Liver Disease in Pregnancy: What's New

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Liver disease in pregnancy may present as a disorder that is unique to pregnancy or as an acute or chronic liver disease occurring coincidentally in pregnancy. Hepatic diseases that are unique to pregnancy include hyperemesis gravidarum; preeclampsia/eclampsia; the syndrome of hemolysis, elevated liver enzymes, and low platelets; intrahepatic cholestasis of pregnancy; and acute fatty liver of pregnancy. Acute and chronic forms of primary hepatic disorders that are seen in pregnancy include viral hepatitis, autoimmune hepatitis, nonalcoholic fatty liver disease, and cirrhosis. Because of the need to consider both maternal and fetal health, there are special considerations for the implementation of diagnostic strategies and pharmacologic therapies for liver disease that occurs in pregnancy. An understanding of the pathogenesis and expression of liver diseases in pregnancy has been evolving, and various diagnostic and prognostic tools have been studied in order to determine noninvasive approaches to identifying and staging of such diseases. Investigations have also been underway to evaluate the safety and utility of existing and new therapeutic agents that previously were thought to not be compatible with pregnancy. This review will explore updates in the epidemiology, diagnosis, and management of various liver diseases seen in pregnancy. (*Hepatology Communications* 2020;4:145-156).

There are increasing data about the prevalence, natural history, and management of liver diseases in pregnancy and in women of childbearing age. Rates of liver disease are increasing among adolescents and young adults. Data from the National Health and Nutrition Examination Survey across 1988-1994 and 1999-2012 demonstrated a significant increase in the prevalence of chronic liver disease in women between 15 and 39 years of age, noting chronic liver disease rates in this subpopulation of 10.4% during 1988 to 1994, 26.1% during 1999 to 2004, and 24.9% during 2007 to 2012.[1] As the most common liver disease in this study cohort, nonalcoholic fatty liver disease (NAFLD) was noted to have a prevalence of 6.8% during 1988 to 1994, 20.3% during 1999 to 2004, and 18.1% during 2007 to 2012. The prevalence of alcohol-related liver disease also rose significantly, whereas the prevalence of hepatitis C virus (HCV) infection decreased during the study periods. From 2000 to 2015, death rates for chronic liver disease and cirrhosis in women aged 25 to 44 years increased by 18%.[2] Another study that examined trends in liver disease among hospital admissions in women who were pregnant during 2002 to 2010 demonstrated that liver diseases unique to pregnancy and gallstone disease were the two most common hepatic diseases, occurring at rates of 7.18 per 1,000 pregnancy hospitalizations and 4.65 per 1,000 pregnancy hospitalizations, respectively.[3] The rates of liver disease per each 3-year interval over the entire 9-year study period increased for all examined liver diseases (hepatitis B, hepatitis C, gallbladder disease, biliary tract disease, alcohol-related liver disease, and various liver disorders that are unique to pregnancy), and the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) was observed as the most costly liver disease seen during pregnancy hospitalizations. Such epidemiologic data suggest that women who are pregnant and women of childbearing age are at risk of significant morbidity and mortality due to liver disease.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFLP, acute fatty liver of pregnancy; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver enzymes, and low platelets; HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; kPa, kilopascal; MELD, Model for End-Stage Liver Disease; MTCT, mother to child transmission; NAFLD, nonalcoholic fatty liver disease; TIPS, transjugular portosystemic shunt; UDCA, ursodeoxycholic acid.

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A number of physiologic changes occur throughout pregnancy in order to sustain the growth and development of the fetus. This can lead to expected changes in some laboratory findings, inclusive of minimal to slight decreases in hepatic transaminases and elevations in alkaline phosphatase levels (Table 1).[4] Despite these findings, there is a 3% to 5% incidence of liver enzyme abnormalities in pregnancy.[5] Due to the need to consider the health of the mother and fetus, a number of special considerations must be accounted for in the diagnosis and management of hepatic disorders in pregnancy (Table 2).[6,7] Initial assessments of liver enzyme abnormalities in pregnancy should begin with noninvasive testing, which can include laboratory and radiographic studies. Radiographic investigations for liver disease in women who are pregnant should begin with ultrasound. If subsequent radiographic assessment is required, magnetic resonance imaging without contrast is an acceptable modality in the setting of pregnancy. Use of gadolinium should be avoided in pregnancy due to its association with teratogenicity, and the use of computed tomography in pregnancy must be carefully weighed against the risks of ionizing radiation to the fetus. Invasive testing, such as liver biopsy and endoscopy, may be considered if required to facilitate appropriate management of the presenting liver disorder.

