24 Hepatic disorders in pregnancy

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Liver disease in pregnancy is uncommon, and in the majority of cases, there is no need for a change in the management of liver disorder till pregnancy ceases. Most often, abnormalities in liver tests are related to conditions not specific to pregnancy. The liver is affected both physiologically and anatomically during the course of pregnancy. As pregnancy progresses, the liver is squeezed toward the chest and, therefore, a palpable liver below the right subcostal region is indicative of under-going hepatic disorder.

Liver diseases in pregnancy are classified into those not specific to pregnancy and those unique to pregnancy. Furthermore, liver diseases unique to pregnancy are classified according to their onset during pregnancy and their association with pre-eclampsia. In this chapter, we will review changes in liver anatomy and function during pregnancy, liver diseases not specific, and liver diseases unique to pregnancy.

LIVER ANATOMY, HISTOLOGY, AND FUNCTION IN PREGNANCY

Anatomically, the liver is generally not palpable below the right costal margin secondary to the enlarging gravid uterus. Both liver size and gross appearance do not change during pregnancy. Furthermore, minimal histologic changes occur in pregnancy. These include cellular and nuclear pleomorphism, increased numbers of binucleate cells, steatosis, increased cellular and nuclear glycogen, hypertrophied Kupffer cells, and some lymphocytic infiltration of the portal tracts. During normal pregnancy, plasma volume is increased by 50% to 70% and reaches its maximum by 32 to 34 weeks of pregnancy. This results in hemodilution of all serum protein concentrations. Serum albumin concentration decreases, but the rates of albumin synthesis and catabolism are not affected. Hypoalbuminemia can occur in the third trimester regardless of liver disease. However, prolongation of prothrombin time (PT) and hyperbilirubinemia would raise the concern of significant liver disease. Other serum protein concentrations such as alpha-2-macroglobulin, alpha-1-antitrypsin, and ceruloplasmin are increased. Pregnancy is characterized by a hypercoagulable state and increased risks of deep venous thrombosis. Almost all coagulation factors increase during pregnancy except protein S. Moreover, fibrinolysis is inhibited. This physiologic state tends to decrease the risk of bleeding during delivery; however, it increases the risk of maternal venous thrombosis. Indeed, PT is generally not affected during pregnancy and any changes in PT should be considered abnormal and justify further investigation. Serum lipid concentrations increase in late pregnancy secondary to increased levels of estrogen and progesterone. Elevations in estrogen and progesterone levels enhance cholestasis and production of lithogenic bile and reduce gallbladder motility. These alterations predispose pregnant women for gallstone and biliary sludge formation. Measurement of serum lipids in

pregnancy is rarely useful unless in the setting of acute pancreatitis. During pregnancy, the total red cell mass is actually increased but rapidly decreases as pregnancy ceases. The cardiac output increases but the absolute hepatic blood flow remains unchanged. Plasma volume increases specially during the second trimester resulting in falling hemoglobin levels due to hemodilution. Serum aminotransferases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] are not altered by pregnancy and are considered the most useful test indicative of hepatocellular injury. Serum alkaline phosphatase activity levels rise during the third trimester as a result of increased production of placental and bone isoenzymes. Indeed, measurement of serum alkaline phosphatase activity is not a suitable test for the diagnosis of cholestasis during pregnancy. Total and free bilirubin concentrations are decreased during pregnancy partly due to hemodilution (Table 1). Gilbert's syndrome is characterized by an increase in unconjugated hyperbilirubinemia with absolute normal aminotransferases. The management of pregnant women with Gilbert's syndrome is not any different than those who are not pregnant, and medical reassurance should be provided. The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is associated with indirect hyperbilirubinemia and should be differentiated from Gilbert's syndrome. Pregnancy is also associated with mild increase in serum bile acids secondary to reduced bile salt transport. Measurement of serum bile acid concentrations may be useful for the diagnosis of cholestasis during pregnancy.

PHYSICAL EXAMINATION DURING NORMAL PREGNANCY

Spider naevi and palmar erythema are commonly observed during pregnancy and in oral contraceptive receivers. Spider naevi consist of a central arterial vessel from which small capillaries lead off radially. These are found in 53% by the 9 months of pregnancy (1) and tend to be more common among white women. Palmar erythema is frequently observed in patients with chronic liver disease and in pregnancy. It manifests itself as a diffuse patchy erythema of the palms up to the start of the wrist joint. Occasionally, the soles of the feet are also affected, hence the name plantar erythema. Palmar erythema is observed in 63% of white women and 35% of black women during pregnancy (2). Scratch marks and pruritus are found in cases with cholestasis and biliary cirrhosis. Pregnancy is considered a pruritogenic state. The cause of this unbearable itching is deemed to be due to a decrease in bile salt transport secondary to a reduction in both sinusoidal and canalicular bile salt transporters. The concentration of bile salts in blood is within normal range in most pregnant women, but levels of unconjugated chenodeoxycholic acid are higher in late pregnancy. Anatomically, the liver

is displaced toward the chest by an enlarging uterus and palpable liver is considered abnormal in pregnancy. It is important to screen for cirrhosis in the physical examination of pregnant women with viral hepatitis. Detection of cirrhosis may not always be easy because spider angioma and palmar erythema can be seen in both cirrhotic and pregnant states. However, evidence for splenomegaly is suggestive of cirrhosis.

LIVER DISEASE NOT SPECIFIC TO PREGNANCY

Viral Hepatitis

Viral hepatitis is the most common cause of jaundice in pregnancy. The hepatotropic viruses (hepatitis A, B, C, D, E, non-A, and non-B) are responsible for the majority of these infections and accounts for 40% of jaundice in pregnant women in the United States (3). The course and outcome of viral hepatitis is no different in pregnant patients than in other individuals except in the case of hepatitis E, which has been associated with a higher morbidity and mortality in pregnant women in the third trimester (4).

