



Liver disease in pregnancy

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INTRODUCTION

Liver diseases in pregnancy are usually categorized into liver disorders that occur only in pregnancy and liver diseases that occur coincidentally in pregnancy. There are five liver disorders that are pregnancy-specific: hyperemesis gravidarum, preeclampsia/eclampsia, syndrome of hemolysis, elevated liver tests, and low platelets (HELLP), acute fatty liver of pregnancy, and intrahepatic cholestasis of pregnancy. These disorders typically occur at specific times during the course of pregnancy (Table 1), and they may lead to significant maternal and fetal morbidity and mortality. There is a role for certain medications in these disorders, but the risks and benefits of the use of such therapies must be considered (Table 2). Delivery of the fetus usually terminates the progression of these disorders. Chronic liver diseases that occur coincidentally in pregnancy include cholestatic liver disease, autoimmune hepatitis, Wilson disease, and viral hepatitis. Some of the pharmacological agents used to treat chronic liver disease may be used in pregnancy, but there are other agents whose teratogenicity precludes use in pregnancy. Although uncommon, women with cirrhosis may become pregnant and may have a relatively benign course of pregnancy. However, the presence of portal hypertension may contribute to maternal complications. Given the complexity of these disorders and the potential risks to both the mother and the fetus, it is important that obstetricians and gastroenterologists/hepatologists collaborate in providing management of liver disease in pregnancy.

Abstract

Liver diseases in pregnancy may be categorized into liver disorders that occur only in the setting of pregnancy and liver diseases that occur coincidentally with pregnancy. Hyperemesis gravidarum, preeclampsia/eclampsia, syndrome of hemolysis, elevated liver tests and low platelets (HELLP), acute fatty liver of pregnancy, and intrahepatic cholestasis of pregnancy are pregnancy-specific disorders that may cause elevations in liver tests and hepatic dysfunction. Chronic liver diseases, including cholestatic liver disease, autoimmune hepatitis, Wilson disease, and viral hepatitis may also be seen in pregnancy. Management of liver disease in pregnancy requires collaboration between obstetricians and gastroenterologists/hepatologists. Treatment of pregnancy-specific liver disorders usually involves delivery of the fetus and supportive care, whereas management of chronic liver disease in pregnancy is directed toward optimizing control of the liver disorder. Cirrhosis in the setting of pregnancy is less commonly observed but offers unique challenges for patients and practitioners. This article reviews the epidemiology, pathophysiology, diagnosis, and management of liver diseases seen in pregnancy.

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HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum (HG) is defined as intractable nausea and vomiting during pregnancy that often leads to fluid and electrolyte imbalance, weight loss of 5% or greater, and nutritional deficiency requiring hospital admission^[1]. The incidence of HG varies from 0.3%-2% of all live births^[2]. HG often occurs between the 4th and 10th wk of gestation and usually resolves by the 20th wk.

Table 1 Features of pregnancy-associated liver diseases

Disease	Timing of occurrence	Clinical features	Histology
Hyperemesis gravidarum	First trimester	Nausea, vomiting, weight loss, nutritional deficiency	No distinct histopathology, may see normal tissue or hepatocyte necrosis, bile plugs, steatosis
Preeclampsia/eclampsia	Second/third trimester	Hypertension, edema, proteinuria, neurological deficits (headaches, seizures, coma)	Periportal hemorrhage, necrosis, fibrin deposits, may see microvesicular fat
Syndrome of hemolysis, elevated liver tests, and low platelets (HELLP)	Third trimester	Abdominal pain, nausea, vomiting, edema, hypertension, proteinuria	Necrosis, periportal hemorrhage, fibrin deposits
Acute fatty liver of pregnancy (AFLP)	Third trimester	Nausea, vomiting, abdominal pain, fatigue, jaundice	Microvesicular fat
Intrahepatic cholestasis of pregnancy (ICP)	Second/third trimester	Pruritus, jaundice, fatigue, abdominal pain, steatorrhea	Centrilobular cholestasis, no inflammation