This review will provide updates on the management of liver diseases that are unique to pregnancy and primary liver diseases that are concurrent with pregnancy.

TABLE 1. EXPECTED VALUES FOR LIVER TESTS IN PREGNANCY

Laboratory Value	Expected Trend in Pregnancy
Albumin	Decrease
Alkaline phosphatase	Increase
ALT	No expected change/slight decrease
AST	No expected change/slight decrease
Bilirubin	No expected change/slight decrease
Bile acid	No expected change
GGT	No expected change/slight decrease
Platelets	No expected change
Prothrombin time	No expected change

Abbreviation: GGT, gamma glutamyl transpeptidase.

Liver Diseases That Are Unique to Pregnancy

HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum (HG) is seen earlier than other liver diseases that are unique to pregnancy, typically presenting in the first trimester and resolving by the twentieth week of gestation. Occurring in about 0.3% to 2% of pregnancies, HG presents as intractable nausea and vomiting with subsequent dehydration, weight loss, electrolyte imbalance, and nutritional deficiency.[8] Liver involvement is seen in 50% to 60% of patients with HG.[9] Biochemical changes include elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, which are typically mildly elevated but have been observed to rise to as high as 1,000 in some patients with HG.[10] Jaundice is rare, occurring more commonly in severe cases of HG. The etiology of elevated liver enzymes in HG is unclear but has been proposed to involve liver cell injury due to multiple factors, including dehydration, starvation, and placental-derived cytokines, including tumor necrosis factor alpha.[11,12] It is noted that liver enzyme levels return to normal levels after resolution of HG, and thus there are no long-term sequelae of HG on liver-related health.

HG treatment involves administration of intravenous fluid, antiemetic therapy, and vitamin and mineral

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TABLE 2. DIAGNOSTIC MODALITIES FOR LIVER DISEASE IN PREGNANCY AND LACTATION

Modality	Pregnancy Considerations	Lactation Considerations	Other Issues
Ultrasound	Acceptable modality	Acceptable modality	No available data on contrasted ultrasound in pregnancy and lactation
CT	Risk of ionizing radiation exposure to fetus during pregnancy	Acceptable modality	Greatest risk of radiation exposure is at 8 to 15 weeks of gestation
			Oral and iodinated contrast not teratogenic
			Less than 1% of iodinated contrast is excreted in breast milk
MRI	Acceptable modality when performed without contrast	Acceptable modality with and without contrast	Gadolinium is associated with teratogenicity; crosses the placenta and is found in amniotic fluid and fetal circulation. Less than 0.04% is excreted into breast milk
Liver biopsy	Can be performed in pregnancy	Acceptable modality	Limited data on preterm births seen when performed during pregnancy
			Transjugular liver biopsy confers radiation exposure
Transient elastography	Not approved by the FDA for use in pregnancy	Not contraindicated in lactation	–
Endoscopy	Upper endoscopy is acceptable in pregnancy and typically recommended to occur in the second trimester	Acceptable modality with consideration of compatibility of sedating medications with lactation	Ensure proper informed consent with discussion about fetal risks
	Consideration of compatibility of sedating medications with pregnancy		Ensure adequate oxygenation and hemodynamic stability during procedure
			Ensure left lateral decubitus position to avoid IVC compression

Abbreviations: CT, computed tomography; FDA, U.S. Food and Drug Administration; IVC, inferior vena cava; MRI, magnetic resonance imaging.

supplementation. Thiamine and folic acid supplementation are particularly emphasized, and metoclopramide, promethazine, and ondansetron are anti-emetic therapies that are considered as compatible with pregnancy. Dietary modification should focus on consumption of small, frequent, low-fat meals with high carbohydrate content. Enteral or parenteral nutrition can be cautiously considered in severe HG cases.

