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The liver in pregnancy: Disease vs benign changes

ABSTRACT

Liver dysfunction in a pregnant woman may be caused by the pregnancy, it may be unrelated to the pregnancy, or it may be a chronic condition that existed before the pregnancy. In any case, the clinical clues of liver dysfunction in pregnancy are not specific, and certain "abnormalities" in liver function tests may represent benign changes of pregnancy. On the other hand, prompt recognition of the signs of liver disease in pregnant patients leads to timely management and may save the life of both mother and baby.

KEY POINTS

Palmar erythema, spider angiomas, low serum albumin levels, and high serum alkaline phosphatase levels are usually signs of benign changes in the liver during pregnancy. High levels of serum liver aminotransferase or bilirubin signal a problem.

Acute viral hepatitis is the most common cause of jaundice in pregnant women but rarely affects the outcome of pregnancy.

The US Centers for Disease Control and Prevention recommends screening all pregnant women for hepatitis B viral infection, since the risk of transmitting the virus to the baby is high and since transmission is preventable.

Though not true hepatic conditions, preeclampsia and eclampsia affect about 5% to 7% of all pregnancies and involve the liver in 10% to 20% of cases, often resulting in the need for urgent delivery.

L IVER DISEASE MAKES a normal pregnancy a high-risk pregnancy. Extreme vigilance is needed to detect early signs and symptoms of liver dysfunction and to distinguish these from the anticipated benign hepatic changes of pregnancy. Prompt management can save the life of the mother and the baby.

Management of liver disease in pregnancy requires a concerted effort between the primary care physician, liver specialist, obstetrician, and, on rare occasions, a liver transplant team.

GENERAL CONSIDERATIONS

The clinical presentation of a pregnant woman with liver disease may be similar to that in a woman who is not pregnant: ie, she may have abnormal liver function tests but no symptoms, or she may have symptoms with complications of liver disease.

Physiologic and biochemical changes
Pregnancy induces physiologic and biochemical changes that are often mistaken for signs of liver disease (**TABLE 1**).[1] Palmar erythema and spider angiomas—ordinarily signs of liver disease—are common in pregnant women and do not necessarily indicate a liver problem.[2] Also, especially in the third trimester, the enlarging uterus displaces the liver superiorly and posteriorly, making the normal liver difficult to palpate. If the liver can be palpated, it may be enlarged and needs further evaluation.

Abnormal liver function tests are seen in 10% of pregnancies although these changes often do not represent liver disease.[2] Low serum albumin levels and high serum alkaline phosphatase levels are usually signs of benign

TABLE 1

Physiologic changes during pregnancy

Increased
Blood volume and cardiac ouput rise by 35%–50%
Alkaline phosphatase levels rise threefold or fourfold due to placental production
Clotting factor changes create a hypercoagulable state

Decreased
Gallbladder contractility
Hemoglobin
Uric acid levels
Albumin, total protein, and antithrombin III concentrations

No change
Liver aminotransferase levels (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase)
Bilirubin level
Prothrombin time

TABLE 2

Spectrum of liver diseases in pregnancy

Preexistent liver diseases
Portal hypertension, cirrhosis, primary biliary cirrhosis
Autoimmune hepatitis
Wilson disease
Chronic infection with hepatitis B or hepatitis C virus
Alcoholic liver disease

Liver diseases coincidental with but not induced by pregnancy
Acute viral hepatitis and other viral infections
Alcohol-related diseases
Gallstone disease
Budd-Chiari syndrome

Liver diseases induced by pregnancy
First trimester
    Hyperemesis gravidarum
Second and third trimesters
    Acute fatty liver of pregnancy
    Intrahepatic cholestasis of pregnancy
    Preeclampsia, eclampsia, and the HELLP syndrome
      (hemolysis, elevated liver enzymes, low platelet counts)

- Liver diseases that existed before the pregnancy (portal hypertension, cirrhosis, autoimmune hepatitis, Wilson disease)
- Liver diseases that occur during but not because of pregnancy (viral hepatitis, herpes simplex infection, cytomegalovirus infection, alcohol-related problems, gallstone disease, Budd-Chiari syndrome)
- Liver diseases induced by pregnancy, ie, hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, preeclampsia and eclampsia, and the HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts).

