Interpretation and Management of Hepatic Abnormalities in Pregnancy

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The spectrum of liver disease in pregnancy includes liver disease unrelated to pregnancy, liver diseases that occur with increased frequency or severity in pregnancy, and liver disease specific to pregnancy. Diseases of the liver unique to pregnancy reliably occur at specific points in the gestational spectrum. Thus, gestational age, a comprehensive history, and a clinically driven diagnostic evaluation is critical in approaching a pregnant patient with abnormal liver chemistries or function. Early recognition of these conditions is important and although management may be expectant, some patients require targeted therapy or necessitate prompt delivery, which can be life-saving to both mother and child.

Keywords: Acute Fatty Liver of Pregnancy; HELLP Syndrome; Intrahepatic Cholestasis of Pregnancy.

Liver disease in pregnancy encompasses a wide range of disorders, ranging from abnormalities in liver chemistries to life-threatening problems that warrant urgent intervention. Hepatic laboratory abnormalities are seen in approximately 3% to 5% of pregnancies. The ability to discern benign etiologies from potentially life-threatening conditions is critical when determining appropriate evaluation and management. This is especially true in the management of incidental abnormalities found on routine screening of asymptomatic patients. Liver abnormalities in a pregnant patient can be divided into 4 categories: (1) physiologic changes in the liver during normal pregnancy; (2) newly acquired liver disease not specific to, but more prevalent in, pregnancy; (3) liver disease that is unique to pregnancy; and (4) pregnancy occurring in a patient with preexisting liver disease (which is not covered by this review). The management of cirrhosis, portal hypertension, and liver transplantation during pregnancy recently was reviewed elsewhere.[1]

The goal of this review is to provide a practical guide to evaluation and management of the pregnant patient with abnormal liver chemistries or function.

Physiologic Changes in Pregnancy

In pregnancy, the liver is affected primarily by circulatory and hormonal changes. Pregnancy is associated with a hyperdynamic circulation in which cardiac output increases in the second trimester and plateaus in the third trimester, with a 40% increase in circulating blood volume. Blood flow to the liver remains unchanged, but the percentage of cardiac output to the liver is reduced, which may impair clearance of substances requiring extensive hepatic metabolism.[2,3] Although pregnancy-related changes in sex hormones have direct effects on biliary smooth muscle contractility and modulate biliary transporters, these changes do not produce symptoms in normal pregnancy.[4] In some cases, hormone-induced changes in biliary transport and metabolism can lead to symptomatic cholestasis. For the most part, abnormalities in liver chemistries in the context of normal pregnancy are limited to an increase of alkaline phosphatase level (placental origin) and a decrease in albumin level (as a result of hemodilution) and are not indicative of pathology unless markedly abnormal or accompanied by other hepatic abnormalities.

Newly Acquired Liver Disease, Not Specific to Pregnancy

Abnormal liver chemistries during pregnancy should prompt an evaluation for pregnancy-specific diseases (guided by gestational period) and also should involve the exclusion of liver disorders not specific to pregnancy, as well as those that might be more prevalent in pregnancy or associated with worse outcomes. A complete history and physical, and serologic evaluation guided by the nature of abnormalities (as in a nonpregnant patient) should be performed. Hepatic ultrasound with Doppler flow should be part of the initial evaluation to exclude a biliary process or a vascular obstruction. Although not common, the development of acute hepatic or portal vein thrombosis should be considered. Management of newly diagnosed/acquired liver disease requires special considerations in pregnant women, particularly in those with viral hepatitis and gallstone disease.

Viral Hepatitis

Viral hepatitis acquired during pregnancy can increase both maternal and fetal morbidity and mortality in the acute phase.

Hepatitis A infection typically is acute and self-limited, and its management is supportive. Infection acquired in the second and third trimesters can be associated with premature contractions, placental separation, premature rupture of membranes, fetal distress, and preterm labor.[5] In rare cases, fulminant hepatitis may develop, and has been linked to poor nutritional state, advanced maternal age, or co-existent hepatitis B infection. Vaccination is recommended for all women traveling to endemic areas, and appears to be safe in pregnancy. Vertical transmission

Abbreviations used in this paper: AFLOP, acute fatty liver of pregnancy; HCV, hepatitis C virus; HELLP, syndrome of hemolysis, increased liver enzymes, and low platelets; HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; SBA, serum bile acid; UDCA, ursodeoxycholic acid.