Table 2 Safety of drugs used in pregnancy-associated liver diseases

Drug	FDA pregnancy category	Comments
Antiemetics		
Promethazine	C	Possible respiratory depression if drug is administered near time of delivery
Metoclopramide	B	Available evidence suggests safe use during pregnancy
Ondansetron	B	Additional studies are needed to determine safety to the fetus, particularly during the first trimester
Prochlorperazine	C	There are isolated reports of congenital anomalies; however, some included exposures to other drugs. Jaundice, extrapyramidal signs, hyper-/hyporeflexes have been noted in newborns
Antihypertensives		
ACE inhibitors	C/D	First trimester exposure to ACE inhibitors may cause major congenital malformations. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios and anuria, hypotension, renal failure, skull hypoplasia, and death in the fetus/neonate
Beta blockers	C/D	Fetal bradycardia, hypotension, risk of intrauterine growth retardation
Calcium channel blockers	C	Teratogenic and embryotoxic effects have been demonstrated in small animals. There are no adequate and well-controlled studies in pregnant women
Anticoagulation		
Aspirin	C (1st/2nd trimesters) D (3rd trimester)	Adverse effects in the fetus include intrauterine growth retardation, salicylate intoxication, bleeding abnormalities, and neonatal acidosis. Use of aspirin close to delivery may cause premature closure of the ductus arteriosus. Data have shown low-dose aspirin (60-150 mg/day) may be safe in pregnancy
Enoxaparin	B	No adequate and well-controlled studies using enoxaparin. Postmarketing reports include congenital abnormalities and also fetal death
Heparin	C	Does not cross the placenta
Intrahepatic cholestasis		
Ursodeoxycholic acid	B	Relatively low risk
S-adenosyl-L-methionine	Not evaluated by FDA	Relatively low risk
Cholestyramine	C	Cholestyramine is not absorbed systemically, but may interfere with vitamin absorption

United States Food and Drug Administration (FDA) pregnancy categories: Category A: Well-controlled studies failed to show a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in the second or third trimesters). Category B: Animal reproduction studies failed to show a risk to the fetus, and there are no adequate studies in pregnant women. Category C: Animal reproduction studies have shown an adverse effect on the fetus. There are no adequate studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: There is evidence of human fetal risk based on data from investigational or marketing experience or studies in humans. However, the potential benefits may warrant use of the drug in pregnant women despite potential risks. Category X: Data have demonstrated fetal abnormalities in animals and humans, and/or there is positive evidence of human fetal risk based on data from investigational or marketing experience. The risks of the use of the drug in pregnant women outweigh potential benefits.

However, in approximately 10% of HG patients, symptoms continue through pregnancy and resolve only with delivery of the fetus^[5].

HG remains a poorly understood condition and most likely involves a combination of hormonal, immunologic, and genetic factors. Data have shown increased levels of human chorionic gonadotropin (HCG) in HG, and proposed mechanisms for the effect of HCG on HG include stimulation of secretory processes of the upper gastrointestinal tract and stimulation of the thyroid gland^[4-7]. Other proposed factors contributing to HG

include elevations of estrogen, decreases in prolactin levels, and overactivity of the hypothalamic-pituitary-adrenal axis^[6]. It has been speculated that immune and inflammatory mechanisms also contribute to HG. In particular, increased levels of tumor necrosis factor- α have been observed in HG patients^[8]. Higher levels of immunoglobulin G (IgG), immunoglobulin M (IgM), C3, and C4 levels, as well as increased lymphocyte counts and natural killer and extra-thymic T cell levels have been observed in HG patients^[9,10].

Liver involvement is seen in about 50%-60% of

patients with HG^[11]. Most commonly seen are mild serum aminotransferases elevations, but there are reported cases of severe transaminase elevations (alanine aminotransferase (ALT) levels 400 to over 1000 U/L)^[12]. Mild hyperbilirubinemia with mild jaundice can be seen as well. Other complications include disturbances in electrolytes and in water and acid-base balance that can usually be treated adequately with hydration.

While maternal morbidity is well documented, the effects of HG on the fetus are less clear. Some data suggest no differences between fetuses born to mothers with HG and non-HG mothers^[13], but other data show increased rates of fetal abnormalities including undescended testicles, hip dysplasia, and Down Syndrome^[2]. In one large cohort study, infants of HG mothers were found to have lower birth weights and higher rates of being small for gestational age^[14]. However, no significant effect on perinatal survival has been shown.

Treatment of HG is primarily supportive. Patients should avoid triggers that aggravate nausea, and eat small, frequent, low-fat meals. Intravenous fluids, thiamine and folate supplementation, and antiemetic therapy may be administered. Promethazine is a first-line agent, but other medications such as metoclopramide, ondansetron, and steroids have also been used. Enteral feeding is effective, and in severe cases, total parenteral nutrition may be used cautiously.

