe elevations in AST and ALT (>1000 IU/L) or severe abdominal pain should undergo cross-sectional imaging to assess for hepatic complications.[63,64] Most contained hematomas can be monitored and treated with supportive care; however, surgery is indicated for enlarging hematomas, rupture, or hemodynamic instability.[12]

Although progression can be rapid, symptoms and laboratory values normalize within 48 hours of delivery.[55] Fetal complications include prematurity and intrauterine growth restriction, and the fetal mortality rate can be as high as 30% to 40%.[65] The therapeutic protocol for HELLP syndrome includes the use of glucocorticoids to accelerate pulmonary maturity in pregnancies less than 34 weeks, magnesium sulfate to prevent maternal seizures and for fetal/neonatal neuroprotection, and administration of antihypertensives to control severe hypertension and headaches.[66] Delivery is recommended after 34 weeks if the pregnant patient and the fetus are stable; if unstable, emergency delivery is warranted.[67]

Acute Fatty Liver of Pregnancy

AFLP is associated with elevated liver tests and occurs in the third trimester of pregnancy, typically between 30 to 38 weeks of gestation.[2] AFLP is rare, affecting 1 in 7000 to 1 in 15,000 pregnancies.[29,68] The presenting symptoms include but are not limited to nausea, vomiting, and abdominal pain. Laboratory findings include elevated aminotransferases (5-10 times the upper limit of normal), elevated total bilirubin (usually not greater than 10 mg/dL), hypoglycemia, uremia, leukocytosis, elevated creatinine, and coagulopathy (Table 2).[29,69] Although a liver biopsy is not required to make a diagnosis, if it is performed, the biopsy will show microvesicular steatosis. Deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) enzyme in the fetus is linked to fatty oxidation defects that may predispose the mother to AFLP.[70,71] LCHAD deficiency in the fetus leads to accumulation of fatty acid metabolites, which enter maternal circulation and are hepatotoxic. Most women do not have LCHAD abnormalities.

If the patient meets at least 6 of the 14 criteria listed in the Swansea criteria (Table 3), a diagnosis of AFLP can be made. Owing to the high risk of morbidity and mortality for both mother and fetus, management includes prompt delivery of the fetus regardless of gestational age

Table 3. Swansea Criteria for Acute Fatty Liver of Pregnancy Diagnosis[67]

Symptoms
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Laboratory Tests
Elevated bilirubin (>0.82 mg/dL)
Hypoglycemia (<72 mg/dL)
Elevated uric acid (>5.7 mg/dL)
Leukocytosis (>11 × 10^9/L)
High AST or ALT (>42 IU/L)
High ammonia (>66 µmol)
Renal impairment (Cr >1.7 mg/dL)
Coagulopathy (PT >14 s or aPTT >34 s)
Imaging
Ascites or bright liver on ultrasound
Histology
Microvesicular steatosis on liver biopsy

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; Cr, creatinine; PT, prothrombin time.

and supportive treatment for the mother.[29] After delivery, most patients recover spontaneously; however, treatment of coagulopathy and other complications may continue for days or weeks after delivery.[27] Nonetheless, the mother should be closely monitored for multiorgan failure in addition to liver failure requiring liver transplant.[72] Given the association between LCHAD deficiency in the fetus and AFLP in the mother, it is recommended that the newborn be monitored for complications such as hypoglycemia and fatty liver. Although not absolute, it is recommended that both mother and newborn undergo molecular testing for LCHAD deficiency postdelivery.[12] In all circumstances, liver tests should be monitored for normalization postdelivery.

Conclusion

Clinical management of the pregnant patient is challenging because of overlapping findings seen in the pregnant vs nonpregnant patient. When evaluating a pregnant patient for liver disease, clinicians must first exclude liver disease unrelated to pregnancy such as biliary disease, viral hepatitis, and autoimmune disease. Second, clinicians should take into account trimester status and pay special attention to clinical clues such as severe vomiting, nocturnal pruritus, hypertension, proteinuria, and the presence of hemolysis and thrombocytopenia, all of which can help guide the correct diagnosis and provide the appropriate care for both mother and child.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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