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders of pregnancy that involve the liver include preeclampsia/eclampsia and the HELLP syndrome. Preeclampsia is seen in about 3% to 5% of pregnancies, and it is defined by the presence of new onset hypertension with a systolic blood pressure of ≥140 mm Hg and a diastolic blood pressure of ≥90 mm Hg measured on at least two occasions that are 4 to 6 hours apart and proteinuria of greater than 300 mg/day.[13] Eclampsia occurs in about 1.4% of pregnancies; it is defined by the development of generalized seizures during preeclampsia. HELLP syndrome occurs in 0.2% to 0.6% of pregnancies and complicates 10% to 20% of cases of preelampsia/eclampsia.[14] Whereas preeclampsia is typically described as occurring after the twentieth week of gestation, HELLP syndrome is predominantly considered as occurring in the third trimester between weeks 28 and 36 of gestation. In 30% of cases, HELLP syndrome presents in the early postpartum period.

HELLP syndrome has been viewed as representing one presentation on a spectrum of clinical manifestations of preeclampsia/eclampsia.[15] Other manifestations of preeclampsia can involve hypertension in the absence of proteinuria, and in this clinical scenario, the presence of end-organ injury in the setting of gestational hypertension can help to define preeclampsia. Due to the dilemma of distinguishing HELLP syndrome along the spectrum of preeclampsia/eclampsia, two diagnostic criteria for HELLP syndrome have been established. The Tennessee Classification categorizes HELLP syndrome as complete HELLP syndrome or partial HELLP syndrome, and the Mississippi Triple Class System divides HELLP syndrome into three classes (Table 3).[16] Both of these classification systems define subtypes of HELLP based on the severity of observed thrombocytopenia, liver enzyme elevations, and hemolysis.

The pathophysiology of preeclampsia/eclampsia and HELLP syndrome is not well understood and likely

TABLE 3. CLASSIFICATION SYSTEMS FOR HELLP SYNDROME

HELLP Class	Mississippi Classification	Tennessee Classification
Class 1 (severe)	AST or ALT ≥70 IU/L LDH ≥600 IU/L Platelet count ≤50 × 10^9/L	AST ≥70 IU/L LDH ≥600 IU/L or bilirubin ≥1.2 mg/dL
Class 2 (moderate)	AST or ALT ≥70 IU/L LDH ≥600 IU/L Platelet count 50-100 × 10^9/L	N/A
Class 3 (mild)	AST or ALT ≥40 IU/L LDH ≥600 IU/L Platelet count 100-150 × 10^9/L	N/A
Partial HELLP syndrome	Presence of severe preeclampsia plus one of the following: ELLP, EL, HEL, LP	

Abbreviations: EL, elevated liver enzymes; ELLP, elevated liver enzymes and low platelets (missing hemolysis); HEL, hemolysis and elevated liver enzymes; LDH, lactate dehydrogenase; LP, low platelets; N/A, not applicable.

involves a combination of immunologic maladaptation, chronic placental ischemia, an increased maternal inflammatory response to trophoblasts, and increases in inflammatory cytokines.[17] Vasospasm is a feature of preeclampsia that likely results from hemoconcentration in conjunction with imbalances between vasoconstrictors (thromboxane A_2 and endothelins) and vasodilators (prostacyclin and nitric oxide), and it may be a contributor to liver injury, which can involve fibrin deposition, periportal hemorrhage, necrosis or infarction of hepatocytes, and microvesicular fat infiltration.[13] Severe liver involvement can lead to hepatic hematoma or rupture. Thrombocytopenia is thought to result from increases in platelet activation and consumption.[18]

The observation of imbalances in thromboxane A_2 and prostacyclin have led to the use of low-dose aspirin in the management of hypertensive disorders of pregnancy. Low-dose aspirin preferentially inhibits thromboxane A_2.[19,20] Meta-analyses and systematic reviews have demonstrated reductions in the risks of preeclampsia, fetal growth restriction, and fetal death with use of low-dose aspirin, and thus it is recommended that low-dose aspirin (81 mg daily) is instituted between 12 weeks and 28 weeks of gestation in patients with high-risk factors for preeclampsia.[13,21-23]