PREECLAMPSIA/ECLAMPSIA

Preeclampsia is a disorder defined by the triad of hypertension, edema, and proteinuria. It affects about 5%-10% of all pregnant women and usually occurs late in the second trimester or in the third trimester. In preeclampsia, hypertension is defined as having a systolic pressure greater than 140 mmHg and a diastolic pressure greater than 90 mmHg on at least two occasions that are at least 4 to 6 h apart in a previously normotensive patient, and proteinuria is defined as equal to or greater than 300 mg of protein in a 24 h urine collection or 1+ protein or greater on urine dipstick testing of two random urine samples collected at least 4 to 6 h apart^[15]. Eclampsia involves all features of preeclampsia and includes neurologic symptoms such as headaches, visual disturbances, and seizures or coma. Risk factors for preeclampsia and eclampsia include nulliparity, extremes of maternal age, insulin resistance, obesity, and infection^[15,16]. The pathophysiology of preeclampsia/eclampsia is thought to involve procoagulant and proinflammatory states that create glomerular endotheliosis, increased vascular permeability, and a systemic inflammatory response that results in end-organ damage and hypoperfusion.

Abnormal laboratory values include a 10- to 20-fold elevation in aminotransferases, elevations in alkaline phosphatase levels that exceed those normally observed in pregnancy, and bilirubin elevations of less than 5 mg/dL. Liver histology generally shows hepatic sinusoidal deposition of fibrin along with periportal

hemorrhage, liver cell necrosis, and in severe cases, infarction; these changes are likely due to vasoconstriction of hepatic vasculature^[17]. Microvesicular fatty infiltration has also been observed in some cases of preeclampsia, suggesting a possible overlap with acute fatty liver of pregnancy^[18].

Maternal mortality from preeclampsia/eclampsia is rare in developed countries, but may approach 15%-20% in developed countries^[15]. Likewise, the fetal mortality rate is rare, occurring in 1%-2% of births. Maternal and neonatal morbidity may include placental abruption, preterm delivery, fetal growth restriction or maternal renal failure, pulmonary edema, or cerebrovascular accident.

The only effective treatment for preeclampsia is delivery of the fetus and placenta. However, if mild preeclampsia is evident before fetal lung maturity at 36 wk gestation, one may consider expectant management with intensive monitoring. Pharmacological agents used in preeclampsia include antihypertensives such as calcium channel blockers and low-dose aspirin. Magnesium sulfate may be administered if eclampsia develops.

HEMOLYSIS, ELEVATED LIVER TESTS AND LOW PLATELETS

HELLP syndrome is a multisystemic disorder of pregnancy involving hemolysis, elevated liver tests, and low platelets. About 70% of cases occur antenatally, and most cases occur during the last trimester of pregnancy^[19]. The pathogenesis of HELLP is thought to involve alterations in platelet activation, increases in proinflammatory cytokines, and segmental vasospasm with vascular endothelial damage. An association with a defect in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) has also been described, suggesting a possible overlap of HELLP syndrome and acute fatty liver of pregnancy.

Most patients present with right upper quadrant abdominal pain, nausea, vomiting, malaise, and edema with significant weight gain. Less commonly associated conditions include renal failure (with increased uric acid), diabetes insipidus, and antiphospholipid syndrome. Other late findings of HELLP include disseminated intravascular coagulopathy (DIC), pulmonary edema, placental abruption, and retinal detachment. Hypertension and proteinuria may be seen, but in 20% of patients, hypertension is absent^[19]. Laboratory findings include hemolysis with increased bilirubin levels (usually less than 5 mg/dL) and lactate dehydrogenase (LDH) levels greater than 600 IU/L, moderately elevated aspartate aminotransferase (AST) and ALT levels (200 IU/L to 700 IU/L), and thrombocytopenia (less than 100 000/mL). In early stages, prothrombin time and activated partial thromboplastin time are normal, but in later phases, DIC may be present with increased levels of fibrin degradation products and D-dimer, and thrombin-antithrombin complexes. The pathogenesis

of hepatic damage in HELLP syndrome involves intravascular fibrin deposition and sinusoidal obstruction that can lead to hepatic hemorrhage and infarction. Histologically, one may see focal hepatocyte necrosis, periportal hemorrhage, and fibrin deposits.