Table 1 Biochemical Changes During Normal Pregnancy	
Test	Change
White cell count	↑
Hemoglobin	↓
Platelets	—
Albumin	↓
Aminotransferases	—
Alkaline phosphatase	↑
GGT	—
Bilirubin	—/↓
Prothrombin time	—
Fibrinogen	↑
Globulins	↑ in α and β globulins and ↓ in γ globulin
Glucose	—
Creatinine	—
Uric acid	—
Bile acids	—
Cholesterol	↑
Triglycerides	↑
Alpha-fetoprotein	↑
Ceruloplasmin	↑
Ferritin	↑
Abbreviation: GGT, gamma glutamyl transpeptidase.	

Herpes hepatitis is an extremely rare disease in immuno-competent adults with an associated mortality of 39% (5). Most infections occur in the third trimester of pregnancy. Altered CD4/CD8 lymphocyte ratio and impaired natural killer cell function are blamed for the development of systemic herpes virus infection. Hepatitis manifests with coagulopathy, markedly elevated liver transaminases (>1000IU), and low bilirubin. Liver biopsy reveals coagulative necrosis, multi-nucleated cells with ground-glass intranuclear inclusions, and peripheral chromatin condensation (6). Early treatment with intravenous acyclovir is lifesaving.

The diagnosis of viral hepatitis is usually made on the basis of serologic testing (Table 2). Although viral hepatitis is not associated with teratogenicity, transmission of viral infection to the fetus may occur, which may result in premature labor. Transmission of infection is believed to occur primarily during the peripartum. For some infections, measures can be taken to prevent or lessen the severity of hepatitis in the newborn.

Hepatitis A

Hepatitis A virus (HAV) is a small, spherical RNA virus that usually causes a self-limiting clinical hepatitis. The virus is transmitted by the fecal–oral route and replicates exclusively within the hepatocytes and is excreted in bile. HAV infection does not lead to chronic hepatitis but relapsing cholestatic hepatitis have been described (7). The average incubation period is about 28 days (range 15–50 days). Fecal shedding occurs for about 2 weeks after infection. The overall case-fatality ratio is less than 1%. Intrauterine transmission of HAV is very rare but perinatal infection could occur. Acute HAV infection during pregnancy is associated with high risk of maternal complications and preterm labor (8). Serologic diagnosis of acute HAV is made by the presence of anti-HAV IgM. Anti-HAV IgM is typically present for several weeks but may be present for up to 1 year. The presence of anti-HAV IgG antibody denotes immunity either by previous infection or vaccination and confers long-lasting immunity. Intrauterine transmission of HAV is very rare; however, perinatal transmission can occur. Neonates of mothers who acquire HAV in the last trimester should receive immune globulin (IG) at the time of delivery (9). Pregnant women who travel to an endemic area should receive prophylactic IG. Individuals who are exposed to acute HAV should receive IG within 10 days of exposure. Studies show that post-exposure prophylaxis can prevent

Table 2 Serologic Diagnosis of Common Viral Hepatitis in Pregnancy				
Virus	Acute	Chronic	Recovered	Immunity
Hepatitis A	Anti-HAV IgM	Not applicable	Anti-HAV IgG	Anti-HAV IgG
Hepatitis B	Anti-HBc IgM	Anti-HBc total	Anti-HBc total	Anti-HBs Ag
	HBs Ag	HBs Ag		
	HBe Ag	HBe Ag ^a /e Ab	Anti-HBs Ag	
Hepatitis C	HCV RNA	Anti-HCV Ab	Anti-HCV Ab	Not applicable
	Anti-HCV Ab +/-	HCV RNA	HCV RNA -	
Hepatitis D	Anti-HDV IgM	Anti-HDV	Anti-HDV Total ^b	Not applicable ^c
	HD Ag ^b	HD Ag ^b		
	HBs Ag	HBs Ag		
Hepatitis E	Anti-HEV IgM	Anti-HEV IgG	Anti-HEV IgG	Not applicable
^a HBeAg will be present during periods of high replication. ^b Markers of hepatitis B infection will also be present because HDV cannot replicate without HBV. ^c Although no specific vaccine for hepatitis D exists, individuals vaccinated for HBV will be protected from infection with HDV. <i>Abbreviations:</i> HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.				

infection or lessen its severity in those who become infected. Mothers infected with HAV are encouraged to breast-feed and HAV infection is not a contraindication for breast-feeding (10).

Hepatitis B

Hepatitis B virus (HBV) is a 3.2kb, circular, partially double-stranded deoxyribonucleic acid (DNA) virus belongs to the Hepadnavirus group. HBV can result in both acute and chronic infections. Carriers with chronic HBV are at risk for the development of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (11). A person is said to be a hepatitis B surface antigen (HBsAg) carrier if serum HBsAg has persisted for more than 6 months; if the clinical and chemical findings fail to show any signs of acute hepatitis; and if no or minimal histologic changes are detectable. HBV is generally noncytolytic but liver injury is attributed to host immune response. In contrast to HCV that replicates in the cytoplasm of the hepatocytes, HBV (dsDNA) enters into the nucleus and is converted to covalently closed circular form known as cccDNA (12). This is remarkably a stable species from which all viral mRNAs are transcribed and is resistant to antiviral therapy. The virus is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact. Vertical transmission is very infrequent in the first and second trimesters, yet prevails in the third trimester. With the coexistence of HBsAg, HBeAg, and high HBV DNA in the third trimester, the child is nearly always infected. Perinatal transmission of HBV infection represents the single largest cause of chronically infected individuals worldwide (13). An estimated 350 million persons worldwide are chronically infected with HBV (14). North America, Northern Europe, and the Oceanic areas are low prevalence areas (<2%) (15,16). In the United States, there are an estimated 1.25 million hepatitis B carriers, defined as persons positive for HBsAg for more than 6 months (16). The incubation period is 25 to 180 days. The age at which HBV infection occurs is an important factor affecting the outcome. The earlier the infection occurs, the higher is the risk for chronicity. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers to 25% to 30% in infants and children under 5 and to less than 5% in adults. The diagnosis of acute HBV infection is established by the presence of positive serum HBsAg and the IgM fraction of the antibody to hepatitis B core (anti-HBc IgM). Pregnant women who had an immediate exposure to hepatitis B virus may be given injection of hepatitis B immunoglobulin (HBIG) ideally within 72 hours of exposure and hepatitis B vaccine within 7 days of exposure (17). Hepatitis B vaccine is generally safe in all trimesters of pregnancy. The current HBV screening guidelines from the Centers for Disease Control and Prevention, the American College of Obstetrics and Gynecology, and the Immunization Practices Advisory Committee recommend that all pregnant women be tested for HBsAg during each pregnancy and that women at high risk for chronic hepatitis B be screened on admission for delivery, even if they previously have been tested or vaccinated (18). HBsAg-positive women who are pregnant should be counseled and make sure that their providers are informed so hepatitis B immune globulin (HBIG) and hepatitis B vaccine can be administered to their newborn immediately after delivery.

