Review Article

Current Concepts

Liver Disease in Pregnancy

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LIVER disease is a rare complication of pregnancy, but when it occurs it may do so in a dramatic and tragic fashion for both mother and infant. Diseases such as acute fatty liver of pregnancy (AFLP) may begin innocuously with mild symptoms and liver-enzyme abnormalities but, if left untreated, can progress to jaundice, liver failure, and death.

Some of the normal physiologic changes of pregnancy can mimic abnormalities associated with liver disease. In an uncomplicated pregnancy, many laboratory-test results may appear abnormal according to standards derived from a nonpregnant population. Serum albumin concentrations decrease from a mean of 4.2 g per deciliter in nonpregnant women to 3.1 g per deciliter near the end of gestation because of an increase in plasma volume.[1] Serum alkaline phosphatase concentrations rise above the normal range for nonpregnant women during the fifth month of pregnancy and continue to rise to values two to four times normal by the end of gestation because of the leakage of placental alkaline phosphatase into the maternal blood.[2] However, values for serum 5′-nucleotidase, γ-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, and bilirubin are normally unchanged.[1,3] Any increase in these values may therefore reflect hepatobiliary pathology. Hepatosplenomegaly should be absent in a normal pregnancy, but because examination of the abdomen may be difficult when the uterus is gravid, the condition may be difficult to detect. Telangiectasia, particularly on the chest, back, and face, and palmar erythema occur in up to 60 percent of normal pregnant women but disappear after delivery.[4] Liver biopsies performed during uncomplicated pregnancies reveal no pathologic changes.[3,5]

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Table 1 summarizes the common symptoms associated with liver disease in pregnancy. Pruritus occurs with only a few liver diseases, and its presence helps to limit the differential diagnosis. In the diagnosis of liver disease in pregnancy, it is important to establish the week of gestation. Unlike diseases such as viral hepatitis, which may occur at any time, liver diseases specifically associated with pregnancy occur at characteristic times. For example, nausea and vomiting with jaundice in the first trimester will be due to hyperemesis gravidarum, unless they are related to a liver disease not specifically associated with pregnancy, such as viral hepatitis. AFLP has not been reported in the first trimester.[6]

Analyzing the pattern of serum liver-enzyme abnormalities is also helpful in making the diagnosis (Table 2). Cholestatic liver diseases are the result of impaired bile secretion. Characteristically, the alkaline phosphatase and bilirubin concentrations are elevated, but there are only mild changes in the aminotransferase values. By contrast, a pattern indicative of hepatocellular injury will show marked elevations in aminotransferase values as in viral hepatitis or AFLP. Jaundice may occur with either cholestatic disease or hepatocellular injury, but it occurs late in the course of hepatocellular disease and indicates severe hepatic dysfunction. Thrombocytopenia is one of the hallmarks of the HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count in association with preeclampsia) and may be seen early in the course of thrombotic thrombocytopenic purpura. Disseminated intravascular coagulation is a prominent feature of AFLP (found in more than 75 percent of cases), fulminant hepatitis due to viruses such as herpes simplex, thrombotic thrombocytopenic purpura, and the hemolytic–uremic syndrome.[7,8] Disseminated intravascular coagulation is found in only 7 percent of cases of preeclampsia or eclampsia, and in 20 to 40 percent of cases of the HELLP syndrome.[9-12]

CHOLESTATIC DISEASE

In cholestatic liver disease, pruritus, jaundice, or both are the main features of the presentation, but there is no abdominal pain. Included in this group of diseases are hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, hepatotoxic effects of drugs, and primary biliary cirrhosis. Although rare, the Dubin–Johnson syndrome (caused by an inherited defect in the hepatic excretion of organic anions, including conjugated bilirubin) may be exacerbated by pregnancy and marked by the development of jaundice during the second or third trimester. It is a be-