The reported maternal mortality from HELLP is 1%, and the perinatal mortality rate ranges from 7%-22% and may be due to premature detachment of placenta, intrauterine asphyxia, and prematurity^[11]. Other complications of HELLP syndrome include acute renal failure, adult respiratory distress syndrome, pulmonary edema, stroke, liver failure, and hepatic infarction. The only definitive treatment for HELLP syndrome is delivery. If the pregnant woman is greater than 34 wk gestation, immediate induction is recommended. If gestational age is between 24 wk and 34 wk, corticosteroids are administered to accelerate fetal lung maturity in preparation for delivery 48 h later. After delivery, close monitoring of the mother should continue, as data have shown worsening thrombocytopenia and increasing LDH levels up to 48 h postpartum^[20]. However, most laboratory values (transaminases, bilirubin, LDH) normalize in 48 h, and the presence of persistent or worsening laboratory abnormalities by the fourth postpartum day may signal postpartum complications^[21]. For patients with ongoing or newly developing postpartum symptoms of HELLP, modalities such as antithrombotic agents, plasmapheresis, and dialysis may be employed.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is a rare but serious maternal illness that occurs in the third trimester of pregnancy. With an incidence of 1 in 10000 to 1 in 15000 pregnancies, it has a maternal mortality rate of 18% and a fetal mortality rate of 23%^[17,22]. AFLP is more commonly seen in nulliparous women and with multiple gestation.

The pathophysiology of AFLP involves defects in mitochondrial fatty acid beta-oxidation. Under normal circumstances, an individual that is heterozygous for enzymatic mutations in fatty acid oxidation will not have abnormal fatty oxidation. However, when a heterozygous woman has a fetus that is homozygous for such mutations, fetal fatty acids accumulate and return to the mother's circulation. The extra load of long-chain fatty acids and subsequent triglyceride accumulation lead to hepatic fat deposition and impaired hepatic function in the mother. A deficiency in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) is thought to be associated with the development of AFLP. LCHAD is a component of an enzyme complex known as the mitochondrial trifunctional protein (MTP), and it is believed that the G1528C and E474Q mutations of the MTP are responsible for causing LCHAD deficiency that subsequently leads to AFLP^[23].

Patients with AFLP typically present with a 1 to 2 wk history of nausea, vomiting, abdominal pain, and fatigue. Jaundice occurs frequently, and some women experience

moderate to severe hypoglycemia, hepatic encephalopathy, and coagulopathy. Approximately 50% of these patients will also have signs of preeclampsia, although hypertension is generally not severe^[24]. Laboratory findings include elevations in aminotransferase levels, which may range from being mildly elevated to approaching 1000 IU/L. Many cases involve neutrophilic leukocytosis, and as the disease progresses, thrombocytopenia (with or without DIC) and hypoalbuminemia may occur. Rising uric acid levels and impaired renal function may also be seen.

Since AFLP can lead to significant maternal and fetal morbidity and mortality, prompt diagnosis must be made. The most definitive test is liver biopsy. Histopathologic findings reveal swollen, pale hepatocytes in the central zones with microvesicular fatty infiltration that can be identified on frozen section with oil red O staining. Electron microscopy may also show megamitochondria and paracrystalline mitochondrial inclusions. Although liver biopsy may be helpful, it is often not done due to the presence of coagulopathy. Imaging studies, including ultrasound and computed tomography (CT), are inconsistent in detecting fatty infiltration^[25,26]. Therefore, the diagnosis of AFLP is usually made on clinical and laboratory findings.

As with most pregnancy-associated liver diseases, the treatment of AFLP involves delivery of the fetus. However, many laboratory abnormalities may persist after delivery and may initially worsen during the first postpartum week. In rare cases, patients will progress to fulminant hepatic failure with need for liver transplantation^[27]. In addition to monitoring the mother closely, careful attention should also be paid to the infant given the increased risk of cardiomyopathy, neuropathy, myopathy, nonketotic hypoglycemia, hepatic failure, and death associated with fatty acid oxidation defects in newborns. Finally, affected patients should be screened for defects in fatty acid oxidation as recurrence in subsequent children is 25%, and recurrence of AFLP in mothers is also possible^[11,23].