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to the fetus is rare, but horizontal transmission in a woman caring for her newborn is possible.

Hepatitis B infection acquired during pregnancy does not differ significantly from the nonpregnant patient, and treatment mainly is supportive, except in the rare case of fulminant hepatitis, in which lamivudine and tenofovir may be used to decrease viral load before liver transplantation or decrease the risk of fetal infection. Vertical transmission of hepatitis B is a matter of significant concern because most affected infants become chronic carriers. Ninety-five percent of transmission occurs in the third trimester near the time of birth, or in the immediate postpartum period. The risk of transmission is increased if the patient develops acute hepatitis B virus in the third trimester. Mothers who have hepatitis B e antigen positivity and high viral load ($>10^6$ copies/mL) are also at increased risk of vertical transmission.[6,7] Details relating to prophylaxis, prevention, and management of vertical transmission are outside the scope of this review, but were outlined nicely in a recent review by Pan et al.[8]

Hepatitis C virus (HCV) infection typically is diagnosed in a chronic state; however, cases of acute hepatitis C increasingly are reported. A few case reports have described successful management of acute hepatitis C in pregnancy, with early delivery or incomplete interferon therapy, with favorable outcomes for the mother and fetus.[9,10] Viral replication appears to increase despite lower serum aminotransferase levels seen in pregnancy, but they return to pre-pregnancy levels postpartum.[11] Treatment is contraindicated during pregnancy given the teratogenicity of current treatments, which include ribavirin. New HCV treatments with boceprevir and telaprevir have not been studied in pregnancy, but they are both Food and Drug Administration category B and warrant further study. Vertical transmission plays a small role in the transmission of HCV. Data from a large study showed a 5.1% rate of HCV RNA viremia at 1 year in newborns of HCV-positive mothers.[12] Factors associated with an increased risk of transmission include high maternal viremia, maternal peripheral blood mononuclear infection by HCV, premature rupture of membranes (>6 h), and procedures associated with exposure of the infant to maternal blood.

Hepatitis E infection conveys an acute risk to both the mother and fetus, with a 20% mortality rate if acquired in the third trimester in the setting of acute hepatitis. For the fetus, there is a higher rate of spontaneous abortion and intrauterine death.[13] In contrast to hepatitis A, vertical transmission has been documented in women with acute hepatitis E, with poor fetal outcomes. It is endemic in underdeveloped areas with poor sanitation, with the highest prevalence rates in the Indian subcontinent, China, Asia, Africa, and the Middle East.[14] However, prevalence in the United States has been increasing, particularly in southern states. Management is supportive.

Biliary Disease

The onset of biliary disease during pregnancy is common, given hormonal changes and their effect on biliary smooth muscle and bile transporters. Higher estrogen levels also promote gallstone formation through cholesterol supersaturation of bile. In the presence of acute abdominal pain, a cholestatic liver chemistry profile (alkaline phosphatase, γ-glutamyltransferase, and bilirubin) should raise suspicion for gallstone-related biliary obstruction. The simplest initial test should be a transabdominal ultrasound to evaluate for the presence of cholelithiasis and biliary ductal dilatation, although the sensitivity for choledocholithiasis is only 50%.[15] Abdominal imaging with magnetic resonance cholangiopancreatography can be helpful in the evaluation of the biliary tree in this setting. It is performed without gadolinium and is considered safe after the first trimester. In equivocal cases, endoscopic ultrasound can be considered, but requires sedation. Management of choledocholithiasis and its complications may require endoscopic retrograde cholangiopancreatography, which will expose the fetus to radiation, but may lead to increased morbidity if untreated.

Pregnancy-Related Liver Disease

Liver diseases unique to pregnancy have some overlap but generally have distinguishing features. One such feature is the time in which they occur along the gestational spectrum (Figure 1).