Other medical therapy includes administration of intravenous magnesium to prevent seizures, antihypertensive therapy to maintain systolic blood pressures below 160 mm Hg and diastolic blood pressures below 100 mm Hg, and intravenous dexamethasone to improve platelet counts. Such pharmacologic intervention has been described as The Mississippi Protocol.[24] Elevations in aminotransferase and lactate dehydrogenase levels may persist for up to 48 hours postpartum, but ongoing hepatic, renal, or hematologic complications beyond 72 hours postpartum signal potential life-threatening complications that require urgent therapy. Surgical intervention is required for enlarging subcapsular hematomas or hepatic rupture. Hepatic rupture can also be managed with hepatic arterial embolization.[25] Liver transplantation has been performed in cases of hepatic decompensation despite medical therapy and in cases of hepatic rupture or hematoma.[26] The only curative therapy for preeclampsia/eclampsia and HELLP syndrome is delivery of the fetus.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is a rare disorder that occurs in about 1:7,000 to 1:15,000 pregnancies.[5,27] Typically occurring in the third trimester, it involves maternal microvesicular fat deposition in the liver that leads to hepatic decompensation with potential for hepatic failure. Maternal mortality is 10% to 15%, and fetal mortality is up to 20%.[28,29]

It is thought that AFLP is caused by inherited deficiencies of enzymes that are involved in the mitochondrial metabolism of fetal fatty acids. Impairment in fatty acid oxidation in the fetus and placenta can lead to increases in the levels of intermediate products of metabolism that accumulate in the placenta and maternal blood, leading to maternal hepatotoxicity. The most investigated fatty acid oxidation defect that is thought to contribute to AFLP is a deficiency in long chain 3-hydroxyacyl-coenzyme A-dehydrogenase (LCHAD), which is a part of the mitochondrial trifunctional protein (MTP).[30,31] G1528C and E474Q mutations of MTP are thought to be the cause of LCHAD deficiency and development of AFLP.

The diagnosis of AFLP may be challenging as features of its presentation can present similarly in preeclampsia and HELLP syndrome, both of which have been observed to develop in mothers who are heterozygous for fetal fatty acid oxidation defects and pregnant with homozygous fetuses. The classic description of clinical findings in AFLP includes abdominal pain, nausea, vomiting, fatigue, and anorexia; biochemical

abnormalities include aminotransferase elevations up to 20 times the upper limit of normal and hyperbilirubinemia. Proteinuria, a diagnostic feature of preeclampsia/eclamspia, can also occur in AFLP. Coagulopathy with prolongation in prothrombin times can also present in both disorders, but this is due to hepatic dysfunction in AFLP and due to derangements in consumption in preeclampsia/eclampsia. Thus, the presentation of AFLP is often suggestive of liver dysfunction, whereas the presentations of preeclampsia/eclampsia and HELLP syndrome are typically more suggestive of significant liver injury with less impact on hepatic synthetic function.

In AFLP, ultrasound can demonstrate heterogeneity of the liver parenchyma in a manner that is consistent with fatty infiltration. Liver biopsy can confirm the presence of microvesicular fat deposition in the pericentral zone with periportal sparing. Such fat deposition is confirmed with Oil Red O staining that should be performed on fresh-frozen sections. Liver biopsy is not typically required for diagnosis, and the associated coagulopathy of AFLP may preclude performance of liver biopsy. The diagnosis of AFLP can be facilitated by use of the Swansea criteria, which are combined clinical, laboratory, and radiographic features for which the diagnosis can be made if at least six of the features are present (Table 4). The Swansea criteria have been demonstrated to have 100% sensitivity, 57% specificity, 85% positive predictive value, and 100% negative predictive value in the diagnosis of AFLP.[32]

AFLP management involves prompt delivery of the fetus. Despite delivery, laboratory and clinical abnormalities may persist for up to a week postpartum; rarely, there can be progression to liver failure that requires liver transplantation.[33,34] Fetuses born to mothers with AFLP should be monitored closely as they are at risk of developing liver failure, cardiomyopathy, nonketotic hypoglycemia, myopathy, and neuropathy. Recurrence of AFLP can occur in mothers, and up to 25% of children born to mothers with AFLP will carry fatty acid oxidation defects. Thus, affected patients should be screened.

