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).

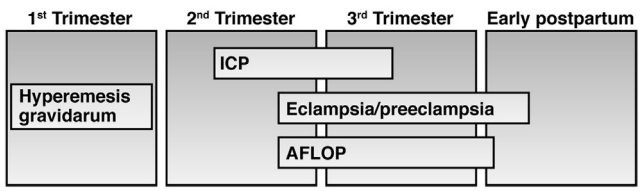

Figure 1. The presentation and duration of pregnancy-related liver disease according to gestational period.