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a rare pregnancy-specific liver condition that occurs in the late second or third trimester and has a prevalence of about 1/1000 to 1/10000. It is significantly more common in South Asia, South America (especially Chile), and Scandinavian countries. ICP is also more common in women of advanced maternal age, multiparous women, and in women with a personal history of cholestasis with oral contraceptive use^[28]. The prognosis for women with ICP is usually good, but it is associated with increased fetal morbidity and mortality, particularly from chronic placental insufficiency, preterm labor, fetal distress, and intrauterine death^[29].

The etiology of ICP is likely multifactorial and

may include genetic, hormonal and environmental variations. Mutations in the phospholipid translocator known as the ATP-cassette transporter B4 (ABCB4) or multidrug resistant protein-3 (MDR3) are associated with the development of ICP^[30]. Changes induced by these genetic mutations lead to increased sensitivity to estrogen, which impairs the sulfation and transportation of bile acids. The pregnancy-associated increase in estrogen may also contribute to ICP. This is supported by the fact that women with multiple gestations and proportional increases in estrogens have an increased risk of ICP^[31]. Estrogens are thought to act on hepatocytes by decreasing membrane permeability and bile acid uptake by the liver. The maternal-to-fetal transfer of bile acids across the placenta becomes impaired, leading to potentially toxic bile acid levels in the fetus^[32]. The elevation in bile acid levels is also thought possibly to affect myometrial contractility and to cause vasoconstriction of chorionic veins in the placenta, which may contribute to preterm deliveries and fetal distress seen in ICP^[33,34].

Maternal complications are much less severe. The classic symptom is pruritus that usually begins in the second or third trimester. It usually occurs in the palms and soles and may progress to the rest of the body, and the pruritus is often worse at night. Pruritus may be severe but is usually relieved within 48 h after delivery of the fetus. Jaundice occurs in approximately 10%-25% of patients and may appear within the first four weeks of the onset of pruritus^[35]. Cholelithiasis and cholecystitis have been observed to occur with greater frequency in women with ICP^[36]. Other symptoms include fatigue, anorexia, epigastric pain, and steatorrhea due to fat malabsorption. Malabsorption may also lead to vitamin K deficiency leading to prolonged prothrombin times and postpartum hemorrhage.

Abnormal laboratory findings include elevated total bile acid levels up to 10- to 25-fold, with an increase in cholic acid and a decrease in chenodeoxycholic acid leading to a marked elevation in the cholic/chenodeoxycholic acid ratio. The glycine/taurine ratio is also reduced. Other findings include mild aminotransferase elevations, which are seen in about 60% of ICP patients. AST and ALT levels rarely exceed two times the upper limits of normal, but may approach 10- to 20-fold elevations in rare cases. Bilirubin levels may be elevated, but are usually less than 6 mg/dL. Serum alkaline phosphatase levels may also be elevated, but this is usually less helpful to follow given typical alkaline phosphatase elevations seen in pregnancy. Histopathologic findings on liver biopsy include nondiagnostic centrilobular cholestasis without inflammation and bile plugs in hepatocytes and canaliculi^[17]. Liver biopsy is usually not required to make the diagnosis of ICP.

The treatment of choice for ICP is ursodeoxycholic acid (UDCA), which helps to relieve pruritus and improve liver test abnormalities. It is unclear how UDCA works, but it is felt that UDCA conjugates help target and insert key transporter proteins, such as MRP2 (ABCC2) or bile salt export pumps (ABCB11) into

the canalicular membranes^[37]. Data have also shown that UDCA increases expression of placental bile acid transporters, which may allow for improved bile acid transfer^[38]. Other medications, such as cholestyramine and S-adenosyl-L-methionine, have been associated with improving pruritus and normalizing biochemical profiles, but studies have found UDCA to be superior over cholestyramine and S-adenosyl-L-methionine^[39,40]. Dexamethasone has also been used, but has shown to be much less effective in reducing bile acids and bilirubin and ineffective in relieving pruritus^[41]. Antihistamines are frequently used to alleviate pruritus, and vitamin K and other fat-soluble vitamin supplementation should also be administered if fat malabsorption is suspected.