TABLE 4. SWANSEA CRITERIA FOR ACUTE FATTY LIVER OF PREGNANCY

Class	Feature*
Clinical features	Vomiting
	Abdominal pain
	Polydispsia/polyuria
	Encephalopathy
Laboratory features	Elevated bilirubin (>14 μmol/L)
	Hypoglycemia (<4 mmol/L)
	Elevated urea (>340 μmol/L)
	Leukocytosis (>11 × 10^9/L)
	Elevated transaminases (>42 IU/L)
	Elevated ammonia (>47 μmol/L)
	Elevated creatinine (>150 μmol/L)
	Coagulopathy (prothrombin time >14 seconds or activated partial thromboplastin time >34 seconds)
Radiographic features	Ascites or bright-appearing liver on ultrasound
Histologic features	Microvesicular steatosis on liver biopsy

*In the absence of other causes, six or more features must be fulfilled in order to meet criteria.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disease. Typically presenting in the second or third trimester of pregnancy, the prevalence of ICP is 0.1% to 2%.[35,36] Epidemiologic data have indicated that it occurs with higher prevalence in South American and Scandinavian countries, and additional risk factors for it include advanced maternal age, multiparity, and a previous history of cholestasis with oral contraceptive use. The classic symptom of ICP is pruritus, but epigastric pain, fatigue, anorexia, and jaundice have also been observed. The typical laboratory finding in ICP is an elevation in bile acid levels. AST and ALT levels range from normal levels to 10 times to 20 times normal.

A number of adverse outcomes are associated with ICP, including preterm birth, meconium-stained amniotic fluid, fetal distress, and stillbirth. Given the severity of these complications, the identification and utilization of predictive markers for ICP have been the focus of numerous published investigations. Earlier data from a large Swedish cohort demonstrated that the likelihood of the development of meconium-stained fluid, spontaneous preterm birth, and fetal asphyxia increased by 1% to 2% for every μmol/L of bile acids.[37] Further analysis in this study demonstrated that such complications developed when bile acid levels were greater than 40 μmol/L. A more recent prospective case-control study from the United Kingdom demonstrated similar adverse events in women with ICP whose serum

bile acids were above 40 μmol/L, with a weaker yet significant association of higher ALT levels with these adverse outcomes.[38] Seven of the 10 patients with ICP whose pregnancies were complicated by stillbirth were also diagnosed with other pregnancy-related conditions, including preeclampsia and gestational diabetes, and the median gestational age at stillbirth was 36 weeks. These observations raised concern regarding the possible presence of other concurrent conditions that could influence outcomes of severe presentations of ICP, and it provided data to support consideration for delivery at 37 weeks of gestation in ICP. More recent data from a systematic review on perinatal outcomes in ICP identified an increased risk of stillbirth in ICP when serum bile acid levels are 100 μmol/L or higher.[39] In this study, transaminase and bilirubin levels were not significant predictors of negative obstetric outcomes; however, increased rates of concurrent preeclampsia and gestational diabetes were seen in women with ICP compared to those without ICP, thus supporting previously identified concerns regarding the presence of other concurrent pregnancy-related conditions that could influence outcomes of severe presentations of ICP. The reason for fetal distress and stillbirths in ICP has not been fully elucidated, but observations of fetal tachyarrhythmia with atrial flutter and left ventricular dysfunction in fetuses of women with ICP provide concern for a cardiac source of these adverse events.[40-42] Earlier clues of this include observations of toxic effects of bile acids on the myocardium of rats, but the pathophysiology of such toxicity is still under investigation.[43-45] Recent data have also demonstrated an association of ICP with later development of hepatobiliary cancer, cardiovascular disease, and immune-related disease, including diabetes mellitus and thyroid disease.[46] However, more studies are needed to elucidate the potential mechanisms for and strength of these associations.

Historically, the recommended treatment for ICP has been ursodeoxycholic acid (UDCA) at a dose of 10-15 mg/kg/day. ICP is thought to be due to a genetic mutation in bile salt transport across the transport membrane. The most common of these mutations is an adenosine triphosphate-binding cassette transporter B4 (ABCB4) mutation that encodes the multidrug resistance protein 3, which is a major transporter of phospholipids across the canalicular membrane into bile.[47] Other mutations include the ABCB11 gene mutation, which is a mutation in the bile salt export pump (BSEP).[48] It is thought that UDCA may increase placental bile transporters and increase BSEP expression.[49] It has been shown to significantly reduce pruritus and reduce ALT and bile acid levels.[50] However, more recent data from a multicenter, randomized, placebo-controlled trial investigating the effect of UDCA on perinatal outcomes concluded that UDCA does not significantly reduce the incidence of fetal death, preterm delivery, or fetal distress.[51] Studies are ongoing to determine if there is pharmacologic intervention for ICP that will significantly reduce the incidence of adverse outcomes.[52] At this time, appropriate delivery planning with consideration for delivery by 37 weeks of gestation is the intervention with clearly demonstrated benefit in obstetric outcomes for pregnancies affected by ICP.