Early Pregnancy

Hyperemesis gravidarum. Although nausea and vomiting are common in pregnancy, hyperemesis gravidarum (HG) is characterized by intractable nausea and vomiting, frequently requiring hospitalization. It occurs, by definition, in the first trimester, in 0.3% to 2.0% of pregnancies. Symptoms are typically severe enough to result in weight loss, dehydration, ketonuria, and electrolyte imbalances.[16] In 10% of women, symptoms persist throughout pregnancy and resolve only with delivery of the fetus.[17,18] HG is more common in the setting of molar pregnancy, twin pregnancies, pre-existing diabetes or hypothyroidism, and psychiatric disorders.[19] The diagnosis of HG is clinical and is accompanied by abnormalities in liver chemistries in up to 50% of cases. A hepatocellular injury pattern is typical, with increases in alanine aminotransferase and aspartate aminotransferase levels ranging from mild to as high as 10 times the upper limit of normal.[20] Jaundice is rare and when present may suggest underlying liver or biliary tract disease.[21] HG is a diagnosis of exclusion; thus, a careful evaluation for pre-existing liver disease or other gastrointestinal illness is essential.

Management. Treatment is supportive, and includes correction of dehydration and electrolyte abnormalities. Thiamine supplementation is recommended to prevent Wernicke encephalopathy. Although the role of corticosteroids is not well established, it may be useful in refractory cases.[22] Successful treatment of HG leads to correction of abnormal liver chemistries without lasting liver complications (Table 1).

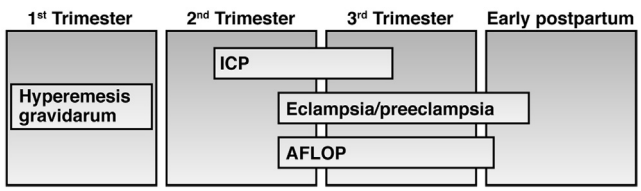

Figure 1. The presentation and duration of pregnancy-related liver disease according to gestational period.

Table 1. Basic Management of Pregnancy-Related Liver Disease

Predominant injury pattern	Considerations	Pregnancy-related liver disease		
Hepatocellular	Exclude viral, NAFLD, AIH, Wilsons, drugs, and so forth	**HG** Hydration Thiamine	**AFLOP** Urgent delivery Screen newborn	**Preeclampsia/eclampsia** IV magnesium Control blood pressure Correct coagulopathy, if present Urgent delivery
Mixed Cholestatic	Liver ultrasound Exclude PBC, PSC if compatible, drugs	**ICP** SBA>40 μm UDCA Delivery at 38 wk		

AIH, autoimmune hepatitis; IV, intravenous; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Mid- to Late Pregnancy

Intrahepatic cholestasis of pregnancy. Intrahepatic cholestasis of pregnancy (ICP) is characterized by generalized pruritus and biochemical evidence of cholestasis that typically affects women during the last trimester of pregnancy, although it also can present in the late second trimester. Although rare, it is the most common pregnancy-related liver disorder, with a prevalence of 1 in 1000 to 1 in 10,000.[23] Geographically, it appears to be more common in South America, particularly in Chile (14%), with the native Araucanian population (24%) overrepresented. Some of these cases have been associated with deficient dietary selenium.[24,25] A higher incidence also has been reported in Scandinavia (1%–2%), particularly in the winter months.[26–28] In North America, the incidence is less than 1%. Risk factors for developing ICP include multiparity, advancing maternal age, twin pregnancies, and a history of cholestasis secondary to oral contraceptive use. The condition recurs in 60% to 70% of subsequent pregnancies, suggesting a genetic predisposition with incomplete penetrance.