GALLSTONES

The formation of biliary sludge and gallstones is associated with parity. The prevalence of gallstones in pregnancy is 18.4%-19.3% in multiparous women and 6.9%-8.4% in nulliparous women^[42]. The etiology for an increased prevalence of biliary sludge and gallstones in pregnancy is multifactorial. Increased estrogen levels, especially in the second and third trimesters, lead to increased cholesterol secretion and supersaturation of bile, and increased progesterone levels cause a decrease in small intestinal motility^[43]. Also, fasting and postprandial gallbladder volumes are larger, and emptying time is reduced^[44]. The large residual volume of supersaturated bile in the pregnant woman leads to biliary sludge and the formation of gallstones. Pre-pregnancy factors observed to be associated with the development of gallstones in pregnancy include a high body mass index, high serum leptin levels, low high-density lipoprotein (HDL) levels, and insulin resistance^[45,46].

Pregnant women with gallstones may present with right upper quadrant pain that may radiate to the flank, scapula, or shoulder. They may also report nausea, vomiting, anorexia, fatty food intolerance, and low-grade fever. Conservative medical management is recommended initially, especially during the first and third trimesters, in which surgical intervention may confer risk of abortion or premature labor, respectively. Medical management involves intravenous fluids, correction of electrolytes, bowel rest, pain management, and broad spectrum antibiotics. However, relapse rates (40%-90%) are high during pregnancy; thus, surgical intervention may be warranted^[47,48]. Laparoscopic cholecystectomy in the second trimester is preferred^[49]. Endoscopic retrograde cholangiopancreatography (ERCP) may also be required if there are concerns about choledocholithiasis, and this can be performed safely in pregnancy by shielding the fetus and minimizing fluoroscopy time^[50].

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease that affects persons in their 30s to 60s^[51]. It is

characterized by progressive destruction of intrahepatic bile ducts and is likely autoimmune in origin, as more than two thirds of patients with PBC have an associated autoimmune disease. The course of PBC may be insidious, often presenting with fatigue and pruritus. Serum aminotransferase, bilirubin, cholesterol, IgM, and erythrocyte sedimentation rate levels are often elevated, and an elevated bilirubin level often portends poor prognosis. Portal hypertension and liver failure may develop^[52].

Early reports have suggested that PBC is associated with reduced fertility, amenorrhea, repeated pregnancy loss, endometriosis, and premature ovarian failure, as well as worsening liver function during the course of pregnancy^[53-55]. However, more recent data suggest that women with PBC may be able to have normal pregnancies. One study of nine pregnancies in six patients with UDCA-treated PBC showed that all women remained asymptomatic during pregnancy with no recurrence of pruritus^[56]. Improvements were seen in laboratory tests including antimitochondrial antibody titers and levels of alkaline phosphatase, ALT, serum bile acid, bilirubin, immunoglobulin G, and immunoglobulin M. However, a flare in disease with increases in liver biochemistries was observed 3 mo postpartum. UDCA has been shown to be safe in pregnancy^[56].

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is a chronic cholestatic syndrome characterized by inflammation, fibrosis, and destruction of intrahepatic and extrahepatic biliary ducts^[57]. Though the course is typically variable, PSC is often progressive and leads to biliary cirrhosis. There is no known effective therapy, and liver transplantation is the only option for patients with end-stage PSC. There are only a few published case reports on PSC in pregnancy; thus, the natural history of PSC in pregnancy is not well understood^[58-61]. Pregnant patients with PSC may experience pruritus, and complications include biliary strictures and choledocholithiasis. If a patient with PSC develops symptoms worrisome for biliary obstruction, an ultrasound should be performed, as it is thought to be safe in pregnancy and may detect the presence of stones or dominant strictures^[61]. Endoscopic retrograde cholangiopancreatography (ERCP) may be considered with caution regarding exposure to radiation and the use of sedation. Empiric use of UDCA should be considered, as it is felt to be safe in pregnancy and improves outcomes of both maternal symptoms and fetal complications^[61].

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) is characterized by progressive hepatic parenchymal destruction that may lead to cirrhosis. The natural history of AIH in pregnant women is not fully understood, but is thought to be variable. Candia *et al*^[62] reviewed 101 cases of AIH in pregnant women reported in the literature between

1966 and 2004 and found that 47 women experienced AIH flares, with 35 occurring during pregnancy and 12 occurring after delivery. Fetal deaths occurred in 19% of pregnancies, and the majority of the fetal deaths occurred before the 20th wk of gestation. However, a more recent review involving a smaller case series of 42 pregnancies in women with AIH reported a fetal loss rate as high as 24%^[63]. Fetal death in pregnant women with AIH has been associated with the presence of prematurity and low birth weight^[62]. Possible etiologic factors thought to be associated with worsening of AIH in pregnancy include changes in the relative concentrations of various hormones during pregnancy and the presence of specific autoantibodies, including antibodies to SLA/LP and Ro/SSA^[63,64].