TABLE 1. SIGNS AND SYMPTOMS OF LIVER DISEASES IN PREGNANCY.*

SYMPTOM OR SIGN	DISEASES ASSOCIATED WITH PREGNANCY (TRIMESTER)	DISEASES UNRELATED TO PREGNANCY
Itching	Intrahepatic cholestasis of pregnancy (2 or 3)	Primary biliary cirrhosis Drug hepatotoxicity
Jaundice	Hyperemesis gravidarum (1) Intrahepatic cholestasis of pregnancy (2 or 3) Dubin–Johnson syndrome (2 or 3) Acute fatty liver of pregnancy (3) Preeclampsia or eclampsia (2 or 3) HELLP syndrome (2 or 3)	Choledocholithiasis Acute viral hepatitis Drug hepatotoxicity Exacerbation of underlying liver disease: chronic hepatitis, autoimmune disease, Wilson's disease, primary biliary cirrhosis
Upper abdominal pain (epigastric or right upper quadrant)	Acute fatty liver of pregnancy (3) Preeclampsia or eclampsia (2 or 3) HELLP syndrome (2 or 3) Acute hepatic rupture (3) Budd–Chiari syndrome (3)	Biliary tract disease Gastroesophageal reflux Acute viral hepatitis Peptic ulcer disease
Nausea or vomiting	Hyperemesis gravidarum (1) Acute fatty liver of pregnancy (3) Preeclampsia or eclampsia (2 or 3) HELLP syndrome (2 or 3)	Biliary tract disease Acute viral hepatitis Drug hepatotoxicity Viral syndrome
Thrombocytopenia with or without disseminated intravascular coagulation	Acute fatty liver of pregnancy (3) Preeclampsia or eclampsia (2 or 3) HELLP syndrome (2 or 3)	Fulminant hepatitis Cirrhosis Thrombotic thrombocytopenic purpura Hemolytic–uremic syndrome

*The numbers in parentheses indicate the trimesters in which a disease commonly presents. Diseases occurring in the third trimester may also present immediately post partum. Liver and gastroesophageal diseases unrelated to pregnancy may present at any time during gestation.

nign condition, without pruritus, and is characterized by mild conjugated hyperbilirubinemia with otherwise normal liver-enzyme values.[13] Biliary tract disease, caused by gallstones, may occur at any time during pregnancy and is accompanied by pain in the right upper quadrant and fever. Jaundice may occur when the common bile duct is obstructed by a stone. Endoscopic retrograde cholangiopancreatography with papillotomy relieves obstruction of the common bile duct and can be performed by an experienced practitioner safely and with minimal radiation to the fetus.[14]

Hyperemesis Gravidarum

Hyperemesis gravidarum is characterized by nausea and vomiting; in severe cases, it may lead to dehydration and malnutrition. It generally occurs during the first trimester of pregnancy, although it may occur as late as the 20th week. Abnormal liver-enzyme values have been reported in up to 50 percent of women hospitalized for hyperemesis.[15] Mild hyperbilirubinemia (a bilirubin value of less than 4 mg per deciliter [68 μmol per liter]) with elevations in both direct and indirect fractions has been found in half the women hospitalized for this condition.[16,17] Alkaline phosphatase may be elevated to twice the normal value, and aminotransferase values can rise to as much as 200 U per liter.[16] On biopsy, the liver tissue either appears normal or has fatty changes.[16,17] The mechanism of hyperbilirubinemia is unknown, but the condition is probably related to malnutrition and impaired excretion of bilirubin, because laboratory-test results return to normal within days after the resumption of adequate nutrition.[16] The mean birth weight of babies born to women with severe hyperemesis gravidarum (defined as a loss of more than 5 percent of body weight) is significantly lower than that of the offspring of women with mild hyperemesis gravidarum.[18]

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy usually presents during the third trimester, at a mean of 30 weeks of gestation.[19,20] Its pathogenesis is unknown. The characteristic symptom is itching (pruritus gravidarum), which involves the trunk, extremities, palms, and soles. The itching may be severe, and it is often worse at night. Jaundice develops in 20 to 60 percent of women one to four weeks after the onset of itching.[19-22] The features of obstructive jaundice, including pale stools and dark urine, may be present, but patients do not have constitutional symptoms. The pruritus, jaundice, or both usually persist until delivery and resolve rapidly thereafter.[19] Intrahepatic cholestasis of pregnancy is more common in women with a personal or family history of the disease and in women who have had cholestasis while taking oral contraceptives.[19]

Laboratory data show a pattern consistent with biliary obstruction. The serum bilirubin concentration