The etiology of ICP is not well described, but likely includes genetic, hormonal, and exogenous factors. Evidence for a strong genetic component is supported by familial clustering, increased prevalence in specific ethnic groups, a higher incidence level in twin pregnancies, and an increased risk in siblings of women affected with ICP.[29] The majority of genetic variation in ICP has been identified in the biliary transporters ATP-Binding Cassette B (ABCB) 4 and ABCB11, with various mutations conferring increased susceptibility to ICP.[30–32] Recent studies also have shown decreased expression of bile acid transporters in the placenta, mainly Organic Anion-transporting Polypeptide (OATP) 1A2 and OATP1B3, in women with ICP.[33] Along with genetic factors, ICP appears to have a strong hormonal association. Symptom severity is highest during the third trimester, when reproductive hormone concentrations are the highest.[29] Pruritus also has been described in women taking exogenous hormones and at particular points in the menstrual cycle, implying a further correlation between hormonal changes and pruritus.[34] Both estrogens (mainly estradiol-17β-D-glucuronide) and progesterone metabolites can promote cholestasis.[26,35] The latter seem to play a more important role, and studies have shown an increase in 3α, 5α isomers of these metabolites in patients with ICP, with a concurrent decrease in their biliary and fecal excretion.[23,36] Relationships between these metabolites and the farnesoid X receptor appear to mediate bile acid homeostasis pathways, as ongoing studies have shown.[29,37,38]

The development of ICP has little lasting consequence for the mother. Morbidity typically is limited to pruritus, which often begins in the palms and soles of the feet and resolves after delivery, with normalization of serum bile acid (SBA) levels. Some women may present with jaundice, malabsorption, and clinically significant gallstone disease.[34,39] In contrast, morbidity and mortality for the fetus is increased, particularly in women with SBA levels of 40 μm or greater.[28,40] Specifically, ICP increases the risk of preterm delivery (19%–60%), fetal distress (22%–41%), and fetal loss (0.4%–1.6%).[41–45] The incidence of fetal hypoxia, meconium-stained amniotic fluid, and intrauterine death also appears to be higher, and recent studies have shown that delivery at 38 weeks may improve perinatal outcomes.[40,43,46] Perinatal outcomes in patients with SBA levels less than 40 μm do not appear to be significantly worse; thus, these patients should be managed symptomatically, without induction of preterm labor.[28]

Management. The treatment of ICP has evolved over the years. Studies have examined the role of antihistamines, phenobarbital, benzodiazepines, cholestyramine, dexamethasone, S-adenosyl-L-methionine, and ursodeoxycholic acid (UDCA), with the latter showing the most robust data for symptom amelioration and prevention of adverse fetal outcomes.[17,47–51] In patients with SBA levels of 40 μm or greater, UDCA decreases the severity of pruritus, SBA levels, alanine aminotransferase, and bilirubin. Data on the impact on fetal complications are mixed. However, a more recent meta-analysis confirmed the safety and efficacy of UDCA in improving pruritus, liver chemistries, and fetal outcomes.[52] This improvement in pruritus may be related to a direct effect of UDCA on hormonal mechanisms impairing biliary transporter function.[53] Interestingly, treatment with UDCA also can improve morphologic placental abnormalities present in ICP.[54] Based on the current data, UDCA (10–15 mg/kg) is the preferred treatment for ICP, coupled with consideration of early delivery, particularly in patients with SBAs of 40 μm or greater (Table 1).

Toxemia of pregnancy. Toxemia of pregnancy encompasses preeclampsia, eclampsia, and the syndrome of hemolysis, increased liver enzymes, and low platelets (HELLP) (Figure 2). It represents a spectrum of hepatic abnormalities that can lead to fatal complications both for the mother and the fetus. Preeclampsia is present in 0.6% to 1.2% of pregnancies, of which 20% of severe cases go on to develop HELLP syndrome. Risk factors for the development of severe preeclampsia and HELLP include a history of diabetes, chronic hypertension, multiparity,

