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Approach to Liver Disease in Pregnancy

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Liver disease in pregnancy is a rare phenomenon, but its presence represents a challenging scenario as it can have harmful effects on both the mother and the fetus. Certain liver diseases are unique to pregnancy only, including hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, preeclampsia, hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and acute fatty liver of pregnancy. Concurrently, pregnant patients remain susceptible to acquiring liver disorders that may be encountered in general population including viral hepatitis, gallstones or Budd-Chiari syndrome. Some conditions may predate pregnancy such as cirrhosis, autoimmune hepatitis, Wilson disease or a prior liver transplant. In pregnancy, serum alkaline phosphatase levels are increased but elevation of serum aminotransferases and bilirubin level usually indicates a pathological process. Management of these disorders is imperative to avoid development of maternal and fetal complications.

INTRODUCTION

Liver disease in pregnancy is a rare phenomenon, occurring in 2-3% of pregnancies.[1] The presence of liver disease, however, can represent a challenging scenario as it can have harmful effects on both the mother and the fetus.[2] Certain liver diseases are unique to pregnancy only; these include hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy (ICP), preeclampsia, acute fatty liver of pregnancy (AFLP) and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Concurrently, pregnant patients remain susceptible to acquiring liver disorders that may be encountered in general population including viral hepatitis or gallstones, whereas some diseases may predate pregnancy such as autoimmune hepatitis or Wilson disease.

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Normal Physiology

Heart rate and cardiac output increase in pregnancy but systemic vascular resistance is reduced. Overall, these physiological changes lead to lowering of systemic blood pressure and a hemodynamic state mimicking decompensated liver disease.[3] Elevation of alkaline phosphatase due to additional production from placenta may be observed as a normal change in liver enzymes in pregnancy. Conversely, increase levels of serum alanine aminotransferase (ALT), aspartate aminotransferase

(AST), gamma-glutamyl transpeptidase (GGT) and bilirubin may suggest a pathological process.[4]

Liver Diseases Unique to Pregnancy

Liver diseases unique to pregnancy can be divided by their predominance in a particular trimester. It must be noted that although some of these liver disorders may be specific to a one trimester, most overlap between trimesters and may even be present post-partum.

First Trimester

Hyperemesis Gravidarum (HG)

Hyperemesis gravidarum (HG) usually presents in the first half of pregnancy and typically resolves within 4-6 weeks of the second trimester. It has an incidence of 0.3–2% and with predisposition in pregnant females with increased body-mass index, molar pregnancy, multiple pregnancies and patients with co-morbid conditions such as diabetes.[5] Clinical features include intractable vomiting that can result in dehydration and ketosis.

Mild elevation of serum bilirubin and aminotransferases is common while other biochemical abnormalities, likely related to the underlying symptoms, may also be observed including hypokalemia, hypomagnesemia and elevation of serum creatinine. Vomiting may be severe enough to cause weight loss along with ketonuria that is a diagnostic finding. Viral hepatitis should be ruled out during the workup as it may also present with similar clinical features.

HG is associated with premature delivery, low birth weight and small for gestational age babies but is not linked with perinatal death.[6] Management is supportive with anti-emetics and intravenous (IV) fluids. Thiamine supplementation is necessary to prevent Wernicke's encephalopathy.[7] Recurrence of HG is common, with a risk of 15% in the second pregnancy compared to 0.7% without a prior history of hyperemesis.[8]

Second and Third Trimester

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease unique to pregnancy. It is more common in multiple gestation pregnancies, with prevalence of 0.4 – 5%.[9, 10] ICP typically presents in the second half of pregnancy but can even occur in the first trimester. Patients present with pruritus, usually involving the palms and the soles of the feet, which may be worse at night. Jaundice can also occur but is not as common as pruritus. ICP is characterized by elevation of serum aminotransferases, up to 10 to 25 times upper limit of normal (rising to >1,000 U/L), and bile acids. Fat-soluble vitamin deficiencies may also be observed, which can lead to reduction of vitamin K-dependent coagulation factors and subsequent elevation of prothrombin time. Bile acid levels of >10 μmol/l is diagnostic of ICP but levels of >40 μmol/l are associated with adverse outcomes in pregnancy and fetal complications such as spontaneous preterm deliveries, asphyxia events and meconium staining of amniotic fluid, placenta and membranes.[11]