TABLE 2. CHARACTERISTICS OF LIVER DISEASES IN PREGNANCY.*

DISEASE	SYMPTOMS	JAUNDICE	TRIMESTER	INCIDENCE IN PREGNANCY	LABORATORY VALUES†	ADVERSE EFFECTS
Hyperemesis gravidarum	Nausea, vomiting	Mild	1 or 2	0.3–1.0%	Bilirubin <4 mg/dl, ALT <200 U/liter	Low birth weight
Intrahepatic cholestasis of pregnancy	Pruritus	In 20–60%, 1–4 wk after pruritus starts	2 or 3	0.1–0.2% in U.S.	Bilirubin <6 mg/dl, ALT <300 U/liter, increased bile acids	Stillbirth, prematurity, bleeding, fetal mortality 3.5%
Biliary tract disease	Right-upper-quadrant pain, nausea, vomiting, fever	With CBD obstruction	Any	Unknown	If CBD stone, increased bilirubin and GGT	Unknown
Drug-induced hepatitis	None or nausea, vomiting, pruritus	Early (in cholestatic hepatitis)	Any	Unknown	Variable	Unknown
Acute fatty liver of pregnancy	Upper abdominal pain, nausea, vomiting, confusion late in disease	Common	3	0.008%	ALT <500 U/liter, low glucose, DIC in >75%, increased bilirubin and ammonia late in disease	Increased maternal mortality (≤20%) and fetal mortality (13–18%)
Preeclampsia and eclampsia	Upper abdominal pain, edema, hypertension, mental-status changes	Late, 5–14%	2 or 3	5–10%	ALT <500 U/liter (unless infarction), proteinuria, DIC in 7%	Increased maternal mortality (~1%)
HELLP syndrome	Upper abdominal pain, nausea, vomiting, malaise	Late, 5–14%	3	0.1% (4–12% of women with preeclampsia)	ALT <500 U/liter, platelets <100,000/mm^3, hemolysis, increased LDH, DIC in 20–40%	Increased maternal mortality (1–3%) and fetal mortality (35%)
Viral hepatitis	Nausea, vomiting, fever	Common	Any	Same as general population	ALT greatly increased (>500 U/liter), increased bilirubin, DIC rare	Maternal mortality increased with hepatitis E

*ALT denotes alanine aminotransferase, CBD common bile duct, GGT γ-glutamyl transpeptidase, DIC disseminated intravascular coagulation, and LDH lactate dehydrogenase.

†To convert bilirubin values to micromoles per liter, multiply by 17.1.

may be elevated, but it is rarely higher than 6 mg per deciliter (103 μmol per liter).[3,19,20] The alkaline phosphatase value may be four times normal.[20] Aminotransferase values are 2 to 10 times normal, although higher levels have been reported.[19,21] A 10-fold-to-100-fold increase in the serum concentration of total bile acids may be the first, or only, laboratory abnormality in women with intrahepatic cholestasis of pregnancy.[19,23,24] Liver biopsy is rarely necessary to make the diagnosis, but when performed, it shows cholestasis with minimal or no inflammatory changes.[3]

Intrahepatic cholestasis is associated with an increased risk of prematurity and stillbirth.[20,22,24,25] Postpartum bleeding may result from decreased absorption of vitamin K.[19,20,22] The management of intrahepatic cholestasis should aim to maximize the well-being of the fetus and the mother's comfort. Women with intrahepatic cholestasis should be treated at centers capable of caring for premature infants. Cholestyramine, given in divided doses totaling 10 to 12 g per day, may help relieve pruritus.[19,21] Prophylactic vitamin K should be administered parenterally.[19,21] Other potential treatments for pruritus that have been studied in uncontrolled trials include ursodiol[26] and dexamethasone.[27]

HEPATOCELLULAR DISEASE

Upper abdominal discomfort — in the epigastrium or the right upper quadrant — is the second common presenting symptom of liver disease in pregnancy. Jaundice may follow. Symptoms often associated with the discomfort include nausea and vomiting, malaise, and sometimes fever.