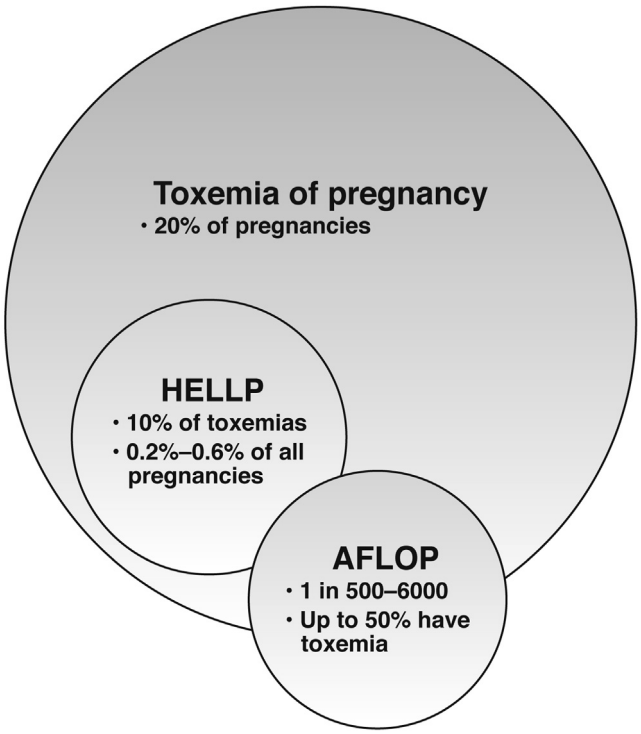

Figure 2. Toxemia of pregnancy and associated disease.

and older age.[55–57] There is a significant overlap between these disorders and hemolytic uremic syndrome, thrombotic thrombocytic purpura, and acute fatty liver of pregnancy (AFLOP), making them difficult to differentiate (Table 2).

Preeclampsia is defined by the development of hypertension (≥140/90 mm Hg) occurring at 20 weeks gestation or later, plus proteinuria (≥0.3 g/24 h). Severe preeclampsia is characterized by blood pressure of 160/90 mm Hg or greater and 5 g protein/24 h or greater, or by the presence of end-organ damage (oliguria, cerebral or visual problems, pulmonary edema, impaired liver function, thrombocytopenia, or fetal growth restriction).[57] In women with pre-existing hypertension, superimposed preeclampsia can be diagnosed when there are sudden changes in blood pressure and proteinuria, or new thrombocytopenia and increased aminotransferase levels develop. Seizures in the setting of any of the earlier-described findings defines eclampsia. Finally, the finding of hemolysis, along with thrombocytopenia and increased liver enzyme levels, suggests the development of HELLP syndrome, which carries the highest risk both for the mother and the fetus. Distinguishing between these 3 entities is important because management and prognostic implications differ.

The diagnosis of HELLP syndrome requires a high index of suspicion. The majority of patients endorse nonspecific fatigue and malaise before presentation, and 50% report epigastric or right upper-quadrant pain. The degree of jaundice usually is mild, and other clinical signs and symptoms may be absent. The main abnormalities noted on biochemical examination include varying degrees of thrombocytopenia and increased liver enzyme levels, increased lactate dehydrogenase as a result of hemolysis, and microangiopathic hemolytic anemia noted on peripheral smear examination. The damage caused by microangiopathic hemolytic anemia is thought to be caused by vascular endothelial injury, fibrin deposition in blood vessels, platelet activation, and consumption.[17] On histology, HELLP is characterized by periportal or focal parenchyma necrosis with hyaline deposition of fibrin material in the sinusoids; however, biopsies rarely are performed in this setting.[58] Sinusoidal obstruction likely explains the right upper-quadrant pain experienced by most patients. Of the several classification systems proposed for HELLP, the most widely used is the Mississippi classification, which stratifies severity based on platelet count and aminotransferase level increase. Generally, thrombocytopenia less than 100,000/mm^3, lactate dehydrogenase level greater than 600 U/L, and aminotransferase levels greater than 70 U/L are consistent with a diagnosis of HELLP.[59,60] Worsening thrombocytopenia is associated with poor outcomes.