Management focuses on both controlling the symptoms and preventing complications along with close monitoring of the fetus. First-line treatment is ursodeoxycholic acid (UDCA), given at 10-15mg/kg maternal body weight. UDCA not only improves pruritis, but also improves bile acid levels and serum aminotransferases. Most importantly, this decrease in bile acid levels can lead to reduction in adverse fetal outcomes such as prematurity and fetal distress.[12] S-adenosyl methionine (SAMe), a glutathione precursor that results in excretion of biliary salts by methylation of hormone metabolites, has also been used as a treatment modality.[13] However, a meta-analysis revealed that SAMe alone was not as effective as UDCA in improvement of pruritus, serum ALT levels or total bile acids.[14] Dexamethasone may improve lung maturity in the fetus but does not have a significant role in treatment of ICP. Delivery at 37 weeks is recommended to avoid the risk of intra-uterine death.[15] Adequate nutritional status maintenance is important, particularly in patients with severe steatorrhea.

Pruritus usually resolves within a few days of delivery followed by normalization of elevated liver enzymes and bile acids. These tests may be repeated 6-8 weeks after delivery. Elevated bilirubin levels at the time of diagnosis or failure of resolution of cholestasis should prompt further investigation into alternative causes. Rarely, such as in familial cases, ICP will lead to chronic liver disease after delivery with cirrhosis and fibrosis.[14]

Therefore, patient follow-up after delivery should be continued in the outpatient setting. Recurrence of ICP is common, in up to 60-70% of subsequent pregnancies.

Preeclampsia

Hypertension in pregnancy, defined as blood pressure of ≥140/90 mmHg, has been associated with adverse outcomes in both the pregnant mother and the fetus. Preeclampsia is now described by International Society for the Study of Hypertension in Pregnancy (ISSHP) as de-novo hypertension present after 20 weeks gestation combined with proteinuria (≥300 mg/24h), other maternal organ dysfunction, including liver involvement, renal insufficiency, neurological or hematological complications, uteroplacental dysfunction, or fetal growth restriction.[16] Complications of the liver include hepatocellular injury, hepatomegaly and hepatic rupture.

Risk factors for this disorder include extremes of age (less than 16 years old or greater than 45 years old), nulliparity, prior history of hypertension, previous preeclampsia episode or positive family history of preeclampsia.[3] Although clinical presentation is variable, patients are mostly asymptomatic, but they may present with right-sided abdominal pain, nausea and vomiting along with headaches and visual disturbances. Liver enzymes may be deranged with elevation of serum aminotransferases predominantly.

Although hypertension control is important, delivery is the definitive treatment. This should be urgent if diagnosis is made at >34 weeks to prevent further complications such as eclampsia or hepatic rupture.[17] For a fetus of less than 34 weeks, corticosteroids may be indicated to improve the maturity of fetal lung followed by delivery.

The United States Preventive Services Task Force (USPSTF) recommends using low-dose aspirin (81 mg/d) after 12 weeks of gestation in women who are at high risk for preeclampsia as a preventive medication (grade B recommendation).[18] They define high risk factors as hypertensive disease during prior pregnancy, chronic kidney disease, autoimmune disease, type 1 or type 2 diabetes, chronic hypertension or multiple pregnancies. Of note, however, the American College of Gastroenterology (ACG) and American Association for the Study of Liver Diseases (AASLD) currently do not endorse this recommendation.

