ABSTRACT

Abnormal liver tests occur in 3%-5% of pregnancies, with many potential causes, including coincidental liver disease (most commonly viral hepatitis or gallstones) and underlying chronic liver disease. However, most liver dysfunction in pregnancy is pregnancy-related and caused by 1 of the 5 liver diseases unique to the pregnant state: these fall into 2 main categories depending on their association with or without preeclampsia. The preeclampsia-associated liver diseases are preeclampsia itself, the hemolysis (H), elevated liver tests (EL), and low platelet count (LP) (HELLP) syndrome, and acute fatty liver of pregnancy. Hyperemesis gravidarum and intrahepatic cholestasis of pregnancy have no relationship to preeclampsia. Although still enigmatic, there have been recent interesting advances in understanding of these unique pregnancy-related liver diseases. Hyperemesis gravidarum is intractable, dehydrating vomiting in the first trimester of pregnancy; 50% of patients with this condition have liver dysfunction. Intrahepatic cholestasis of pregnancy is pruritus and elevated bile acids in the second half of pregnancy, accompanied by high levels of aminotransferases and mild jaundice. Maternal management is symptomatic with ursodeoxycholic acid; for the fetus, however, this is a high-risk pregnancy requiring close fetal monitoring and early delivery. Severe preeclampsia itself is the commonest cause of hepatic tenderness and liver dysfunction in pregnancy, and 2%-12% of cases are further complicated by hemolysis (H), elevated liver tests (EL), and low platelet count (LP) - the HELLP syndrome. Immediate delivery is the only definitive therapy, but many maternal complications can occur, including abruptio placentae, renal failure, subcapsular hematomas, and hepatic rupture. Acute fatty liver of pregnancy is a sudden catastrophic illness occurring almost exclusively in the third trimester; microvesicular fatty infiltration of hepatocytes causes acute liver failure with coagulopathy and encephalopathy. Early diagnosis and immediate delivery are essential for maternal and fetal survival.

<table>
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<th>Disease</th>
<th>Timing of occurrence</th>
<th>Clinical features</th>
<th>Histology</th>
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<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>First trimester</td>
<td>Nausea, vomiting, weight loss, nutritional deficiency</td>
<td>No distinct histopathology, may see normal tissue or hepatocyte necrosis, bile plugs, steatosis</td>
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<tr>
<td>Preeclampsia/eclampsia</td>
<td>Second/third trimester</td>
<td>Hypertension, edema, proteinuria, neurological deficits (headaches, seizures, coma)</td>
<td>Periportal hemorrhage, necrosis, fibrin deposits, may see microvesicular fat</td>
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<td>Syndrome of hemolysis, elevated liver tests, and low platelets (HELLP)</td>
<td>Third trimester</td>
<td>Abdominal pain, nausea, vomiting, edema, hypertension, proteinuria</td>
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<td>Acute fatty liver of pregnancy (AFLP)</td>
<td>Third trimester</td>
<td>Nausea, vomiting, abdominal pain, fatigue, jaundice</td>
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<td>Intrahepatic cholestasis of pregnancy (ICP)</td>
<td>Second/third trimester</td>
<td>Pruritus, jaundice, fatigue, abdominal pain, steatorrhea</td>
<td>Centrilobular cholestasis, no inflammation</td>
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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. The incidence of HG varies from 0.3%-2% of all live births. HG often occurs between the 4th and 10th wk of gestation and usually resolves by the 20th wk. However, in approximately 10% of HG patients, symptoms continue through pregnancy and resolve only with delivery of the fetus. Liver involvement is seen in about 50%-60% of patients with HG. 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). 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 8. 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 7. 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.

**PREECLAMPSIA/ECLAMPSIA**

Preeclampsia 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 4. 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 9. 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 perportal hemorrhage, liver cell necrosis, and in severe cases, infarction; these changes are likely due to vasoconstriction of hepatic vasculature 10. Microvesicular fatty infiltration has also been observed in some cases of preeclampsia, suggesting a possible overlap with acute fatty liver of pregnancy 11. Maternal mortality from preeclampsia/eclampsia is rare in developed countries, but may approach 15%-20% in developed countries 8. Likewise, the fetal mortality rate is rare, occurring in 1%-2% of births. The only effective treatment for preeclampsia is delivery of the fetus and placenta. 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)**

HELLP syndrome is a multisystemic disorder of pregnancy involving hemolysis, elevated liver tests, and low platelets. About 70% of cases occur antenatally, during the last trimester of pregnancy 12. 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. 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.

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 10,000 to 1 in 15,000 pregnancies, it has a maternal mortality rate of 18% and a fetal mortality rate of 23%. 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 longchain 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. 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. Laboratory findings include elevations in aminotransferase levels, which may range from being mildly elevated to approaching 1000 IU/L.

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. Therefore, the diagnosis of AFLP is usually made on clinical and laboratory findings.

Histology of Hemolysis, elevated liver enzymes, low platelet count syndrome

Pathogenesis involve 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, intravascular asphyxia, and prematurity. 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. However, most laboratory values (transaminases, bilirubin, LDH) normalize in 48 h. For patients with ongoing or newly developing postpartum symptoms of HELLP, modalities such as antithrombotic agents, plasmapheresis, and dialysis may be employed.
As with most pregnancy-associated liver diseases, the treatment of AFLP involves delivery of the fetus. In rare cases, patients will progress to fulminant hepatic failure with need for liver transplantation. 24 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.