Immunization with HBIG and vaccine starting at birth reduces the risk of transmission to less than 10% among infants born to HBsAg/HBeAg-positive mothers (19). One such immunization schedule includes three intramuscular injections, the first one given between the time of birth and before the hospital discharge, and the second and third injections given at 1 and 6 months of age, respectively (18). The standard vaccination strategy for infants born to mothers who test positive for HBsAg includes the administration of 100IU HBIG (human hepatitis B Immunoglobulin-VF, CSL Bioplasma) and hepatitis B vaccine [Recombivax HB (5mg), Merck, or Engerix-B (10mg), GlaxoSmithKline] within 12 hours of birth (20). HBIG is given intramuscularly and at a different site from that used for vaccination. Immediate household contacts should also be given HBIG and vaccination. The current vaccines contain noninfectious HBsAg and should cause no potential risk to the fetus.

The current (2009) Federal Drug Administration (FDA)-approved therapy for HBV in nonpregnant patients include subcutaneous injection of interferon/pegylated interferon alpha and orally administered nucleoside/tide analogs such as Lamivudine, Adefovir, Entecavir, Telbivudine, and Tenofovir (21). Interferon is considered FDA category C drug in pregnancy and is not recommended. Lamivudine, an oral nucleoside analog, classified as FDA category C drug in terms of safety, is given to mothers with high HBV DNA during the second and third trimesters to reduce the risk of transmission at the time of delivery. It is generally not recommended for use against HBV in the first trimester of pregnancy. However, potential benefits may justify the potential risk. The data on adefovir, entecavir, telbivudine, and tenofovir safety are limited in pregnancy. Although HBV may be found in breast milk, a study comparing breast-fed versus non-breast-fed babies of seropositive mothers demonstrated no difference in the infection rate.

Hepatitis C

Hepatitis C virus (HCV) is a hepatotropic positive single-stranded RNA virus of the *Hepacivirus* genus and a member of the Flaviviridae family. HCV infection is one of the major causes for development of liver cirrhosis and end-stage liver disease in the world. The prevalence of HCV antibody in pregnant women is equivalent to that of the general population (0.5%) (22). The most remarkable feature of hepatitis C virus is its ability to establish chronic infection in 55% to 85% of acute cases. Approximately 20% of chronically infected patients go on to develop cirrhosis, hepatic decompensation, and HCC after 20 to 30 years of infection (23). Chronic HCV infection is estimated to affect 180 million people worldwide, including 2 to 3 million Americans (1.6% of the general population) (24). There are six HCV genotypes (1, 2, 3, 4, 5, and 6), and a large number of subtypes (1a, 1b, 1c, etc.) have been identified (25). Currently, injection drug use is the primary mode of HCV transmission in the United States. Other risk factors include clotting factor therapy prior to the year 1987, blood transfusion prior to the year 1992, contaminated therapeutic equipment, occupational needle-stick, and sexual and perinatal transmission. The average rate of perinatal transmission is 5% to 6% (26). Infants born to mothers with HCV and human immunodeficiency virus coinfection have increased rate of HCV transmission (14–17%) (27). The risk of perinatal HCV transmission is related to HCV RNA titer and is

unrelated to delivery mode (vaginal vs. cesarean). Factors associated with increased risk of perinatal transmission are prolonged rupture of the membrane for more than 6 hours, amniocentesis, and perineal lacerations. Although HCV can be transmitted intrapartum, prevention by caesarean delivery is not generally indicated. Studies have evaluated breast-feeding of infants born to HCV-infected women, which indicate that the average rate of infection is 4% in both breast-fed and bottle-fed infants (28), and most experts do not consider breast-feeding a mode of transmission. The prevalence of hepatitis C in pregnancy does not differ significantly from that of hepatitis C in the age- and sex-matched general population. Routine prenatal HCV screening is not recommended; however, women with significant risk factors for infection should be offered antibody screening.

Fetal outcomes, such as birth weight, American Pediatric Gross Assessment Record score, and umbilical pH, have not been found to be different in children born to hepatitis C-infected mothers. Similarly, maternal outcome and obstetric complications are not greater in mothers chronically infected with hepatitis C in the absence of cirrhosis and portal hypertension. The diagnosis of acute or chronic HCV infection generally requires testing of serum for both antibody to HCV (anti-HCV) and for HCV RNA with a sensitive quantitative HCV RNA assay (Table 3). Anti-HCV is passively acquired by the infant and may persist for up to 18 months. Moreover, the rate of spontaneous clearance in the perinatal transmission of HCV is high. Infants born to mothers with HCV should not be tested for HCV till 18 months of age (29).