Abnormal liver enzymes tend to resolve within a couple of weeks after delivery. Patients should be followed-up regularly with yearly observation of their blood pressure as well as blood glucose and lipid profile.

Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) Syndrome

Hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome characterizes severe features of preeclampsia. It manifests in 0.1 – 0.9% of pregnancies but may lead to complications in up to 20% of patients with preeclampsia.[19] HELLP syndrome typically occurs after 20 weeks of gestation and but nearly one third of cases can occur post-partum.[20] Risk factors for HELLP syndrome are comparable to preeclampsia including nulliparity, prior history of hypertension or previous episode of HELLP syndrome. Clinical features of HELLP syndrome may also be similar to preeclampsia. Patients may have epigastric or right upper quadrant abdominal pain, nausea and vomiting as well as occasional headaches and visual disturbances. Hypertension may be present but HELLP syndrome can also occur in normotensive patients.

Complications of HELLP syndrome include development of renal failure, pulmonary edema, disseminated intravascular coagulation (DIC), and maternal death.[20, 21] Subcapsular liver hematomas may be present in 0.9% of patients with HELLP syndrome.[20] Hepatic rupture can occur in 1-in-45,000 to 1-in-225,000 deliveries with associated maternal mortality rates of 60–86%.[22] Perinatal mortality due to maternal complications and prematurity has also been reported in up to 70% of cases.[19] The diagnosis of HELLP syndrome is established when a patient has hemolytic anemia, with lactate dehydrogenase (LDH) of > 600 U/L, elevation of liver enzymes including serum aminotransferase and reduced platelet counts of <100 k/mcL.[23, 24] Increase in serum bilirubin levels may also be present. DIC should be considered in the presence of elevated prothrombin time and low fibrinogen levels. Hepatic imaging using computed

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tomography (CT) or magnetic resonance imaging (MRI) is preferred over ultrasonography to detect hepatic hematoma, infarction or rupture.[25] Imaging should be performed in all patients with HELLP syndrome that present with abdominal, neck or shoulder pain or elevation of aminotransferase of > 1,000 U/l to rule out hepatic complications.[23]

Patients with HELLP syndrome need to be closely monitored. The plan should include stabilizing the mother while assessing for fetal distress and determining if urgent delivery is indicated. Just as with preeclampsia, in a pregnancy with >34 weeks of gestation, the decisive treatment is delivery. A fetus of <34 weeks of gestation, in the absence of complications, may benefit from glucocorticoids to improve fetal lung maturity after the mother has been stabilized, but delivery should not be delayed beyond 48 hours of presentation. Small or contained hematomas may be managed with supportive treatment but in patients with hepatic rupture who are hemodynamically stable, percutaneous embolization of hepatic artery may be preferred.[25,26] Surgery is reserved for hemodynamically unstable patients or those with persistent bleeding.

Patients with HELLP syndrome tend to improve after delivery but a small risk of recurrence persists in subsequent pregnancies. Liver enzymes tend to normalize 48 hours postpartum.

Acute Fatty Liver of Pregnancy (AFLP)

Acuter fatty liver of pregnancy (AFLP) is a rare but lethal phenomenon that generally presents in the third trimester, occurring in 1 in 10,000 pregnancies.[27] Risk factors for AFLP include multiple gestations and underweight women.[28]

AFLP has been linked to an inherited defect in mitochondrial beta-oxidation. This fetal mitochondrial beta-oxidation defect, specifically, in the enzyme long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD), results in the accumulation of fatty acids in hepatocytes and maternal circulation.[29,30] This eventually leads to hepatic failure and encephalopathy.