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 1/10 000. 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. 18 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. 19 The etiology of ICP is likely multifactorial and variations. Mutations in the phospholipid translocator known as the ATP-cassette transporter B4 (ABC B4) or multidrug resistant protein-3 (MDR3) are associated with the development of ICP. 20 Changes induced by these genetic mutations lead to increased sensitivity to estrogen, which impairs the sulfation and transportation of bile acids. 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. 21 The elevation in bile acid levels is also thought to possibly 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. 22, 23

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 hours 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. 24 Cholelithiasis and cholecystitis have been observed to occur with greater frequency in women with ICP. 25 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. 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. 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. 26 Other medications, such as cholestramine and S-adenosyl-L-methionine, have been associated with improving pruritus and normalizing biochemical profiles, but studies have found UDCA to be superior over cholestramine and S-adenosyl-L-methionine. 27, 28 Dexamethasone has also been used, but has shown to be much less effective in reducing bile acids and bilirubin and ineffective in relieving pruritus. 29 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.

COMMON LIVER DISEASES AND PREGNANCY

Viral Hepatitis

Viral hepatitis is the most common form of liver disease worldwide and it frequently affects women of childbearing age, either as an acute infection or as a chronic disease. Hepatitis A does not appear to alter the normal course of pregnancy nor does pregnancy appear to influence the natural history of hepatitis A. Acute and chronic viral hepatitis of other types however may have implications for maternal well-being as well as the outcome of gestation.

HEPATITIS ‘E’

Hepatitis E virus infection occurs in non-industrialized nations, usually as an epidemic disease during the monsoon season in central and south Asia and India; it is rare in the West. Acute hepatitis E during the third trimester of pregnancy is a cause of fulminant hepatic failure and has a mortality rate of up to 20%. 30 Maternal Hepatitis E virus infection also has been associated with intrauterine fetal death. 31, 32 The risks of intrauterine death and abortion in any trimester are greater in pregnant women with hepatitis E than they are in their uninfected counterparts. Maternal-fetal transmission of hepatitis E resulting in symptomatic neonatal hepatitis has occurred; no known therapy will prevent vertical transmission of this virus.

HEPATITIS ‘B’

As a rule maternal hepatitis B virus infection does not influence the course of pregnancy nor does pregnancy alter the natural history of maternal hepatitis B. Most women of childbearing age with chronic hepatitis B are healthy virus carriers with a very low risk of developing complications of their disease during gestation. The importance of hepatitis B during pregnancy is related to its role in the perpetuation of chronic infection through vertical transmission. Maternal-fetal transmission of hepatitis B virus is responsible for most cases of chronic hepatitis B worldwide especially in Southeast Asia and Africa. 34 Mothers with a reactive serum test for hepatitis B e antigen (HBeAg) have more circulating...
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Hepatitis B

Women with chronic hepatitis B are not treated with hepatitis B vaccine during the first day of life and at ages 1 and 6 months 37. Women with chronic hepatitis B are not treated with interferon during pregnancy. Therapy with the nucleoside analog, lamivudine is probably safe in pregnant patients and has been reported to reduce the incidence of neonatal vaccination failure 38. Data concerning the toxicity and efficacy in this setting of adefovir dipivoxil a newer nucleotide analog of adenosine monophosphate and of entecavir a guanosine nucleoside analog are insufficient to allow any conclusion.

Hepatitis 'C'

HCV infection in pregnancy has a presentation that is similar to that of HCV infection in non-pregnant patients. 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) 39. 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 40. 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 41.

Combination antiviral therapy with pegylated interferon and ribavirin is generally recommended for HCV-infected patients. Ribavirin has a category X designation by the FDA. Interferon has a designation as category C, as it has been shown to have abortifacent effects in animal models. 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 42-44.

Chronic Liver Disease & Portal Hypertension

Fertility is decreased in women with significant hepatic dysfunction due to hypothyroidic-pituitary dysfunction. However, cirrhosis is not a contraindication, as pregnancy may be tolerated if cirrhosis is well-compensated and without features of portal hypertension 45. Portal hypertension leads to increased maternal complications, including variceal hemorrhage, hepatic failure, encephalopathy, jaundice, malnutrition, and splenic artery aneurysm 46. Bleeding from esophageal varices has been reported in 20%-25% of pregnant women with cirrhosis 47. 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 48. 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 49.

Wilson Disease

Wilson disease in women of childbearing age is associated with amenorrhea and infertility. Treatment of affected individuals to remove excess copper may result in resumption of ovulatory cycles and subsequent pregnancy. Pregnant patients must remain on medication to treat Wilson disease because discontinuation of therapy can cause sudden copper release hemolysis, acute liver failure and death 50. D-penicillamine is potentially teratogenic in humans 51 but has been used safely during pregnancy at doses necessary for copper chelation 52. D-penicillamine is potentially teratogenic in humans but appears to be safe in humans as treatment for copper overload. Zinc is not teratogenic and some experts favor its use during pregnancy as therapy for Wilson disease for this reason 53.

Autoimmune Liver Disease

Autoimmune diseases of all types including autoimmune hepatitis are more common in women than in men. In women, classic (type 1) autoimmune hepatitis typically presents around the expected time of menarche but is associated with amenorrhea. Immunosuppressive therapy is highly effective in controlling the disease in most patients; treated women who subsequently conceive a child should continue taking immunosuppressive medications during pregnancy. The doses of azathioprine prescribed as part of standard treatment regimens are belived not to be teratogenic. Occasionally autoimmune liver disease will worsen during the postpartum period when the physiologic immunosuppression of pregnancy resolves. For this reason affected patients should have frequent measurements of serum aminotransferase levels for approximately 6 months after delivery.
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