The course of hepatitis C can be affected by pregnancy. Some studies have reported an increase in HCV RNA levels in the third trimester of pregnancy, but others have not. On the contrary, serum ALT levels tend to be lower in the third trimester and return to normal by 6 months after delivery.

The currently recommended therapy of chronic HCV infection in nonpregnant patients is the combination of a pegylated interferon-alfa and ribavirin. This regimen has been shown to be effective in 40% to 70% of patients (30–32). In mid 2011, two new direct-acting antiviral agents have been approved in combination with pegylated interferon and ribavirin for hepatitis C therapy in non-pregnant genotype 1 patients. HCV treatment success is measured by sustained virologic response (SVR) (defined as undetectable HCV RNA by a sensitive assay 6 months following discontinuation of treatment). Interferon is classified by the FDA as a category C drug while ribavirin is a category X product, indicating that its use is contraindicated in women who are pregnant. Interferon monotherapy is far less effective than combined therapy with ribavirin and is associated with low SVR rates, and hence the risk of HCV therapy outweighs its benefit during pregnancy.

Hepatitis E
Hepatitis E virus (HEV) is a positive-stranded RNA virus that belongs to the Hepeviridae family. The virus is transmitted via the fecal–oral route, commonly by contaminated water supplies. Vertical transmission of hepatitis E virus ranged between 33% and 50% (33,34). The virus is endemic in the Middle East, India, Southeast Asia, Central Asia, Central America, and South America. Hepatitis E is an acute disease that does not progress to chronicity, although reports of chronic HEV have been described in liver transplant recipients (35,36). The clinical presentation is basically the same as that for HAV. HEV infection is known to cause severe hepatitis, fulminant liver failure, preterm labor, and increased mortality in pregnant women especially in their third trimester with reported maternal mortality rates as high as 20% to 31.1% (4,37). The incubation period is 3–8 weeks, with a mean of 40 days. Cholestatic hepatitis is common. Acute hepatitis E infection is diagnosed by detection of IgM anti-HEV or a rising titer of IgG anti-HEV. The treatment is supportive therapy. A proved effective vaccine against HEV is currently not available. There is no current evidence that HEV infection is transmitted in breast milk.

Autoimmune Hepatitis
Autoimmune hepatitis (AIH) is a syndrome of progressive hepatocellular inflammation and necrosis of unknown cause, frequently leading to cirrhosis (38). The disease is characterized by loss of tolerance to hepatic autoantigens. AIH occurs predominantly among women, particularly in their younger years, and may influence their fertility and pregnancy. Pregnant women with AIH have a reduced fertility rate secondary to amenorrhea and anovulation, which might be related to hypothalamic–pituitary dysfunction. Serious maternal complications can occur in 9% of cases with a high rate (52%) of postpartum flares (39). In one large review by Candia et al. analyzing 101 pregnancies, fetal death rate was observed in 19% with a perinatal mortality of 4% (40). Most fetal deaths occurred before the 20th week of pregnancy.

In the United States, AIH affects 100,000 to 200,000 patients with an incidence of 1.9 per 100,000 per year and a point prevalence of 16.9 per 100,000 persons per year (41). AIH occurs at two age peaks, one in adolescence and young adulthood and the other in the sixth or seventh decade. About 70% of cases involve females, and there is a frequent association with other autoimmune disorders such as thyroiditis.

The diagnosis is based on histologic abnormalities (portal tract inflammation with moderate infiltration with lymphocytes, plasma cells, and piecemeal necrosis), characteristic clinical and laboratory findings (absence of other causes of

Table 3 Interpretation of Serum Hepatitis C Virus (HCV) Antibody and HCV RNA		
Anti-HCV	HCV RNA	Interpretation
Negative	Negative	No previous or current exposure to HCV
Positive	Positive	Acute or chronic HCV infection
Positive	Negative	Resolution of HCV either spontaneously or after response to treatment, false positive ELISA test
Negative	Positive	Acute HCV infection; chronic HCV in setting of immunosuppressed state; false-positive HCV RNA test

liver injury and abnormal aminotransferases), abnormal levels of serum globulins, and the presence of one or more characteristic autoantibodies (42). Immunosuppressive therapy with azathioprine (AZA) and corticosteroids are the principal therapy of AIH. Corticosteroid therapy induces clinical, laboratory, and histologic improvements in 80% of patients with AIH (43). Corticosteroids and AZA are generally safe during pregnancy but birth defects have been described (44). Pregnant women with AIH need careful monitoring during pregnancy and for several months postpartum.

Wilson's Disease

Wilson's disease (WD) is a rare autosomal recessive disorder of hepatic copper metabolism caused by defective copper transporting ATPase in the liver causing a decrease in biliary excretion of copper and abnormal accumulation of copper in many tissues, notably the liver, brain, kidneys, and cornea. The most common gene mutation described in WD is ATP7B. WD is a rare disorder with a worldwide prevalence of 1:30,000. Clinical manifestations depend on the affected organs and include acute or chronic hepatitis, cirrhosis, hemolysis, chorea, tremors, spasticity, and psychiatric changes. A Kayser–Fleischer ring is often observed once neurologic or psychiatric symptoms develop. The diagnosis is made by a low serum level of ceruloplasmin and an elevated concentration of copper in the liver tissue. Women with WD have high rates of infertility due to menstrual irregularities and recurrent miscarriages (45,46). The former is the result of hormonal changes caused by hepatic failure and copper toxicity and the latter is caused probably by increased copper deposition in the uterus. Hemolysis can be a presenting feature in some cases.