Although pregnancy-induced liver disease is uncommon, it should always be suspected because of the potential for acute liver failure and mortality for both mother and fetus. Preexisting liver disease, also uncommon in pregnant women, may lead to liver failure during pregnancy and should be monitored closely.

Diagnosis

Assessment of a pregnant woman with liver disease may require imaging of the liver. Ultrasonography is the imaging examination of choice because of its safety for the fetus. Computed tomography (CT) and endoscopic retrograde cholangiopancreatography may be done if needed, but they involve radiation, so the uterus must be shielded. Magnetic resonance imaging is safe and may be used in pregnant women if other non-ionizing forms of imaging are inadequate.[3]

Drug treatment and pregnancy

Drug therapy is often required to treat liver disorders in pregnant women, and clinicians need to be familiar with drugs that are safe in pregnancy. Although not all drugs have been tested in pregnant women, the US Food and Drug Administration (FDA) classifies them into categories A, B, C, D, and X based on human or animal studies and level of teratogenicity (TABLE 3).

Pregnancy after liver transplantation

Premenopausal women who have received a liver transplant could become pregnant again. Although we will not discuss this topic any

changes in the liver during pregnancy. High levels of serum aminotransferases, bilirubin, or uric acid in a pregnant woman are abnormal (TABLE 1) and should prompt a diagnostic workup.

The differential diagnosis

The differential diagnosis of liver disease in pregnancy (TABLE 2) includes:

US Food and Drug Administration categories for drugs and fetal risk

Category A	Controlled studies show no increased risk of fetal abnormalities
Category B	Animal studies show no evidence of harm to fetus, but no studies yet in pregnant women; *or* Evidence of fetal harm in animal studies, but studies in pregnant women have failed to prove a risk
Category C	Risk to the fetus cannot be ruled out
Category D	Positive evidence of risk to the fetus
Category X	Contraindicated in women who are or may become pregnant

further in this review, we would like to note that pregnancy planned 2 years after liver transplantation may result in excellent outcome for the mother and the fetus.[4,5]

■ PREEXISTING LIVER DISEASES AND PREGNANCY

The diagnosis of preexisting liver disease should always be considered, since the outcome of the pregnancy depends on early recognition and the severity of the underlying liver disease.

Portal hypertension and cirrhosis

Pregnancy is uncommon in women with established liver cirrhosis, including primary biliary cirrhosis, because they tend to be past childbearing age or infertile due to the condition.

A life-threatening complication of liver cirrhosis is variceal bleeding associated with portal hypertension. Treating bleeding esophageal varices with nonselective beta-blockers, band ligation, and octreotide is safe and effective during pregnancy.[6] Ursodeoxycholic acid (FDA category B) at doses of 10 to 13 mg/kg is the treatment of choice for primary biliary cirrhosis and may be continued during pregnancy and breastfeeding.[7]

Autoimmune hepatitis and Wilson disease

Autoimmune hepatitis and Wilson disease often affect young women of childbearing age. Although these two disorders are often recognized and treated before conception, initial presentation during pregnancy is also possible regardless of the age of gestation.

Autoimmune hepatitis. Women with autoimmune hepatitis can become pregnant and can still carry a successful pregnancy. The course of the disease is unpredictable. Although spontaneous remission may occur, maternal death and exacerbation during pregnancy and after delivery have been reported.[8] Therefore, the disease needs to be monitored very closely.

Corticosteroids are the treatment of choice in autoimmune hepatitis and appear to be safe in pregnancy. They seem to induce rapid remission of autoimmune hepatitis, whether during the initial onset or during a flare.