Pregnant women with AIH are often treated with a combination of steroids and azathioprine. While steroids are thought to be safe in pregnancy, there has been controversy over the use of azathioprine, as earlier studies have shown azathioprine to have teratogenic effects in mice and rabbits^[65,66]. It is known that azathioprine crosses the placenta, but more recent data have suggested that azathioprine and its metabolites do not have toxic effects on the fetus^[67,68].

Women of childbearing age with AIH should be advised to consider pregnancy only if their disease is well-controlled. However, patients must be monitored closely throughout pregnancy and in the early postpartum period given the unpredictability of the course of AIH in the setting of pregnancy.

WILSON DISEASE

Wilson disease (WD) is a multisystem autosomal recessive disorder of copper metabolism. Occurring in 1:30 000 to 1:50 000 persons, this rare disorder is due to a mutation of the gene, ATP7B, which is located on chromosome 13q14. ATP7B codes for a P type ATPase that controls copper transportation in the liver^[69], and more than 100 forms of this mutation have been found to be responsible for the development of WD. This mutation leads to copper excess and deposition in the liver and brain. Hepatic disease may present as chronic hepatitis, cirrhosis, or fulminant hepatic failure; neurologic abnormalities occur in 40%-50% and may include an akinetic-rigid tremor similar to Parkinson's disease, tremor, ataxia, and a dystonic syndrome^[70].

Studies on the effect of WD on pregnancy are limited to small case series. It has been proposed that WD may adversely affect fertility due to hormonal fluctuations that can result in amenorrhea; it may also lead to copper deposition in the uterus, resulting in miscarriage due to improper implantation of the embryo^[71,72]. Sinha *et al*^[73] observed a higher rate of recurrent spontaneous abortions among women with WD who were untreated compared to women with WD who underwent treatment.

Penicillamine, trientine, and zinc are drugs approved by the United States Food and Drug Administration (FDA) as treatment for WD. Penicillamine acts by

reducing chelation and enabling excretion of copper in the urine. Trientine works similarly but is less effective than penicillamine. Zinc induces intestinal cell metallothionein that binds to copper and prevents transfer of copper into the blood. Penicillamine has been reported to cause teratogenicity in animals and humans^[74-77]. There is one report of a chromosomal abnormality occurring in a baby delivered by a woman with WD who took trientine during pregnancy, but trientine is known to be teratogenic in animals^[78,79]. Brewer *et al.*^[80] reported that the use of zinc in 26 pregnancies of 19 pregnant women with WD resulted in 24 healthy pregnancies; one baby was born with a heart defect requiring surgery at 6 mo, and a second baby was born with microcephaly.

HEPATITIS B

It is estimated that there are about 350 million chronic carriers of hepatitis B virus (HBV) infection^[81]. Perinatal infection is the predominant mode of transmission. Approximately 10%-20% of neonates born to hepatitis B surface antigen (HBsAg)-positive mothers and 90% of those born to both HBsAg- and hepatitis B e antigen (HBeAg)-positive mothers will become infected with HBV^[82]. HBV infection early in life usually results in chronic infection, and 25% of these infected persons will die prematurely from cirrhosis and liver cancer^[83]. Thus, prevention of vertical transmission is critical.

Immunization with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine at birth can reduce HBV transmission to less than 10% among infants of mothers who are positive for both HBsAg and HBeAg with even less transmission if the mother is HBeAg negative^[84]. All infants born to HBsAg-positive mothers should receive a single hepatitis B vaccine and HBIG (0.5 mL) no later than 12 h after birth, and the hepatitis B vaccination series should be completed, with the second vaccination at one or two months of age and the third vaccination at 6 mo of age^[85]. Post-vaccination testing for HBsAg and hepatitis B surface antibody (anti-HBs) should be performed after the complete series of vaccinations at 9 to 18 mo of age in infants born to mothers who are HBsAg positive^[86]. It is thought that administration of HBIG and the hepatitis B vaccine within 12 h after birth is 85%-95% effective, and post-birth administration of the hepatitis B vaccination alone is 70%-95% effective in preventing HBV transmission^[87].