The current available anticopper agents are penicillamine, zinc, trientine, and tetrathiomolybdate. The main therapy is penicillamine, a copper-chelating agent. Although this agent has been used in pregnancy without teratogenic effect, transient goitrous hypothyroidism in infants born to mothers with WD on penicillamine has been reported (47). Cessation of therapy can lead to fulminant liver failure and death during pregnancy. Zinc intake at a dose of 25 to 50mg three times daily in pregnancy appears to be safe with very minimal teratogenicity (48). Since penicillamine has an antipyridoxine effect, supplementation with vitamin B₆ is recommended.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune cholestatic liver disease characterized by progressive destruction of intrahepatic bile ducts, predominantly seen in middle-aged women. Typical symptoms are fatigue, pruritus, and abdominal pain. Jaundice develops in advanced liver disease. At presentation, about 40% of the patients are asymptomatic, but 30% to 50% already have hepatomegaly and 15% present with splenomegaly. PBC is associated with a large variety of other diseases, such as Sjogren's syndrome, arthropathy, CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome, and autoimmune thyroiditis. The characteristic serologic hallmark of PBC is the anti-mitochondrial antibody, a highly disease-specific autoantibody found in 90% to 95% of patients (49). Up to now, it is not known whether pregnancy was harmful in PBC patients. Previous reports suggested

increased rates of infertility and preterm labor. Ursodeoxycholic acid (UDCA, 10–15 mg/kg/day) is regarded as the first-line treatment for PBC. UDCA appears to be safe and is considered FDA class B in pregnancy. UDCA may improve pruritus and serum liver tests.

Portal Vein Thrombosis

Portal vein thrombosis (PVT) is a rare occurrence during pregnancy. Malignant tumors, cirrhosis, and other causes of intra-abdominal inflammation such as pancreatitis, appendicitis, cholecystitis, duodenal ulcer, and inflammatory bowel disease are the leading local risk factors (50). Management differs in acute and chronic PVT in pregnancy. The goal of treatment of acute PVT is to recanalize the obstructed veins, which may prevent intestinal infarction and subsequent portal hypertension. Correction of the causal factors should be achieved as soon as possible. Anticoagulation should be given for at least 3 months and that a permanent anticoagulation therapy is considered for patients with prothrombotic conditions (51). Pregnant patients with chronic PVT should be offered screening for gastroesophageal varices. In patients with extrahepatic portal hypertension without gastroesophageal varices, labor and vaginal delivery are preferable and less morbid, with a passive second stage of labor in order to avoid increased intra-abdominal pressure. Elective cesarean section is advisable in patients with gastroesophageal varices. Portal vein cavernoma is a rare disease resulting from extrahepatic PVT and development of collateral venous circulation (51). This disease is often accompanied by splenomegaly, portal hypertension, esophageal, gastric, or jejunal varices, and thrombocytopenia. Early diagnosis and treatment of gastroesophageal varices before pregnancy are recommended, which can be accomplished by screening upper endoscopy and therapy with sclerotherapy or esophageal band ligation of esophageal varices and/or institution of nonselective β -blocker therapy is warranted.

Budd–Chiari Syndrome

Budd–Chiari syndrome (BCS), also known as hepatic venous outflow tract obstruction, is characterized by occluded hepatic venous outflow tract at various levels from small hepatic veins to inferior vena cava, resulting from thrombosis or its fibrous sequelae (51,52). Most patients with BCS have a “primary” disorder and share one or more prothrombotic risk factors, mainly myeloproliferative disorders (MPD), oral contraceptive use, factor V Leiden mutation, and antiphospholipid syndrome. MPD, particularly polycythemia vera, are observed in approximately half of the cases of BCS, but fewer than 10% of the subjects with overt MPD develop BCS. The characteristic clinical triad of acute BCS is right upper quadrant pain, hepatomegaly, and ascites (53,54). The diagnosis of BCS is established with Doppler sonography of the hepatic vessels. MRI can provide detailed examination of the hepatic and splanchnic vessels. Chronic thrombosis may evolve to precipitate portal hypertension with the formation of ascites, porto-systemic encephalopathy, and gastroesophageal varices. Women with BCS who desire to become pregnant should be screened for gastroesophageal varices with upper endoscopy, and if found, treatment should be offered preferably with esophageal band ligation or sclerotherapy. Most patients are placed on long-term warfarin therapy if nonpregnant and on

low–molecular weight heparin if pregnant as soon as possible, and preferably before conception.

Cirrhosis and Portal Hypertension

Pregnancy is uncommon in the setting of cirrhosis possibly due to altered sex hormones and hepatocellular injury. The rates of spontaneous abortion, premature birth, and perinatal death are all increased in women with cirrhosis. The incidence of cirrhosis in pregnancy is estimated to be approximately 1 in 5950 pregnancies (55). Maternal morbidity and mortality is high during pregnancy in cirrhotic patients (10.3–18%). Maternal deaths are due primarily to gastrointestinal hemorrhage from varices (56). During pregnancy, a hypervolemic state develops leading to an increase in portal flow and elevation of portal pressure transmitted to the collateral veins with increased risk of variceal bleeding. Esophageal variceal bleeding has been reported in 18% to 32% of pregnant women with cirrhosis and in up to 50% of those with known portal hypertension. Those with preexisting varices, 78% will have gastrointestinal bleeding during pregnancy, with a mortality rate of 18% to 50% (57). The outcome of pregnancy in women with cirrhosis is influenced by the underlying etiology of liver disease. AIH and alcoholic liver disease tend to have a favorable outcome in comparison with those with viral hepatitis. Endoscopic surveillance and banding of esophageal varices are recommended during pregnancy. Upper endoscopy in general appears to be safe during pregnancy. Primary prophylaxis with nonselective beta blockers is recommended. Propranolol and/or nadolol are considered FDA category C. The risks of nonselective beta blockers include fetal bradycardia, hypotension, hypoglycemia, and intrauterine growth retardation. Endoscopic band ligation seems to be a safe procedure in pregnancy. Termination of pregnancy is warranted in the presence of progressive hepatic decompensation. Vaginal delivery is usually safe and early forceps delivery or vacuum extraction should be considered to prevent any rise in portal pressure due to prolonged straining during labor. Cesarean section with general anesthesia is preferable in high-risk patients to avoid increase in portal pressure during labor.