Patients may have complaints of epigastric pain, nausea and vomiting. However, they could also present with serious complications of AFLP such as pulmonary edema, renal or liver failure, proteinuria or DIC. Laboratory work may reveal hypoglycemia as well as elevated serum aminotransferases, bilirubin, ammonia and serum creatinine. Liver biopsy, although not usually performed, may show microvesicular fatty infiltration. The Swansea Criteria has been validated for diagnosis of AFLP. It requires six or more positive clinical or laboratory findings in the absence of another cause (Table 2). It has a positive predictive value of 85% and negative predictive value of 100%.[31]

AFLP is associated with fatal outcomes for the fetus and the mother, and maternal mortality rates of 12.5% have been reported.[2,27] Like HELLP, treatment of AFLP requires stabilization of the mother, including resuscitation, as well as immediate delivery. Symptoms and laboratory abnormalities usually improve thereafter, but the patient may require monitoring in the postpartum period. Fulminant liver failure from AFLP may necessitate the need for liver transplant.[32] Infants born to mothers with AFLP should undergo testing for LCHAD deficiency mutation. Recurrence of AFLP can manifest in future pregnancies if a patient has a mutation for LCAHD deficiency, but it may also occur in those patients without this specific mutation.[33]

Liver Diseases Not Unique to Pregnancy

Cirrhosis and Portal Hypertension

Pregnancy is less common in patients with cirrhosis because of decreased fertility due to derangements in metabolic and hormonal balances that may result in anovulation. Gonadotrophin release is reduced in cirrhosis secondary to hypothalamic-pituitary dysfunction. This, combined with increased serum estradiol and testosterone levels in portosystemic shunts, can result in low fertility.[34]

A pregnant cirrhotic mother presents a unique challenge as these patients are at a higher risk of developing complications that can affect both the mother and the fetus. These patients remain at risk for liver decompensation, including variceal bleeding, encephalopathy and ascites. There is also an increased risk of preterm labor and spontaneous loss of pregnancy.[35] Maternal mortality rates remain elevated at 18-50% from gastrointestinal bleeding.[36] These numbers have improved recently due to more urgent management of variceal bleeding and liver failure.[35]

Table 1. Physiological Changes in Laboratory Tests in Pregnancy

	Unchanged	Increased	Decreased
Laboratory Test	ALT	Alkaline phosphatase	Albumin
	AST	Alpha fetoprotein	Hemoglobin
	Bilirubin		
	GGT		
	Protime/INR		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio

As the plasma volume expands in pregnancy, patients with portal hypertension may develop variceal bleeding, observed in nearly 30% of pregnant cirrhotic patients.[37] Although no formal guidelines exist for screening prior to pregnancy, it is reasonable to perform pre-conception screening for varices just like for other cirrhotic patients.[38,39] Patients should also undergo repeat screening in the second trimester if varices were not observed on preconception screening esophagogastroduodenoscopy (EGD) given the increased variceal bleeding risk in pregnancy.[40] Varices observed on EGD should be treated with endoscopic variceal ligation. Non-selective beta-blockers, such as propranolol, are also indicated in management of esophageal varices in pregnancy despite potential adverse effects such as hypoglycemia, retardation of intrauterine growth and neonatal bradycardia.

Treatment of an acute variceal bleed is similar in both pregnant and non-pregnant females. Patients should receive IV fluids resuscitation and appropriate transfusion of blood products, antibiotic prophylaxis, octreotide and endoscopic therapy to achieve hemostasis. TIPS and liver transplant have also been described in patients with severe variceal bleeding, but this is not commonly practiced. As prolonged vaginal delivery is also associated with an increased risk of variceal bleeding, a short second stage of labor in vaginal delivery is preferable.[40] Cesarean section may also be considered but it is associated with increased bleeding risk. Further studies are still needed to determine the safest mode of delivery. Other complications of cirrhosis, including ascites and hepatic encephalopathy may also be observed in pregnancy but they are managed the same as in non-pregnant patients.[38]