Primary Liver Diseases That Are Concurrent With Pregnancy

HEPATITIS B

The clinical presentation of hepatitis B virus (HBV) infection in pregnancy is similar to the course of HBV infection in patients who are not pregnant. Although many such patients may be asymptomatic, nausea, vomiting, jaundice, and abdominal pain can be seen, particularly in acute HBV infection. However, obstetric outcomes are not significantly affected by HBV infection. Mother to child transmission (MTCT) and early childhood acquisition of HBV infection are modes of transmission in 50% of persons worldwide who develop chronic HBV infection.[53] The presence of hepatitis B e antigen positivity and levels of hepatitis B viremia are the two most significant maternal risk factors for MTCT of hepatitis B. Hepatitis B immunoprophylaxis has been shown to significantly reduce the rate of MTCT of HBV infection, but immunoprophylaxis failures of 8% to 10% have been observed.[54,55] Immunoprophylaxis consists of administration of hepatitis B immunoglobulin and hepatitis B vaccination within the first 12 hours after birth and subsequent scheduled administration

of hepatitis B vaccination at 1-2 months of age and again at 6 months of age. In order to further reduce the risk of MTCT, American Association for the Study of Liver Diseases (AASLD) guidance on hepatitis B recommends antiviral therapy for mothers with HBV DNA levels of greater than 200,000 IU/mL.[56] Whereas lamivudine, telbivudine, and tenofovir have been shown to be compatible with pregnancy, tenofovir is a preferred antiviral therapy due to its potency and lower likelihood of resistance. Breastfeeding is not contraindicated in cases where immunoprophylaxis has been administered, and due to observations of low levels of antiviral agents in breast milk, AASLD guidance does not recommend against breastfeeding in mothers who are on antiviral therapy.

HEPATITIS C

It is observed that the worldwide prevalence of HCV infection is 8%, and the prevalence in the United States is 1% to 2.5%.[57,58] Recent data on a large cohort of U.S. women demonstrated increases in acute HCV infection in women of childbearing age during 2006 to 2014, and this observed increased incidence is thought to be related to the observed rise in injection drug use among this population cohort.[59] MTCT transmission of HCV is 5% to 6% in cases of HCV monoinfection but can rise to as high as 22% in cases of co-infection with human immunodeficiency virus (HIV). Most presentations of HCV infection in women who are pregnant are presentations of chronic asymptomatic infection. Maternal outcomes of HCV infection are similar to HCV outcomes in patients who are not pregnant. However, there are conflicting data about obstetrical outcomes. Although some data have suggested that HCV infection does not affect obstetrical outcomes, other data have indicated associations of HCV infection with gestational diabetes, preterm delivery, low birth weight, requirements for neonatal intensive care, and the presence of ICP.[60,61] No HCV immunoprophylaxis exists, and the mode of delivery of fetuses born to mothers with HCV infection should be based on obstetrical indications. However, it is recommended that fetal scalp monitoring is avoided due to reports of an increased risk of HCV transmission with this peripartum mode of monitoring.[62]