Gall Stones and Biliary Tract Disease

The incidence of gallstones during pregnancy is estimated to be 3% to 12%; however, symptomatic gallstones occur in only 1.2% of these pregnancies (58). Hormonal changes during pregnancy, altered gallbladder motility, and increased cholesterol secretion are major predisposing factors for the development of gallstones and biliary sludge. The commonest clinical presentations are biliary pain and gallstone pancreatitis and the least common is acute cholecystitis. The management of symptomatic uncomplicated biliary tract disease is usually conservative. In patients with symptomatic choledocholithiasis, endoscopic management using endoscopic retrograde cholangiopancreatography (ERCP) is an alternative option. Since fluoroscopy poses a radiation risk to the fetus, abdominal shield to the pregnant patient should be provided. Laparoscopic cholecystectomy can be performed safely during pregnancy with no maternal mortality, although spontaneous abortions and preterm labor have been reported.

Table 4 Classification of Liver Diseases Unique to Pregnancy According to Their Onset in Pregnancy and Association with Pre-eclampsia/Eclampsia

Liver diseases associated with pre-eclampsia/eclampsia	Liver diseases not associated with pre-eclampsia/eclampsia
HELLP syndrome (occurs in second/third trimester)	Hyperemesis gravidarum (occurs mainly in first trimester)
Acute fatty liver disease of pregnancy (occurs mainly in second/third trimester)	Intrahepatic cholestasis of pregnancy (occurs in second and third trimesters)
Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelets.	

LIVER DISEASES UNIQUE TO PREGNANCY

Four unique disorders of liver dysfunction have been recognized during pregnancy. These include (i) hepatic involvement in hyperemesis gravidarum (HG), (ii) intrahepatic cholestasis of pregnancy (ICP), (iii) the syndrome of HELLP, and (iv) acute fatty liver of pregnancy (AFLP) (Table 4).

Hyperemesis Gravidarum

During pregnancy, nausea and vomiting are common; however, in some instances, the entity is protracted and may result in hospitalization. Intense nausea and vomiting in the first trimester associated with 5% weight loss, dehydration, ketonuria and electrolytes imbalance, and metabolic alkalosis are highly suggestive of HG. Risk factors include previous history of HG, previous molar pregnancy, preexisting diabetes, gastrointestinal disorders, asthma, singleton female pregnancy, pregnancy with multiple male fetuses, multiple gestations, hyperthyroid disorders, psychiatric illness, and small pre-pregnancy body weight (59). Maternal smoking prior to pregnancy appears to be protective (60). The most common hepatic abnormality associated with HG is mild elevation of liver transaminases (usually <300IU), and it is thought to be associated with a temporary impairment of mitochondrial fatty acid oxidation (61). Jaundice is infrequent and total bilirubin is generally <4mg/dL. These liver abnormalities are seen only in 20% to 30% of patients. Liver biopsy is generally not indicated unless to rule out other etiologies and, if performed, may show bland cholestasis. Maternal complications include Mallory–Weiss tears, preterm labor, and low birth weight (62). Treatment is supportive and directed at symptomatic relief with intravenous fluid and electrolytes replacement, thiamine and pyridoxine supplementation, and use of antiemetics. Hyperemesis with hepatic abnormalities has been reported to recur in subsequent pregnancies.

Intrahepatic Cholestasis of Pregnancy

ICP is characterized by pruritus and biochemical cholestasis typically presenting in the third trimester. This condition accounts for approximately 20% of jaundice during pregnancy. Although this is an uncommon disorder, it frequently recurs with subsequent pregnancies or the administration of synthetic estrogen compounds. Pruritus gravidarum is a term applied to patients with pruritus and biochemical cholestasis, whereas cholestasis of pregnancy is generally reserved for those patients with jaundice. The prevalence of ICP in the United States is estimated to be around 1/1000 to 1/10,000 pregnancies.

The highest prevalence is seen among the Araucanian (27.6%) and Aymara (11.8%) Indians of Chile (63). Although the exact etiology is unknown, genetic and hormonal factors play a role. Genetic factors have been implicated owing to the frequent history of cholestasis in female family members of index patients. Heterozygous non-sense mutation of the multidrug resistance-associated protein 3 (MDR3) gene has been implicated in familial ICP (64). Estrogens produce lithogenic bile because estrogens decrease bile salt-independent flow and increase diffusion of water from bile to plasma. Pruritus generally involves the palms of the hands and the soles of the feet. Skin examination should be performed to rule out other skin disorders of pruritus. Jaundice may or may not be present. Some patients will have subclinical steatorrhea that may affect nutritional status. The diagnosis is established by the presence of typical history of generalized intractable pruritus in the second or third trimester of pregnancy with elevated maternal serum bile acids in the absence of radiologic evidence of biliary obstruction. Laboratory abnormalities are cholestatic with elevations in alkaline phosphatase up to 10-fold and modest hyperbilirubinemia, typically less than 5mg/dL. Serum aminotransferases are usually elevated but <1000U/L. Cholestatic enzymes such as alkaline phosphatase are also elevated; however, serum gamma glutamyl transpeptidase is normal or slightly elevated. Elevated maternal serum bile acids are the hallmark of cholestasis and are usually 10 μ mol/L (65). A cutoff level of serum bile acids 40 μ mol/L is associated with impaired fetal outcome (66). Currently, genetic tests are performed in research laboratories only and are not applicable for diagnosis or risk stratification. However, mutation analysis of ABCB4 might be considered. Maternal outcome is favorable with prompt resolution of symptoms postpartum. Women with ICP have an increased incidence of gallstones due to lithogenic bile. Liver biopsy is unnecessary for diagnosis; however, if performed, it shows canalicular bile plugs with centrilobular cholestasis and intact parenchymal architecture. ICP recurs in about 70% of patients. Fetal outcome is not so favorable. Premature delivery occurs in 10% to 20%, meconium staining in 35% to 60%, and fetal distress in 19% to 60%.