Although azathioprine is in FDA category D (positive evidence of risk), we have little evidence that it is toxic in pregnancy.[8,9] Data from patients with inflammatory bowel disease suggest it is likely to be safe in pregnancy at dosages less than 100 mg/day.[10]

Wilson disease. If Wilson disease is identified and treated before or during pregnancy, the outcome of the pregnancy should be favorable. Interruption of treatment during pregnancy has resulted in fulminant liver failure.[11]

D-Penicillamine and trientine have been used during pregnancy. However, the dosage should be reduced to the minimum necessary dose, which is about 25% to 50% of the dose the patient had been taking before the pregnancy, especially during the last trimester, to promote better wound healing after cesarean delivery.[12–15] D-Penicillamine (FDA category D) could be associated with teratogenicity in 5% of pregnancies, particularly at dosages higher than 500 mg/day.[16] Zinc is the agent of choice for Wilson disease during pregnancy because of its safety for the fetus. It should be maintained throughout the pregnancy at 50 mg three times a day.[12]

Women with autoimmune hepatitis can have a successful pregnancy

■ LIVER DISEASES DURING BUT NOT INDUCED BY PREGNANCY

Viral hepatitis

The outcome of pregnancy in women with chronic viral hepatitis is generally good but depends on the type of virus and the extent of liver damage. For example, hepatitis E infection and herpes simplex virus infection can cause liver failure and death of mother and fetus. The risk of viral transmission from mother to fetus also depends on the virus; for example, the risk of vertical transmission is higher for hepatitis B than for hepatitis C.

Hepatitis A. Acute hepatitis A infection is self-limited and usually does not affect the outcome of pregnancy. Immunoglobulin G (IgG) antibodies are passively transmitted to the newborn and may remain protective until the child is 2 years old. These antibodies could impair the immunogenicity of hepatitis A vaccine if given to children younger than 2 years old.[17] Therefore, hepatitis A vaccine is recommended in children older than 2 years who reside in high-risk communities in the United States. High-risk communities are those where the prevalence of hepatitis A infection is higher than 20 cases per 100,000, ie, at least double the average risk (see **www.cdc.gov/nip/acip**).

Hepatitis A vaccine is produced from inactivated virus. It confers a very low risk to the fetus and has been shown to be safe during pregnancy. Pregnant women traveling to areas where hepatitis A virus is highly endemic may receive the vaccine and hepatitis A immunoglobulin for urgent prophylaxis.[18]

Hepatitis B. Acute infection with hepatitis B virus during pregnancy should have no effect on the pregnancy.[1] However, the rate of transmission to the fetus is high if envelope antigens are detected (90% if positive vs 10% to 40% if negative), if the viral DNA load is high, and if the infection occurs during the third trimester rather than the first trimester (90% vs 10%).[19–22] Some reports suggest that the rate of transmission via amniocentesis is very low.[23]

Pregnant women should be vaccinated against hepatitis B if they are at risk of exposure. The US Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists recommend screening all pregnant women for hepatitis B surface antigen and vaccination of all newborns. If the mother is positive for hepatitis B surface antigen, the newborn should receive hepatitis B vaccine and hepatitis B immunoglobulin within 12 hours of birth. Breastfeeding is not contraindicated if the child has been vaccinated and has received hepatitis B immunoglobulin.[18,24]

In women with chronic hepatitis B infection, taking lamivudine before becoming pregnant and continuing to take it throughout the pregnancy has been reported to lower rates of transmission of the virus from mother to newborn.[25,26] Lower transmission rates have also been seen in pregnant women with a high viral DNA load who took lamivudine during the last month of pregnancy. Newborns in both groups received passive and active immunity against hepatitis B.[25,26] Other reports did not show the same results.[27] Lamivudine is in FDA category C (risk cannot be ruled out).