Current HCV therapy consists of direct-acting antiviral therapies for which safety data in pregnancy and lactation are lacking. Thus, HCV therapy is not recommended in women who are pregnant or breastfeeding. However, recently presented conference data on a phase 1 study of ledipasvir/sofosbuvir in women who were pregnant and had HCV infection demonstrated achievement of rapidly undetectable HCV viral loads during pregnancy and sustained virologic response without significant adverse events.[63] A recent case report of HCV therapy in a woman who was pregnant and had controlled HIV infection revealed a successful 6-week treatment with sofosbuvir alone that was followed by a 6-week course of sofosbuvir and velpatasvir.[64] The infant born to this patient was without birth defects and was HCV negative at birth. Recent guidance statements from AASLD and the Infectious Diseases Society of America have emphasized a recommendation for universal HCV screening in women who are pregnant.[65] The United States Preventive Services Task Force recently issued a draft statement that recommends screening for hepatitis C in all adults 18 to 79 years of age.[66] Public comment regarding this recommendation has been solicited, and a final recommendation statement is currently pending. Establishment of this recommendation in clinical practice would support the existing societal recommendations for universal HCV screening in women who are pregnant.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) activity is variable in women who are pregnant. Flares can be seen during pregnancy in 20% of women who are pregnant and can occur postpartum in 30% to 50%.[67] Flares occur more commonly in women with AIH who are not on therapy and in women who experienced an AIH flare in the year before pregnancy. It is not well understood as to why some women will have AIH flares either during pregnancy or postpartum, but it is believed that changes in immune tolerance and the effect of hormone concentrations on immunologic responses may influence the likelihood of pregnancy-related AIH flares.[68] Compared to women with AIH but with no cirrhosis, women with AIH-related cirrhosis are more likely to have pregnancies that are complicated by lower birth rates, higher rates of prematurity and need for neonatal intensive care, maternal hepatic decompensation, and need for liver transplantation and death.[69]

Due to the potential for negative health outcomes associated with antepartum and postpartum flares, it is important that AIH activity is monitored closely and is well controlled before and during pregnancy and in the early postpartum period. Standard AIH treatment consists of corticosteroids and azathioprine, although it is noted that mycophenolate mofetil is an acceptable alternative agent if standard therapy is not tolerated.[70] Despite the lack of meta-analyses and systematic reviews on AIH therapy in pregnancy, observational data about the use of corticosteroids and azathioprine in other immunologic diseases support the use of these therapies in AIH.[71] It is recommended that women with AIH who become pregnant continue on an immunosuppression regimen throughout their pregnancies that allowed them to achieve stable liver function before pregnancy. Azathioprine is an acceptable alternative to mycophenolate use in women with AIH who are pregnant and in women who are contemplating pregnancy.

NAFLD

There are emerging data on the epidemiology, natural history, and clinical manifestations of NAFLD in pregnancy. It is estimated that the incidence of NAFLD in women of childbearing age is 10%.[72] NAFLD is considered as a hepatic manifestation of the metabolic syndrome and is an endpoint of a complex combination of adipose tissue dysfunction with increased lipolysis and insulin resistance, defects in hepatic clearance of lipids, *de novo* hepatic lipogenesis, and lipotoxicity with oxidative stress and mitochondrial dysfunction.[73] In the first two thirds of pregnancy, maternal hyperphagia and increases in lipogenesis lead to increased fat stores, whereas maternal catabolism in the third trimester leads to enhanced adipose tissue lipolysis with increased levels of free fatty acids and glycerol that are metabolized and re-esterified for the production of triglycerides, including very low-density lipoproteins.[74] These changes in lipid metabolism as well as observations of pregnancy-related insulin resistance may foster a metabolic milieu that predisposes to the development of NAFLD and its associated comorbid conditions in pregnancy. Data have demonstrated that sonographic evidence of hepatic steatosis is predictive of the development of gestational diabetes mellitus and dysglycemia with impaired glucose tolerance and impaired glucose fasting.[75] Other data have demonstrated an association of gestational diabetes mellitus with increased odds of subsequent NAFLD development in middle age.[76] Adverse obstetric outcomes, including increased odds of preeclampsia, cesarean section, preterm birth, and low birth weight, are associated with NAFLD in women who are pregnant.[77] These observations suggest a need for careful prepregnancy and interpregnancy planning, with careful query of possible factors in personal or family histories that are potential markers for metabolic syndrome as well as the need for postpartum assessments for metabolic syndrome in women with pregnancies that have been complicated by states of metabolic disarray, such as obesity, gestational diabetes mellitus, and preeclampsia.[78]

CIRRHOSIS AND PORTAL HYPERTENSION

Pregnancy in cirrhosis has been reported to occur at a rate of 45 cases of cirrhosis per 100,000 childbearing women.[79] This lower likelihood of pregnancy in women with cirrhosis is related to hypothalamic–pituitary dysfunction in cirrhosis that leads to amenorrhea and anovulation. In pregnancy, portal pressures increase due to plasma volume expansion and compression of the inferior vena cava during the second and third trimesters, and this pregnancy-related rise in portal pressures can augment the expression of complications of portal hypertension, which include ascites and varices.