Compared with severe preeclampsia or partial HELLP, women with HELLP require more blood transfusions, have a higher incidence of disseminated intravascular coagulation, acute renal failure, pulmonary edema, wound hematomas, intracerebral hemorrhage, subcapsular liver hematomas (including rupture), and death.[58] Complications decrease significantly with advanced gestational age as fetal risk diminishes, and some studies have shown this is irrespective of the diagnosis of HELLP versus severe preeclampsia.[61]

Management. Management of HELLP requires immediate hospitalization, often in an intensive care unit. Management of patients with preeclampsia includes institution of intravenous magnesium sulfate as prophylaxis against seizures, and antihypertensives to lower blood pressure to less than 160 mm Hg systolic. Fetal well-being should be assessed using standard methods and, finally, the timing of delivery should be established. Definitive management for HELLP is delivery of the fetus, which typically results in resolution of symptoms within 5 days, although complications still can present postpartum. The general approach is to deliver the fetus if the gestational age is older than 34 weeks. If younger than 34 weeks,

Table 2. Similarities and Differences Between Diseases Associated With Toxemia of Pregnancy and Other Syndromes

	HUS	TTP	Preeclampsia	Eclampsia	HELLP	AFLOP
Headache	✓	✓			✓	
Acute kidney injury	✓	✓				✓
Low platelets	✓	✓	✓	✓	✓	✓
Altered mental status		✓		✓		✓
Fever		✓				
Hypertension			✓	✓		
Seizure				✓		
Increased liver chemistries	✓	✓	✓	✓	✓	✓
Disseminated intravascular coagulopathy		✓				✓

HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytic purpura.

the administration of glucocorticoids followed by delivery in 48 hours is preferred. However, there is considerable debate regarding the timing of delivery and the utility of administering corticosteroids in cases of HELLP. Randomized controlled trials are needed to validate current practice.[62] Conservative therapy is not effective, although a recent case report using eculizumab, a targeted inhibitor of complement C5, prolonged pregnancy by 17 days without adverse events.[63] In most cases, both maternal and fetal complications are common without prompt delivery. In the setting of hemodynamic instability from the development of hepatic subcapsular hematoma and hemorrhagic shock, surgical exploration, percutaneous embolization of the hepatic artery, and liver transplantation all have been pursued with some success[64–66] (Table 1).

Acute fatty liver of pregnancy. AFLOP is a rare condition that affects 1 in 7000 to 20,000 pregnancies, almost exclusively in the third trimester.[67–69] It is more common in nulliparous women and in twin pregnancies. It is characterized by microvesicular fatty infiltration of the liver, and is associated with varying degrees of hepatic failure. It can be complicated by encephalopathy, thrombocytopenia, disseminated intravascular coagulopathy, and renal failure, potentially resulting in maternal and fetal death.[16] It never develops after delivery, although the clinical course can linger after delivery and can be difficult to distinguish from HELLP because 50% of patients with AFLOP have co-existing preeclampsia.

The pathophysiology of AFLOP is largely unknown, but many cases have been linked to fetal defects in mitochondrial fatty acid oxidation, specifically in defects in 2 key enzymes: the mitochondrial trifunctional protein and its α subunit, long-chain-3-hydroxyacyl-coenzyme A dehydrogenase.[70] The corresponding mutation that is associated most commonly with these defects is G1528C/E474Q. The exact mechanism by which deficiencies in these enzymes lead to clinical AFLOP is unknown. However, one hypothesis suggests that the accumulation of 3-hydroxyacyl metabolites produced by the fetus is toxic and can lead to disease in a predisposed mother.[71] Despite the association between long-chain-3-hydroxyacyl-coenzyme A dehydrogenase deficiency and AFLOP, only 20% of babies born to mothers with AFLOP have the mutation.