Viral Hepatitis

Viral hepatitis in a pregnant patient may be acute or chronic. These viral infections may account for up to 40% of jaundice in pregnant patients.[41] The presence of hepatitis B virus (HBV) poses no risk to mother unless cirrhosis is present. However, the number of at-risk infants is increasing with an estimated 25,000 infants at risk for vertical transmission of HBV in the United States.[42] The American College of Obstetricians and Gynecologists (ACOG) recommends screening all pregnant women for hepatitis B at the first pre-natal visit.[43] Management with antivirals is avoided in women of childbearing age or in the first trimester of pregnancy as exposure to the medical treatment can result in adverse effects on organogenesis in the fetus. If the pregnant patient is known to have cirrhosis or fibrosis, however, the treatment may be initiated or continued. AASLD and ACG guidelines recommend antivirals in the third trimester of pregnancy if patients have positive hepatitis B surface antigen (HBsAg) and subsequent HBV DNA >200,000 IU/mL.[40, 44] The treatment should continue until birth or three months postpartum. Perinatal transmission of hepatitis B when HBV DNA < 200,000 IU/mL has not been reported. Although positive hepatitis B e antigen (HBeAg) has also been linked to increased rate of transmission, the presence of HBV DNA is the most important predictor of persistent infection in the infant.[45] Tenofovir and telbivudine are first-line therapies for HBV infection. A high-risk pregnant patient with negative hepatitis B surface

antibody (HBsAb) may be vaccinated safely during pregnancy. Infants born to HBV-infected mothers should receive both hepatitis B immune globulin (HBIG) and the hepatitis B vaccination series, which provide passive and active immunization respectively. The first dose of the vaccine should be delivered within 12 hours of delivery while the additional two doses are administered within 6-12 months. These interventions appear to have reduced the rate of transmission from more than 90% to less than 10% presently.[44] Current guidelines do not favor one mode of delivery over the other; therefore, elective cesarean section and vaginal delivery both remain an option. Breastfeeding is supported regardless of the mother's treatment status.

Hepatitis C virus (HCV) infection, similarly to HBV, does not pose a risk to the mother unless she is cirrhotic. However, HCV was associated with a higher risk for preterm births in a meta-analysis.[46] Unlike HBV, current guidelines recommend screening for HCV in only those pregnant women with risk factors for HCV. Overall, mother-to-child transmission rates of up to 5% have been reported in HCV positive mothers but some co-morbidities are associated with an increase the rate of transmission.[47] Vertical transmission of HCV virus is enhanced to 19.4% if human immunodeficiency virus (HIV) co-infection exists, whereas intravenous drug use increases the rate of transmission to 8.6%.[47] Other risk factors that have been associated with increased risk of transmission include a viral load of more than 2.6 million and invasive procedures in pregnancy. Treatment of HCV is generally not pursued, as it usually does not require urgent therapy. Additionally, ribavirin is teratogenic and the new antivirals have not been well studied in pregnant patients thus far. Cesarean section and vaginal delivery both are an option for the patient as there are no guidelines favoring one mode of delivery to another. Breastfeeding is not discouraged if there is no skin breakdown or cracked nipples.

Acute hepatitis A virus (HAV) infections occur at the same frequency in pregnant and non-pregnant patients. HAV infection may increase gestational complications, including preterm labor, but overall, no differences in maternal and fetal outcomes has been observed.[48] Treatment is supportive, but it is recommended that a neonate receive HAV immunoglobulin if the mother has HAV infection within two weeks of delivery.[40]

Table 2. Swansea Criteria for Diagnosis of Acute Fatty Liver of Pregnancy

Six or more following features in the absence of another cause
Abdominal pain
Vomiting
Encephalopathy
Hypoglycemia <4 mmol/l
Elevated aminotransferases (AST or ALT) >42 IU/l
Elevated bilirubin >14 μ mol/l
Elevated urea >340 μ mol/l
Leukocytosis >11×10^6 cells/l
Elevated ammonia >47 μ mol/l
Renal impairment, creatinine >150 μ mol/l
Coagulopathy; prothrombin time >14 s or APPT>34 s
Ascites or bright liver on ultrasound
Microvesicular steatosis on liver biopsy