Hepatitis C. The rate of vertical transmission of hepatitis C is less than 5%.[28–31] The risk is higher if the mother is co-infected with human immunodeficiency virus (HIV), if she is viremic at the time of delivery, if her viral DNA load is greater than 1 million copies/mL, and if the time from the rupture of membranes to delivery is more than 6 hours.[32–36]

The mode of delivery does not seem to influence the rate of transmission from mother to child. Although some reports indicate that the rate of vertical transmission ranges from 0% (elective cesarean delivery) to 7% (vaginal delivery),[34,37] these results have not been confirmed by others, making it difficult to recommend a specific mode of delivery for mothers infected with hepatitis C.[36]

Breastfeeding is not considered a risk factor for transmission, even though viral RNA has been detected in breast milk.[36,38]

Spontaneous resolution of infection in the mother[39] and in the newborn may occur.[32] Therefore, newborns of infected mothers should be tested at 12 to 18 months of age, when IgG antibodies to hepatitis C virus that may have passively transferred from the pla-

Hepatitis E and herpes simplex can cause liver failure and death of mother and fetus

centa to the fetus would have been lost,[40] and the persistence of hepatitis C viral RNA would indicate infection with hepatitis C.

Interferon is in FDA category C, and ribavirin is in category X. Both drugs are contraindicated in pregnancy. If a woman gets pregnant while on combination therapy, then both drugs should be stopped, and she should be advised that she has already put the fetus at risk of teratogenicity.

Hepatitis E infection is responsible for large epidemics in Asia, the Middle East, and Africa. It is self-limited in nonpregnant women, but causes a high rate of death (25%) in pregnant women. Premature delivery, stillbirth, and miscarriage have occurred. Pregnant women should avoid traveling to areas where hepatitis E virus is highly endemic, especially during the third trimester. Scrupulous hand-washing is recommended to prevent infection.[41,42]

Herpes simplex virus can cause fulminant liver failure and death if infection occurs during pregnancy, and the rate of transmission to the fetus can reach 30% to 50% if the primary episode occurs at delivery. About 90% of pregnant women with this infection have abnormal liver enzyme tests and an abnormal prothrombin time. Acyclovir (FDA pregnancy category B) is very effective if promptly given at doses of 400 mg three times daily for 5 to 7 days, and early delivery is not required according to 2002 CDC guidelines (**www.cdc.gov/STD/treatment/2-2002TG.htm#GenitalHerpes**). Cesarean delivery is preferable if active lesions are present during labor.[43,44]

Cytomegalovirus infection may remain asymptomatic in pregnant women, and the prognosis is favorable. The risk of transmission to the fetus and of congenital abnormalities is highest when acute infection occurs in the first 22 weeks of pregnancy. Termination of the pregnancy may be an option after appropriate counseling regarding the potential serious risks to the infected fetus.[45,46]

Alcohol use

Women are two to four times more likely than men to develop alcoholic liver disease for the same amount of alcohol ingested, and they exhibit a tendency to disease progression even with abstinence.[47] Continued drinking during pregnancy may lead to miscarriage, stillbirth, prematurity, growth retardation, and the fetal alcohol syndrome (growth retardation, behavioral disturbances, brain defects, cardiac defects, spinal defects, and craniofacial anomalies).[48,49] Alcohol abstinence throughout pregnancy should be emphasized.

Gallstone disease

Pregnancy is a risk factor for sludge and gallstone formation. By the end of the third trimester, 10% to 12% of pregnant women have gallstones. Most gallstones disappear spontaneously without causing symptoms. If symptoms develop, the treatment may be conservative or surgical, depending on the severity of the symptoms. Laparoscopic surgery seems to be safe and should be considered. The optimal time for it appears to be during the second trimester, when fetal organogenesis is completed and the size of the uterus does not interfere with the surgery.[50,51]

Budd-Chiari syndrome

Budd-Chiari syndrome is very rare and often insidious, manifesting after delivery. It is characterized by thrombosis of the hepatic veins and portal hypertension. Its clinical manifestations include ascites, hepatomegaly, and abdominal pain. Pregnancy is a hypercoagulable state, and the factor V Leiden mutation is a major cofactor in the development of Budd-Chiari syndrome in pregnancy. Women with myeloproliferative disorders are also predisposed to this syndrome.