Viral Hepatitis

Acute viral hepatitis in pregnancy is a systemic illness with fever, nausea, vomiting, and fatigue. Jaundice is usually evident at presentation, and aminotransferase concentrations are markedly elevated (higher than 500 U per liter, and usually higher than 1000 U per liter). Viral hepatitis, except for hepatitis E, does not occur more frequently or with greater severity during pregnancy.[28] Hepatitis E is more dangerous in pregnant women, among whom the mortality is 15 to 20 percent, than in the general

population. The disease occurs in India, Africa, and the Middle East.[29,30] Hepatitis due to herpes simplex virus has also been reported in pregnancy, with a mortality rate of 43 percent.[8] Distinguishing features of herpetic infection are oral or vulvar vesicles, mild elevation in bilirubin values as compared with the aminotransferase values, and coagulopathy.[8] Because hepatitis due to herpes simplex is rare, a liver biopsy showing typical intranuclear inclusions is usually required for diagnosis. Accurate diagnosis is critical because prompt antiviral therapy markedly improves survival.[8]

Liver Diseases of Late Pregnancy

Three diseases of late pregnancy, AFLP, preeclampsia or eclampsia with hepatic involvement, and the HELLP syndrome, may present in a similar fashion and progress to severe liver dysfunction. Approximately half the patients with AFLP also have evidence of preeclampsia or eclampsia, and many have laboratory-test results characteristic of the HELLP syndrome.[6,31]

In the Budd–Chiari syndrome, thrombosis of the hepatic veins leads to elevated pressure in the hepatic sinusoids, hepatocellular necrosis, and signs of portal hypertension. The syndrome is a very rare complication of pregnancy. Women present with the triad of abdominal pain, hepatomegaly, and ascites, though jaundice is quite uncommon.[32] A definitive diagnosis is made with hepatic venography or with a liver biopsy showing central venous congestion.[33]

Acute Fatty Liver of Pregnancy

AFLP is characterized by the accumulation of microvesicular fat within hepatocytes. The disease is estimated to occur in 1 in 13,000 deliveries.[34] Women carrying more than one fetus or in their first pregnancy are most often affected.[6] The symptoms begin at a mean of 36 weeks of gestation, although cases have become evident as early as the 28th week.[6,34] The initial manifestations of the condition are nonspecific and may be misleading: nausea and vomiting (in 70 percent of cases), pain in the right upper quadrant or epigastric pain (in 50 to 80 percent), or a viral-like syndrome with malaise and anorexia.[6,7,35] Jaundice often follows these nonspecific symptoms in one to two weeks, but pruritus is rare.[35,36] If untreated, AFLP typically progresses to fulminant hepatic failure with encephalopathy, renal failure, pancreatitis, uncontrollable gastrointestinal or uterine bleeding, disseminated intravascular coagulation, seizures, coma, and death.[35,36] Before 1980 both the maternal and fetal mortality rates associated with the disease were about 85 percent.[36]

When AFLP is present, pregnancy should be terminated promptly. Some authors favor expectant management of mild cases.[6] However, the condition of a woman with AFLP may deteriorate suddenly and rapidly, endangering both her and the fetus.[36] Jaundice, liver dysfunction, and disseminated intravascular coagulation may progress for one to two days after delivery but then improve.[7] Liver transplantation has been successful in women with fulminant hepatic failure due to AFLP whose condition did not improve with delivery and intensive supportive care.[37]

Since 1980, the maternal and fetal mortality associated with AFLP has been reduced to less than 20 percent.[7,36,37] Survivors have no long-term sequelae, and histologic features of the liver return to normal.[6,38] The recurrence of AFLP in subsequent pregnancies is very uncommon; only two cases have been reported.[31]

Preeclampsia and Eclampsia

Preeclampsia is characterized by a triad of hypertension, proteinuria, and edema. Hypertension is defined as an elevation of 30 mm Hg (systolic) or 15 mm Hg (diastolic) above the value in the first trimester or any value above 140/90 mm Hg. Preeclampsia may be recognized by visual changes, headache, edema, hyperreflexia, funduscopic changes, and the presence of proteinuria and hyperuricemia. Eclampsia is marked by seizures or coma in addition to the signs of preeclampsia. The causes of preeclampsia and eclampsia are unknown, but they are related to abnormal endothelial reactivity that leads to hypertension and to the intravascular deposition of fibrin with end-organ damage.[39] In severe cases, cerebral edema, hepatic infarction, acute renal failure, congestive heart failure, or respiratory distress may develop.[40,41]