ALT, alanine aminotransferase; APPT, activated partial thromboplastin time; AST, aspartate aminotransferase

Acute hepatitis E virus (HEV) infection is the most common viral cause of acute liver failure in pregnancy.[49] Maternal and fetal mortality, as well as obstetrics complications, are significantly elevated in the presence of HEV infection. Fulminant liver failure has a reported mortality of 10-25% in pregnant women with HEV.[50] Therefore, all pregnant females presenting with acute hepatitis should have HEV-IgM levels checked. Management is supportive, although a successful liver transplant has been reported in a patient with acute liver failure from HEV infection.[51]

Herpes simplex virus (HSV) infection is a rare cause of liver failure in pregnancy even though pregnant females are at an increased risk of developing serious infections.[9] Mortality has been reported to be as high as 74% in patients with HSV hepatitis,[52] which should be suspected in patients who present with fever and elevated LFTs in the absence of jaundice. Pathognomonic

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mucocutaneous lesions are seen in <50% of the patients making the diagnosis challenging. HSV PCR is recommended to diagnose HSV infection due to the poor sensitivity and specificity of HSV-IgM testing. Nonetheless, as the results of HSV PCR may not be known immediately, if HSV infection is suspected, treatment with acyclovir should be promptly initiated. Acyclovir appears to be safe in pregnancy without an increased risk of birth defects in patients who have received this medication.[53]

Gallstones

There is an increased risk for gallstone formation in pregnancy due to supersaturation of cholesterol, particularly in the second and third trimester of pregnancy. Decreased motility of the gallbladder in pregnancy and stasis of bile also promote lithogenicity. Gallstones can result in biliary colic, acute cholecystitis, or acute gallstone pancreatitis. Ultrasonography is a safe imaging modality that can be used to detect acute cholecystitis with a sensitivity of 85-95% and specificity of 95%.[54] In the past, conservative management with intravenous (IV) fluids, antibiotics and bed rest was the standard of care for pregnant patients with acute cholecystitis. Surgery was reserved for only those patients that failed conservative management. However, currently, it is recommended to perform laparoscopic cholecystectomy for symptomatic cholecystitis as this appears to be a safe procedure in pregnant patients.[55] Surgical interventions are also necessary in patients with intractable biliary colic and acute gallstone pancreatitis. As pregnant mothers with symptomatic cholelithiasis are at an increased risk of recurrent gallstones later in pregnancy, patients with episodes associated with severe complications should also undergo cholecystectomy.[56]

Endoscopic retrograde cholangiopancreatography (ERCP) may be indicated for treatment of symptomatic choledocholithiasis, cholangitis, or biliary pancreatitis.[48, 57] It is a safe procedure to perform in pregnancy, especially if exposure of fluoroscopy is minimized.[57] Complications of ERCP during pregnancy include post-ERCP pancreatitis, post-ERCP bleeding and pre-term births.[58,59]

Table 3. Viral Causes of Liver Diseases in Pregnancy

Hepatitis A	• Supportive treatment • Vaccinate neonate with HAV immunoglobulin if mother was infected with HAV within 2 weeks of delivery
Hepatitis B	• Screen for HBV at the first pre-natal visit • May treat with tenofovir or telbivudine in 3rd trimester if HBV DNA > 200,000 IU/mL until birth or 3 months postpartum • Vaccinate high-risk pregnant patients • Infants should receive both active and passive vaccinations if born to HBV-infected mothers
Hepatitis C	• High-risk patients should be screened for HCV • Treatment is not recommended during pregnancy
Hepatitis E	• May cause fulminant liver failure with high maternal and fetal mortality • Supportive treatment
Herpes simplex	• May result in liver failure with high mortality rates • Diagnose by testing for HSV PCR • Empiric treatment with IV acyclovir should be started immediately when HSV infection is suspected

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) may worsen in pregnancy or in the postpartum period.[60] Completion of pregnancy is possible if a patient's disease is well managed but poor control of AIH is associated with prematurity.[61] If a patient has a history of AIH,

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their maintenance medications should be continued during pregnancy. Azathioprine has the best safety data when compared to other immunosuppressants. While congenital malformations have been described in pregnant mice from azathioprine, it is associated with favorable outcomes in pregnancy in humans.[62] Flares of the disease during pregnancy are usually treated with corticosteroid monotherapy,[40] but these flares can lead to hepatic decompensation and need for liver transplant or even death.