Proper diagnosis and management require imaging studies such as Doppler ultrasonography and CT and liver biopsy. Treatment with anticoagulants, thrombolytics (warfarin is contraindicated in pregnancy), diuretics, and portocaval shunting may be required. Liver transplantation is indicated when hepatic decompensation develops.[52]

■ LIVER DISEASES UNIQUE TO PREGNANCY

Liver diseases or conditions unique to and induced by pregnancy include hyperemesis gravidarum, acute fatty liver of pregnancy,

Breastfeeding is not considered a risk factor for vertical transmission of hepatitis C

TABLE 4

Liver diseases exclusive to pregnancy

Hyperemesis gravidarum
Presentation: during first trimester, resolves after 20 weeks
Prevalence: < 1%
Symptoms: nausea, vomiting, ketosis
Laboratory features: elevated serum aspartate aminotransferase (AST) and serum alanine aminotransferase levels
  (> 200 U/L) (normal range for AST 20–48, for ALT 10–40)
Treatment: supportive, intravenous (IV) fluids
Outcome: benign for mother and fetus

Acute fatty liver of pregnancy
Presentation: during third trimester; 50% of patients have eclampsia
Prevalence: 1/10,000 to 1/13,000; higher prevalence in multiple gestation, primiparous women, male fetus
Symptoms: nausea, vomiting, abdominal pain, jaundice; can progress rapidly to hepatic failure, hypoglycemia
Laboratory features: platelets <100,000 (normal 150–450 ×10^9/L); AST and ALT 300–1,000 U/L; decreased antithrombin III;
  elevated prothrombin time; low fibrinogen; elevated bilirubin; disseminated intravascular coagulation
Treatment: prompt delivery; liver transplant
Outcome: maternal death rate ≤ 10%; fetal death rate up to 45%

Intrahepatic cholestasis of pregnancy
Presentation: third trimester; rarely before week 26
Prevalence: < 10%; higher in multiple gestation, multiparous women
Symptoms: pruritus, which resolves postpartum; jaundice
Laboratory features: AST and ALT < 1,000 U/L; normal gamma-glutamyl transferase; elevated alkaline phosphatase
  and bile acids; normal prothrombin time; total bilirubin rarely > 6 mg/dL (normal 5–21)
Treatment: ursodeoxycholic acid; delivery at fetal maturity if no fetal distress
Outcome: increased incidence of gallstones; may recur with subsequent pregnancies; fetal death rate 10% – 20%; prematurity

Preeclampsia and eclampsia
Presentation: after week 22
Prevalence: 5% to 7%; higher in multiple gestation
Symptoms: high blood pressure; proteinuria; edema; seizure; renal failure; pulmonary edema
Laboratory features: platelets > 70,000; signs of renal failure
Treatment: blood pressure control, beta-blockers, methyldopa, magnesium sulfate, early delivery
Outcome: maternal death rate 1%

HELLP syndrome
Presentation: second or third trimester or after delivery; 20% of patients also have eclampsia
Prevalence: 0.1% of all pregnancies
Symptoms: abdominal pain, mild renal dysfunction may progress to seizure or renal failure
Laboratory features: platelets < 100,000; hemolysis; AST and ALT levels may reach 6,000 U/L; prothrombin time may
remain normal; normal fibrinogen
Treatment: prompt delivery
Outcome: maternal death rate 5%; hepatic rupture in 1%; fetal death rate 1% to 30%

intrahepatic cholestasis of pregnancy, preeclampsia, eclampsia, and the HELLP syndrome (**TABLE 4**). Each occurs at a specific time during gestation.

Hyperemesis gravidarum
Hyperemesis gravidarum occurs during the first weeks of pregnancy and is characterized by severe nausea, vomiting, and ketosis, with a mild rise in aminotransferase and bilirubin levels. It usually resolves by the end of the first trimester and leaves no ill effect on the mother and the baby. Treatment is supportive.[53]

Acute fatty liver of pregnancy
Acute fatty liver of pregnancy is rare but potentially fatal. It typically occurs during the

second half of the pregnancy, usually the third trimester. It is characterized by microvesicular steatosis of the liver. When it occurs, rates of illness and death are high.