Data have also shown that use of lamivudine in the last month of pregnancy in HBsAg-positive women may lead to decreased HBV transmission rates, and it has been shown to be safe for use in the last trimester of pregnancy despite its FDA designation as a category C drug^[88,89]. Breastfeeding appears not to confer an increased risk of HBV transmission; thus, breastfeeding is not contraindicated in infants of HBsAg mothers^[90].

HEPATITIS C

The prevalence of hepatitis C (HCV) in pregnant women

in the United States ranges between 1%-2% but may be as high as 4% in some inner-city populations^[91]. HCV infection in pregnancy has a presentation that is similar to that of HCV infection in non-pregnant patients. Reports regarding the risk of obstetrical complications among pregnant women infected with HCV are varied. One large cohort study of 506 HCV-positive pregnant women found that HCV infection was associated with the development of gestational diabetes mellitus, lower birth weight, lower Apgar scores, and more admissions to the neonatal intensive care unit for respiratory problems, prematurity, and infections^[92]. However, in another study looking at the long term outcomes of 36 women in Ireland inadvertently infected with HCV after exposure to contaminated anti-D immunoglobulin, there were no differences in the rates of spontaneous miscarriage, or birth weights between the HCV-infected group and controls^[93].

HCV-infected women do not need to be advised against pregnancy, but they should be counseled on the risks of mother-to-infant transmission of HCV. The risk for vertical transmission of HCV is about 5%-10%. The risk of perinatal transmission of HCV is associated with the presence of HCV RNA in maternal blood at the time of birth and coinfection with human immunodeficiency virus (HIV)^[91]. HIV coinfection in pregnant women increases the risk of perinatal HCV transmission by 2-fold, and in more than 25% of cases, both HCV and HIV are transmitted together. Prolonged rupture of membranes (greater than 6 h) has also been associated with an increased risk of perinatal HCV transmission; thus, it is advised that the second stage of labor be kept short in HCV-infected pregnant women^[94]. Data on the effects of the mode of delivery on HCV transmission are conflicting; therefore, there are no recommendations regarding the method of delivery that should be used in HCV-infected pregnant women.

Although HCV is detectable in breast milk, there is little documented evidence of transmission of HCV *via* breastfeeding. However, the Centers for Disease Control and Prevention (CDC) recommend that HCV-infected women with cracked or bleeding nipples should abstain from breastfeeding^[95].

Combination antiviral therapy with pegylated interferon and ribavirin is generally recommended for HCV-infected patients who are eligible for therapy. However, ribavirin has a category X designation by the FDA as it has been shown to be teratogenic and embryocidal in animal models. Interferon has a designation as category C, as it has been shown to have abortifacient effects in animal models, and there are no adequate studies of its use in pregnant women. Therefore, combination antiviral therapy is not recommended for HCV-infected pregnant women. There are a few reports of women becoming pregnant while on interferon monotherapy for HCV, and in these cases, healthy babies were delivered and were found to have normal growth and development at follow up^[96-98]. However, given the uncertainty about safety during pregnancy, it is still recommended that interferon be

avoided by HCV-infected women who are attempting to conceive or are already pregnant.

CIRRHOSIS

Fertility is decreased in women with significant hepatic dysfunction due to hypothalamic-pituitary dysfunction. However, cirrhosis is not a contraindication, as pregnancy may be tolerated if cirrhosis is well-compensated and without features of portal hypertension^[99]. Portal hypertension leads to increased maternal complications, including variceal hemorrhage, hepatic failure, encephalopathy, jaundice, malnutrition, and splenic artery aneurysm^[100]. Bleeding from esophageal varices has been reported in 20%-25% of pregnant women with cirrhosis^[101]. All pregnant women with cirrhosis should be screened for varices starting in the second trimester and started on beta-blockers if indicated. The treatment of variceal bleeding consists of both endoscopic and pharmacologic treatment. However, vasopressin has been shown to cause placental ischemia, necrosis, and amputation of fetal digits and is contraindicated in pregnancy; there is a paucity of information about the use of octreotide in pregnancy^[102]. Finally, though there are no good studies evaluating the impact of vaginal delivery of the risk of variceal bleeding, it is recommended that patients have cesarean section to avoid increased straining^[103].

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