Data are evolving regarding the incidence of medical and obstetrical complications of cirrhosis and portal hypertension. Historically, rates of bleeding from esophageal varices in pregnancy were reported to be as high as 30% with a risk of variceal hemorrhage increasing to 50% to 78% in the setting of preexisting varices.[79-81] However, more recent data from the United States Nationwide Inpatient Sample database have observed rates of variceal hemorrhage of 5% in women with cirrhosis who were pregnant, and recent data from the Swedish Medical Birth Register and Swedish National Patient Register identified only one case of bleeding esophageal varices in 103 pregnancies in women with cirrhosis.[82,83] Reported obstetrical complications in women who are pregnant have included increased rates of low birth weight, placental abruption, preterm delivery, and cesarean section.

Endoscopy as screening for varices is recommended in women with cirrhosis who are pregnant and should be performed during the second trimester because organogenesis has occurred by that stage of pregnancy.[84] Management of varices in pregnancy is similar to management of varices in patients who are not pregnant. If variceal band ligation is pursued for esophageal varices, this should continue with a goal of eradication of varices as in patients who are not pregnant. Although there have been reported associations of beta blockers with intrauterine growth retardation and neonatal bradycardia, nonselective beta blocker therapy can be used as variceal bleeding prophylaxis in pregnancy. Nadolol has low protein binding and low rate of excretion and is less favored than propranolol, which is thought to be compatible with pregnancy. Historically, there have been concerns about the safety of transjugular portosystemic shunt (TIPS) insertion during pregnancy, mostly due to concerns about radiation risks. Data on TIPS insertion in pregnancy are limited mostly to case reports and case series. Although one such case series reported one fetal death that was not related to TIPS, other data have suggested that TIPS insertion can occur without maternal or fetal mortality.[85,86] Ascites and hepatic encephalopathy can be managed in pregnancy similar to how such cirrhosis-related complications are managed in patients who are not pregnant.

Future Directions: Noninvasive Testing and Prognostic Models

In recent years, significant advances have been made in the development and implementation of noninvasive tests and scoring systems for the diagnosis, staging, and prediction of outcomes of liver diseases. Multiple investigations have evaluated whether such noninvasive testing can be predictive of outcomes of liver disease in pregnancy. The Model for End-Stage Liver Disease (MELD), MELD-sodium, United Kingdom End-Stage Liver Disease (UKELD), and Child-Pugh scores were evaluated in a cohort of 29 women with cirrhosis who were pregnant, and higher MELD (greater than or equal to 10) and UKELD scores (greater than or equal to 47) at conception were identified as significant predictors of liver-related adverse events, such as variceal hemorrhage, hepatic encephalopathy, and the development of significant ascites.[87] In this cohort, it was also observed that a platelet count before conception of 110×10^9 cells/L or less had 78% sensitivity and 89% specificity in predicting the presence of varices on screening endoscopy performed during the second trimester of pregnancy. A more recent investigation of the albumin–bilirubin score and the AST to platelet ratio index determined that these measures in preconception were predictive of live birth and of the ability of pregnancies in women with chronic liver disease and cirrhosis to progress beyond 37 weeks of gestation.[88] Investigators in Germany performed transient elastography on healthy women who were pregnant and on women with pregnancy-related liver disease (preeclampsia and ICP).[89] They observed that liver stiffness increased in healthy women who were pregnant across pregnancy (mean kilopascal [kPa] score of 4.5 kPa in the second trimester to mean kPa score of 6.0 kPa in the third trimester); a liver stiffness score of greater than 8 was seen in 6% and greater than 12.5 kPa was seen in 1.5% of healthy women who were pregnant. Liver stiffness scores declined after delivery. Mean liver stiffness scores were significantly higher in preeclampsia (17.9 kPa) and in ICP (6.9 kPa) than in healthy women who were pregnant. It is noted that transient elastography is currently not approved by the U.S. Food and Drug Administration for use in pregnancy. Such noninvasive testing in pregnancy needs further study but may offer future opportunities for lower risk assessments of the severity of liver disease in women who are pregnant.

The successful management of liver disease in pregnancy requires a multidisciplinary approach with close collaboration between internists, hepatologists, and obstetricians. Evolving data have been helpful in expanding insights into the impact of liver disease on maternal and fetal health. Efforts are underway to explore newer diagnostic and therapeutic approaches to such diseases.

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