Treatment of ICP is largely symptomatic. UDCA, a tertiary bile acid, is the main treatment to alleviate pruritus and cholestasis. The recommended dose is 15mg/kg/day in divided doses. UDCA improves liver transaminases, lower serum bile acids, and improve pruritus (67,68). Other treatment such as hydroxyzine, Ondansetron, and S-adenosyl-L-methionine (SAME) has shown to be of some benefit (69). Fat-soluble vitamins should also be administered. In addition to the symptomatic relief of pruritus, a strict fetal monitoring must be carried out especially during the last few weeks of pregnancy, where rates of fetal morbidity and mortality are increased.

HELLP

Pre-eclampsia develops in 5% to 11% of all pregnancy and is characterized by the triad of proteinuria (greater than 300 mg in 24 hours), edema, and hypertension (>140/90 mmHg) after 20 weeks of gestation and/or within 48 hours after delivery. If the central nervous system becomes involved, for example, seizures or coma, the disorder is termed eclampsia. Hepatic involvement is a sign of advanced pre-eclampsia/eclampsia and may manifest as HELLP syndrome or hepatic rupture. The incidence

of HELLP syndrome is approximately 0.6% of pregnancies and 3.1% to 12% of patients with pre-eclampsia (70). HELLP syndrome occurs mainly in the antepartum period in 70% to 92% of cases and postpartum in 8% to 30%.

The symptoms include right upper quadrant abdominal pain, headache, malaise, nausea, and vomiting. Concomitant signs and symptoms of pre-eclampsia (hypertension, proteinuria, and edema) may or may not be present. Jaundice and bleeding, due to thrombocytopenia, are a very uncommon mode of presentation. Severe right upper quadrant abdominal pain that is radiated to the neck or shoulder may herald impending hepatic rupture or presence of hepatic hematoma. Serum aminotransferases range from 300 to 3000U/L and serum bilirubin is usually less than 5mg/dL, but higher values have been reported. Hepatic parenchymal injury results from microangiopathic hemolytic anemia, thrombocytopenia, and localized segmental vasospasm and may lead to hepatic infarction, hematoma, and rupture resulting in maternal death. Disseminated intravascular coagulation (DIC) is found in 8% to 21% of patients. If hepatic parenchymal injury is severe, hypoglycemia may be observed. Liver biopsies or autopsy specimens show periportal fibrin deposition and hemorrhage; portal tracts are usually involved but in some cases lesions may be focal. More recently, hepatic microvesicular fat similar to that seen in AFLP has been observed in histologic specimens, leading to speculation that pre-eclampsia and AFLP may be different presentations of the same process. Physicians should be aware of other causes that may resemble HELLP such as acute viral hepatitis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, and AFLP. Both HELLP syndrome and AFLP occur in the third trimester and have similar presentations, but liver dysfunction is usually more pronounced in the latter and is more frequently associated with coagulopathy, hypoglycemia, and renal failure (Table 5). The coagulopathy of the AFLP is due to liver failure, whereas in HELLP syndrome, coagulopathy develops as a part of DIC syndrome.

Initial therapy is directed at control of hypertension and prevention of seizures, and optimal management includes prompt delivery. Frequent monitoring of serum glucose is warranted and intravenous dextrose solution is infused as needed. Maternal outcomes are generally favorable with mortality ranges from 2% to 4% in reported cases. Corticosteroids have been shown to improve maternal laboratory values but did not affect overall outcome. Platelet transfusion is recommended in the case of bleeding or severe thrombocytopenia (platelet count <20 $\times 10^9$ /L).

Liver rupture is a rare, life-threatening complication of HELLP that carries a very high maternal mortality. It is usually preceded by an intraparenchymal hemorrhage progressing to a contained subcapsular hematoma in the right hepatic lobe in patients with severe thrombocytopenia. Hepatic rupture usually requires immediate laparotomy with evacuation of the hematoma with pressure packing and drainage, followed by consideration of hepatic artery embolization or ligation, partial hepatectomy, or oversewing of the laceration.

AFLP

AFLP is a rare disorder (1 per 13,000 deliveries) unique to pregnancy, which occurs in the third trimester or peripartum (71).

Table 5 Features of Liver Diseases Unique to Pregnancy

Disease/features	HG	ICP	HELLP	AFLP
Incidence	0.3–2%	0.1–0.01%	0.2–0.6%	0.005–0.01%
Onset (trimester)	first trimester	second/third	second/third	third
Presence of pre-eclampsia	No	No	Yes	>50%
Clinical features	Nausea, vomiting, weight loss, dehydration	Generalized pruritus, jaundice, elevated maternal serum bile acids	Abdominal pain, edema, hypertension, hemolysis, thrombocytopenia	Liver failure with coagulopathy, encephalopathy hypoglycemia, and DIC
Aminotransferases	Usually <300 U/L	Mild to 20-fold increase	Typically >500 U/L	Typically 300–500 U/L
Bilirubin	Usually <4 mg/dL	<5 mg/dL	<5 mg/dL	<5 mg/dL
Imaging	Normal	Normal	May show hepatic rupture or infarction	May show fatty infiltrate
Histology	Normal/bland cholestasis	Cholestasis	Periportal necrosis, hemorrhage	Microvesicular steatosis in zone 3
Outcome	Preterm, low birth weight	Preterm, low birth weight, meconium staining	Prematurity, fetal death	Fetal death

Abbreviations: HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; HELLP, hemolysis, elevated liver aminotransferases, and low platelets; AFLP, acute fatty liver disease of pregnancy; DIC, disseminated intravascular coagulation.