Wilson Disease

Wilson disease (WD) is an autosomal recessive disorder that affects biliary copper excretion resulting in deposition of copper in the brain, liver and kidneys. Patients typically present with elevated serum aminotransferases, hyperbilirubinemia and hemolytic anemia. Alkaline phosphatase levels may be low. Treatment should be maintained during pregnancy as interruptions can lead to liver failure.[63] Management of WD in pregnancy usually consists of zinc sulfate or chelating agents, penicillamine and trientine. AASLD recommends continuing zinc sulfate at the same dosage but the chelating agents should be dose-reduced by 25-50% to promote wound healing if cesarean section becomes necessary.[64] Patients on D-penicillamine are discouraged from breastfeeding due to concern for potential harm to the infant. Spontaneous abortions have been attributed to WD, particularly if it is poorly controlled.[65]

Liver Transplant

Most patients with liver transplant have fertility restored within 6-12 months post-transplant, but higher rates of preeclampsia, preterm births and cesarean sections have been observed in these patients.[66] With the use of immunosuppressive medications including azathioprine, cyclosporine, tacrolimus and steroids, pregnant patients with history of a liver transplant can have a good quality of life.[67] Mycophenolic acid is avoided in pregnancy due to its association with congenital malformations and embryopathy.[68] Pregnancy should be avoided for at least one year following transplant to optimize graft function and subsequently, permit the use of a lower dose of immunosuppressive medications.[3]

Thrombosis

Pregnant women are at an increased risk for venous thromboembolism with an estimated incidence of 0.76 to 1.72 per 1000 pregnancies.[69] Pregnancy is associated with an increase in fibrinogen and clotting factors levels.[70] When thrombosis is observed, it is imperative to search for additional causes of hypercoagulable states due to a high recurrence risk.[70]

Budd-Chiari syndrome (BCS) can be triggered by pregnancy. It is characterized by obstruction of hepatic venous outflow. Patients may complain of right upper quadrant pain, abdominal distention and jaundice. Ascites and icterus may be evident on examination. Although hepatic failure and portal hypertension are both common complications of BCS,[71] anticoagulation therapy has improved fetal and maternal mortality.

Patients with a prior history of thrombosis should continue anticoagulation. Women on warfarin should be switched to low molecular weight heparin (LMWH) prior to conception due to the teratogenic effects of warfarin. Direct oral anti-coagulants (DOACs) are also teratogenic; therefore, these medications should be discontinued in pregnancy in favor of LMWH.[72]

Medications and Pregnancy

Previously, medications used in pregnancy were assigned a risk category defined by the Food and Drug Administration (FDA) as A, B, C, D and X based on limited research data on their safety derived from animal and human studies. As this classification system was not able to completely elicit the risks versus the benefits of medical therapy and provided limited information on the medication's effects in labor or lactation, the FDA introduced a new labeling system in June 2015. The new pregnancy and lactation labeling system includes narratives with general pregnancy information, fetal risk summary, clinical considerations and data on human and animal studies.[73]

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CONCLUSION

Pregnancy is associated with various physiological changes, affecting many organs, including the liver. It is important to differentiate between physiological and pathological processes in pregnancy to ensure timely diagnosis and management, particularly for the diseases unique to pregnancy. However, chronic liver diseases may present differently in pregnancy and that can pose a diagnostic and therapeutic dilemma. ■

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