Initial symptoms are nonspecific and include abdominal pain, nausea, and vomiting. Jaundice occurs 1 to 2 weeks later. Pruritus is rare and suggests another diagnosis. Frank liver failure with encephalopathy, jaundice, hypoglycemia, and coagulopathy may ensue.

This condition is more common in primiparous women over the age of 30 who are carrying a male fetus or more than one fetus.[54–58] Aminotransferase and bilirubin levels may be moderately high. Serum creatinine and uric acid levels are commonly high. Antithrombin III activity is profoundly and consistently decreased. Disseminated intravascular coagulation may occur.[59,60]

Prompt delivery rapidly improves liver tests and function. Liver transplantation may be required.[55,61–63]

In 10% to 20% of women with acute fatty liver of pregnancy, the condition results from a genetic mutation in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase, which leads to increased deposition of triglycerides and microvesicular steatosis.[57,58,64] Infants homozygous for this mutation develop rapidly fatal hypoglycemia and fatty liver early in life. Every pregnant woman with acute fatty liver of pregnancy and her baby should be tested for this mutation.[57,58,64]

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy is a relatively benign cholestatic disorder that occurs during the second or third trimester, is more common in multiparous women, and may recur with subsequent pregnancies. Pruritus is the main symptom.

The physical examination is nonspecific. Jaundice may be seen in 20% to 60% of patients, but the bilirubin level remains under 6 mg/dL. Aminotransferase levels are mildly elevated. Typically, levels of serum bile acids and alkaline phosphatase are markedly high.

Ursodeoxycholic acid (FDA category B) is the treatment of choice.[65–68] Prognosis is excellent for the mother.[69] Fetal distress has been reported. Aggressive monitoring for fetal distress is recommended, and prompt delivery is needed if fetal compromise is detected.[70–72]

Preeclampsia and the HELLP syndrome

Preeclampsia, eclampsia, and the HELLP syndrome often overlap. Most experts consider the HELLP syndrome as part of a spectrum of disease extending from preeclampsia and eclampsia to acute fatty liver of pregnancy.[73]

Preeclampsia and eclampsia are associated with abnormalities in liver function tests in 25% to 30% of cases. Preeclampsia is characterized by hypertension, proteinuria, and edema with weight gain. Eclampsia occurs when seizures develop. Preeclampsia and eclampsia together affect about 5% to 7% of pregnant women, often in association with the HELLP syndrome. They are more common after 22 weeks of gestation. Control of hypertension with methyldopa or a beta-blocker reduces the risk of mortality and morbidity in the mother but may not improve the risk for the fetus. Magnesium sulfate is used both to reduce blood pressure and to abort seizures. Early delivery is often required.[74]

The HELLP syndrome complicates 0.1% of pregnancies and could be associated with eclampsia.[75,76] It occurs in the second or the third trimester. Abdominal pain is common. Aminotransferase levels range from 200 to as high as 6,000 IU/L. Platelet counts drop below 100,000/mm^3, and mild renal dysfunction is universal.[77]

In rare instances, the HELLP syndrome may be associated with disseminated intravascular coagulation. In such situations, maternal morbidity is high, especially when eclampsia, pulmonary edema, and acute renal failure occur. Intrauterine growth retardation, prematurity, and neonatal death have been reported in up to 30% of cases. Prompt delivery is the definitive treatment and should be done within 24 hours of diagnosis of the HELLP syndrome.[78]

Hepatic rupture is a serious complication that occurs after acute subcapsular hepatic hemorrhage. Maternal and fetal death result in 50% to 70% of cases unless surgical repair is attempted.[79]

Acute fatty liver is rare, but can be fatal, and usually occurs in the third trimester

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