Women typically present in the third trimester with nausea, vomiting, and abdominal pain, in the setting of increased serum aminotransferase levels. Jaundice is not common, and signs of preeclampsia may be present. In cases of acute liver failure, encephalopathy and coagulopathy may be part of the initial clinical presentation. Although the mechanism is not clear, polyuria and polydipsia are noted in about 5% of cases and are almost pathognomonic for AFLOP once diabetes has been ruled out.[72] Although serum aminotransferase levels are increased, they are lower than what one sees in the setting of acute viral hepatitis. Hypoglycemia also may be noted, which is uncommon in other pregnancy-related liver diseases. Thrombocytopenia also is common, but this also can be seen in HELLP and preeclampsia, as noted previously. The diagnosis of AFLOP is based on clinical criteria, imaging suggestive of steatosis (although because it is microvesicular fat, it is not seen reliably on imaging), and liver biopsy showing microvesicular fatty change (Figure 3). The Swansea criteria have been proposed to screen for AFLOP without the need for liver biopsy. This algorithm has a high negative predictive value, but does not help to distinguish from other causes of liver disease in pregnancy, which somewhat limits its usefulness.[68,73,74] More recently, Vigil-de Gracia and Montufar-Rueda[75] proposed an "AFLOP-triad" including symptoms, laboratory findings, and complications suggestive of AFLOP that should trigger an evaluation to rule out AFLOP. Although liver biopsy is the gold standard, it carries risk and should be pursued only when the diagnosis is in question and/or urgent delivery is not optimal.

Management. AFLOP is an obstetric emergency that requires urgent delivery to prevent maternal and fetal complications. Signs of acute liver failure (coagulopathy, encephalopathy) require monitoring in an intensive care unit, with supportive care, which may include intracranial pressure monitoring in some centers. Delivery results in resolution of symptoms and hepatic recovery for the mother, but close monitoring is required for the child because of the risk of an associated fatty acid oxidation defect. Some investigators advocate screening newborns of mothers with AFLOP to assist with genetic counseling and nutritional therapy.[76] Thanks to advances in intensive care support, early detection of AFLOP, and improved principles of early delivery, maternal mortality has decreased from 90% to less than 10% over the past 30 years.[72,77] Fetal mortality previously was reported to be 50% but also has decreased substantially to levels similar to current maternal

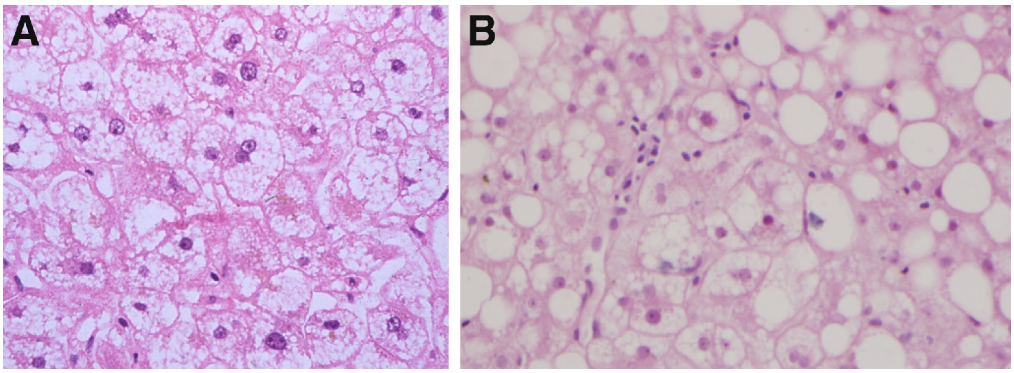

Figure 3. (*A*) Microvesicular hepatic steatosis as seen in AFLOP. (*B*) Macrovesicular hepatic steatosis with cellular ballooning, as seen in nonalcoholic steatohepatitis. Note that there may be some small droplet fatty change in the setting of nonalcoholic steatohepatitis, macrovesicular fat as shown in panel *B* should not be prominent in AFLOP. Also note that the nucleus is displaced laterally and compressed in macrovesicular steatosis, in contrast to microvesicular steatosis where it is centrally located. H&E, ×40.

outcomes. It is important to emphasize that maternal complications still may occur in the early postpartum period and patients should be monitored with these in mind (Table 1).

Conclusions

Liver disease in a pregnant patient can occur as a result of, or irrespective of, pregnancy. The presence of liver disease in a pregnant patient often is associated with increased morbidity for both the mother and the fetus. Diseases of the liver unique to pregnancy reliably occur at specific points in the gestational spectrum. Thus, gestational age, a comprehensive history, and a clinically driven evaluation can help narrow the differential diagnosis and guide management. Early recognition of these conditions is essential to optimize maternal and fetal outcome.

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Conflicts of interest

The authors disclose no conflicts.