Preeclampsia is a complication of approximately 5 to 10 percent of pregnancies and occurs late in the second trimester or in the third.[41] Risk factors for preeclampsia include preexisting hypertension, extremes of childbearing age, a first pregnancy, and multiple gestation.[9,41] Maternal and fetal outcomes depend on proximity to term and the severity of signs and symptoms. In mild preeclampsia at term, the rate of perinatal morbidity approaches that of uncomplicated pregnancies.[9] Maternal mortality is less than 1 percent at institutions experienced in treating preeclampsia and eclampsia.[9] Over 80 percent of maternal deaths are due to central nervous system complications. Hepatic complications, including subcapsular hematoma and rupture (Fig. 1), infarction, and fulminant failure, account for most of the remaining mortality.[40,42-44] Complications of preeclampsia and eclampsia for the fetus include abruptio placentae, prematurity, and intrauterine growth retardation.[9]

The HELLP Syndrome

The HELLP syndrome is a complication of severe preeclampsia.[45] It affects approximately 0.1 to 0.6

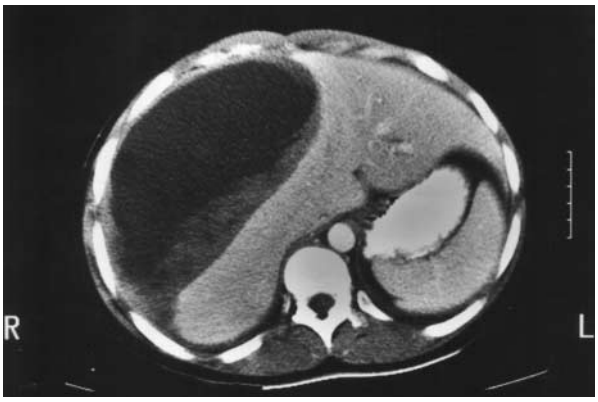


Figure 1. Abdominal Computed Tomographic Scan after Oral and Intravenous Administration of Contrast Medium, Showing Acute Hepatic Hemorrhage of the Right Lobe of the Liver with a Subcapsular Hematoma.

The figure was provided by Mark S. Bankoff, M.D.

percent of all pregnancies and 4 to 12 percent of women with severe preeclampsia.[10] Seventy percent of cases occur between the 27th and 36th week of gestation, and about one third occur post partum.[10] The syndrome is marked by a spectrum of abnormal laboratory findings that peak one to two days post partum: a microangiopathic, hemolytic anemia with elevated serum lactate dehydrogenase concentrations; serum aminotransferase concentrations 2 to 10 times normal; and a low platelet count (no more than 100,000 per cubic millimeter).[45,46]

Women with the HELLP syndrome typically present with right-upper-quadrant or epigastric pain (65 to 90 percent of patients), malaise (90 percent), nausea or vomiting (36 to 50 percent), and headache (31 percent). Jaundice is evident in only 5 percent.[10,47] Physical examination shows right-upper-quadrant tenderness (80 percent of patients) and weight gain with edema (60 percent), but hypertension may be absent in 20 percent of patients.[47]