This was first described by Sheehan in 1940, who termed it obstetric acute yellow atrophy. The disorder is more common in primigravidas, twin gestations, and those with a male fetus. The disease occurs at any age in the childbearing period. Characteristically, it develops in the last 10 weeks and usually in the last 4 weeks of pregnancy.

Typically patients present with nausea and vomiting for several days, followed by jaundice and then progressive encephalopathy. Right upper quadrant pain and epigastric abdominal pain are common (50–80%) (72). Fever, headache, diarrhea, back pain suggestive of acute pancreatitis, and myalgias are occasionally initial presentation. Hepatic failure may ensue. Approximately 50% of patients may also have features of pre-eclampsia. Physical examination may reveal only right upper quadrant tenderness. Laboratory abnormalities include elevated serum aminotransferases usually 300 to 500 U/L, moderate increase in serum bilirubin 5 mg/dL and variable degrees of leukocytosis (73), DIC, hypoglycemia, hyperuricemia, and bacteremia. Patients may develop gastrointestinal hemorrhage, pancreatitis, and renal failure. Radiographic evaluations may suggest the diagnosis from steatosis seen by ultrasound, computerized tomography, or magnetic resonance imaging. However, this finding may not be universally present and normal studies do not exclude the diagnosis.

AFLP is characterized by a microvesicular fatty infiltration of the hepatocytes involving perivenular and mid-zones (74). Extensive hepatocellular necrosis, a common histologic feature of HELLP syndrome, is absent in AFLP, while microvesicular fatty infiltration, the predominant feature of AFLP, is generally absent in HELLP syndrome (72).

There is a strong association between AFLP and a deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in the fetus, a disorder of mitochondrial fatty acid beta-oxidation (75). In a study by Ibdah and colleagues, 79% of women who carried LCHAD-deficient fetuses developed AFLP (76). Infants born to mothers with AFLP may exhibit immediate or delayed nonketotic hypoglycemia, hepatic encephalopathy, cardiomyopathy, slowly progressing

peripheral neuropathy, skeletal myopathy, or sudden unexpected death (77,78). Other studies reported involvement of fetal hepatic carnitine palmitoyltransferase (CPT I) deficiency and maternal medium-chain acyl-CoA dehydrogenase deficiency in AFLP (79,80). It is recommended that neonates born to pregnancies complicated by AFLP be tested for the common LCHAD G1528C mutation (81) and that this testing when done early after birth can be lifesaving as it may identify LCHAD-deficient children before they manifest the disease allowing early dietary intervention by institution of a diet low in fat and high in carbohydrate, and by substitution of the long-chain fatty acids with medium-chain fatty acids. This strong association between AFLP and the common G1528C mutation in the fetus is significant (82,83), and hence screening the offspring of women who develop AFLP at birth for this mutation can be lifesaving.

Successful management of AFLP is dependent upon prompt delivery and supportive care. Overall previous reported maternal and fetal mortality is 26% and 32% respectively, but more recent series suggest improving maternal and fetal mortality with prompt delivery. Fetal mortality is believed to occur as a result of rapid maternal decompensation, a high rate of premature delivery, and the maternal DIC resulting in fibrin deposition in the placenta, culminating in uteroplacental insufficiency, infarct, and fetal asphyxia (84). Immediate delivery would therefore be expected to improve fetal outcome, since basic organ systems are developed. AFLP may recur in subsequent pregnancy, particularly in mothers with a fatty acid oxidation defect in the offspring (72).

Liver Transplantation and Pregnancy

Since the first pregnancy in a transplant recipient in 1958, pregnancy in recipients of solid organ transplants has become increasingly common. The first successful pregnancy in a liver graft recipient was reported in 1978 (85). Given the improving success of liver transplantation over the past two decades and decreasing levels of immunosuppression, most organ transplant recipients lead happy and healthy lives with an average

1-year survival rate of >85% at better transplant programs. As of January 2007, there were 1595 pregnancies in female transplant recipients reported to the National Transplantation Pregnancy Registry (NTPR). In 131 liver transplant recipients in the NTPR, 219 pregnancies and 223 outcomes were reported (86,87). Children born to female liver recipients have a greater risk of prematurity and low birth weight than the general population; however, no congenital malformation patterns have been observed. Majority of women after liver transplantation will deliver a healthy baby. In a large single-center experience that evaluated the outcome of 71 pregnancies after liver transplantation, pregnancy-induced hypertension was seen in 20%, pre-eclampsia in 13%, acute cellular rejection in 17%, and renal impairment in 11% (88). Pregnancies occurring within 1-year post-transplantation had an increased incidence of prematurity (58% vs. 29%), low birth weight, and acute cellular rejection (33% vs. 14%) compared with those occurring later than 1 year (88). Although no statistically significant differences in outcome were identified, rates of acute rejection and graft loss are similar to nonpregnant liver recipients. An NTPR analysis of liver recipients noted that those who reported rejection during pregnancy had poorer newborn outcomes and graft survival (89). If desired, pregnancy should be deferred for 1 year after liver transplantation. This recommendation is supported by NTPR data. Immunosuppression regimens typically include cyclosporin (CyA) or FK506, mycophenolate mofetil, and prednisone with or without AZA. Additional medications for liver transplant recipients may include prophylaxis for *Pneumocystis carinii* infection with trimethoprim/sulfamethoxazole or pentamidine, and for herpes virus infection with acyclovir. Every effort should be exercised to avoid teratogenic medications during pregnancy. Family planning and multidisciplinary team involvement are optimum. Breast-feeding is discouraged while women are on immunosuppressant medication.

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