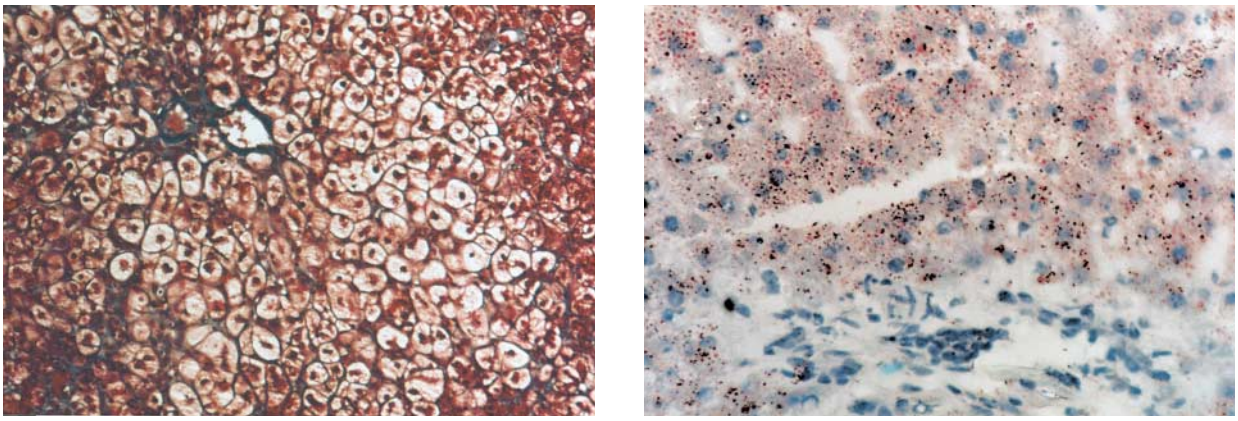
The mortality rate for women with HELLP is about 1 to 3 percent, although rates as high as 25 percent have been observed.[10] Complications include disseminated intravascular coagulation (20 percent of patients), abruptio placentae (16 percent), acute renal failure (7 percent), and pulmonary edema (6 percent).[10] The perinatal mortality of infants is approximately 35 percent (range, 10 to 60 percent), depending on gestational age and the severity of the syndrome at the time of delivery.[48] In addition to prematurity, infants born to mothers with this syndrome are at risk for thrombocytopenia.[48,49] Rates of recurrence in subsequent pregnancies have varied from 3 to 27 percent.[50,51]

Delivery is the definitive treatment for preeclampsia or eclampsia and for the HELLP syndrome. Laboratory abnormalities are most severe in the first two days after delivery, and considerable supportive care, including blood products, is required.[10] If preeclampsia is severe or develops after the 36th week of gestation, and if the fetal lungs are mature, the baby should be delivered. If mild preeclampsia is evident early in the third trimester, expectant management with careful monitoring may be indicated in order to enhance fetal-lung maturity.[41] There is controversy about the treatment of women with HELLP at less than 34 weeks of gestation. Delivery may be postponed for 24 to 48 hours, so long as there is control of hypertension and prevention of seizures with magnesium sulfate, to allow the administration of corticosteroids to promote fetal-lung maturity.[52] Two studies have found a marked improvement in maternal platelet counts and liver function after the administration of corticosteroids, along with a trend toward improved fetal outcome, but this treatment had only a marginal effect in delaying delivery.[49,53,54] Plasmapheresis was used in women who had persistent thrombocytopenia and organ dysfunction for more than 72 hours after delivery.[55]

Differential Diagnosis

The presence of AFLP is suggested by jaundice, hepatic encephalopathy, a small liver, and the absence of signs of preeclampsia (although half the patients with AFLP may have preeclampsia). The characteristic laboratory values in AFLP are an elevated white-cell count (>15,000 per cubic millimeter), an alanine aminotransferase concentration in the range of 300 U per liter, hyperbilirubinemia, hypoglycemia (which is often profound), an elevated ammonia value, a low albumin value, and disseminated intravascular coagulation (in 75 percent of cases).[6,35,36] In contrast, in preeclampsia, eclampsia, and the HELLP syndrome, the liver is normal in size or enlarged.[40] The mean elevation in aminotransferase concentrations is 60 U per liter (with values up to 500 U per liter) in women with preeclampsia or eclampsia and 150 U per liter in women with HELLP.[11,46] Marked elevations in aminotransferase values may occur, but such results should also suggest hepatic infarction, subcapsular hematoma, or viral hepatitis.[40,42] The bilirubin value is normal, or minimally elevated (usually to less than 5 mg per deciliter [86 μmol per liter]), although values as high as 19 mg per deciliter (325 μmol per liter) have been reported in cases with extensive hepatic involvement.[56] Hypoglycemia is distinctly uncommon. Overt disseminated intravascular coagulation is uncommon in preeclampsia or eclampsia alone, but it occurs in 20 to 40 percent of patients with HELLP.[6,10-12]

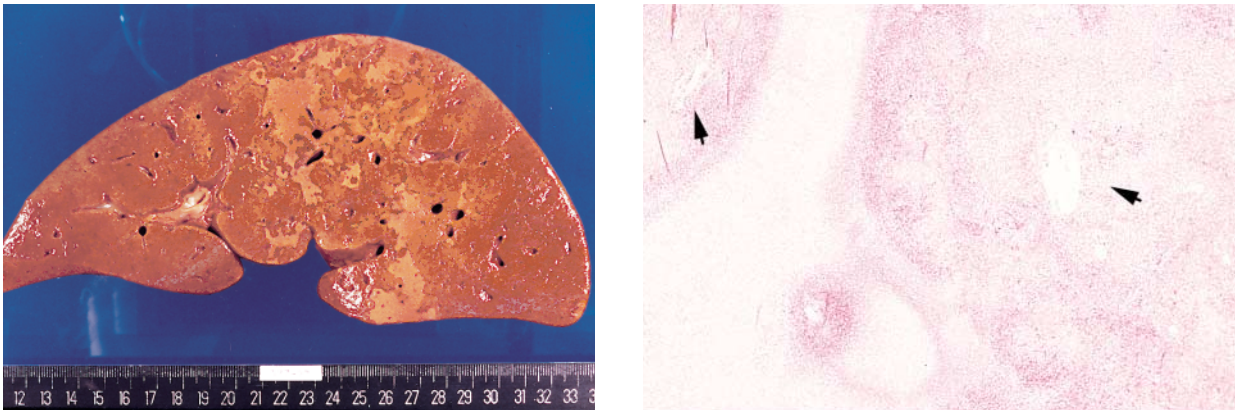
Ultrasound examination and computed tomography, both of which may demonstrate fatty infiltration of the liver, have been used in an attempt to



A B

Figure 2. Liver-Biopsy Specimen from a Woman with Acute Fatty Liver of Pregnancy.

In Panel A, hepatocytes near the central vein are pale and swollen because of the deposition of microvesicular fat. The nuclei are centrally located. (Trichrome stain, ×400.) In Panel B, oil red O stain reveals microvesicular fat (red dots) in the cytoplasm. There are very mild inflammatory changes. (×520.)



A B

Figure 3. Liver of a Woman Who Died of Eclampsia.

An autopsy specimen (Panel A) shows multiple regions of hepatic infarction (serpiginous pale zones). In a microscopical view (Panel B), a band of infarcted tissue extends from and obliterates the portal areas. The area of infarction, with a rim of inflammatory cells, separates two central veins (arrows). The central vein on the right is surrounded by hepatocytes that are still intact. (Hematoxylin and eosin, ×20.) (Courtesy of the Pathology Department, New England Medical Center. Photographs by Sonia Alexander.)

diagnose AFLP.[57] Nevertheless, the sensitivity and specificity of these imaging studies are insufficient to make a definitive diagnosis, and false negative results are common.[7,57]

Liver biopsy can differentiate AFLP from preeclampsia and rule out other liver abnormalities. Histologic features of the liver in AFLP are swollen, pale hepatocytes with central nuclei (Fig. 2A), resulting from engorgement by fat-filled microvesicles. Special stains such as oil red O must be applied to fresh-frozen specimens to demonstrate fat (Fig. 2B).[35,36] There may be patchy hepatocellular necrosis, but widespread necrosis or inflammation, as seen in viral hepatitis, is absent.[35,36] Other causes of microvesicular fat are tetracycline or valproic acid hepatotoxicity and Reye's syndrome.[36] Although microvesicular fat within hepatocytes may sometimes be found in preeclampsia or eclampsia, the characteristic histologic features of those conditions predominate.[38,40,58,59] Typically, these are periportal lesions, with deposition of fibrin in sinusoids and portal tracts, and periportal hemorrhage. Periportal hepatocytes are necrotic, and thrombi may form in small portal arterioles. Livers with severe disease have gross changes typical of infarction that extend from periportal areas (Fig. 3).[40,59] In the HELLP syn-

drome, the extent of abnormal laboratory findings does not predict the severity of the changes in hepatic tissue.[59]

If the patient's coagulative status permits, liver biopsy may be useful to make the diagnosis of AFLP in patients who present atypically, to assist in the treatment of patients who are not close to term, and to rule out other hepatic disorders such as viral hepatitis.[31] However, liver biopsy should not be performed to confirm a classic presentation of AFLP or to distinguish AFLP from severe preeclampsia, because both conditions require the same management, supportive care and rapid delivery.[31,36,60]

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