Liver diseases in pregnancy: Diseases not unique to pregnancy

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Introduction

Pregnancy is a special clinical state with several normal physiological changes that influence body organs including the liver. Liver disease can cause significant morbidity and mortality in both pregnant women and their infants. Challenges arise in reaching an accurate diagnosis in light of such physiological changes. Laboratory test results should be carefully interpreted and the knowledge of what normal changes to expect is prudent to avoid clinical misjudgment. Other challenges entail the methods of treatment and their safety for both the mother and the baby. This review summarizes liver diseases that are not unique to pregnancy.

Key words: Liver; Pregnancy; Viral hepatitis; Autoimmune; Cirrhosis; Gallstones; Adenoma

Core tip: Pregnancy is a special clinical state with several normal physiological changes that influence body organs including the liver. Liver disease can cause significant morbidity and mortality in both pregnant women and their infants. Challenges involve making the diagnosis and the methods of treatment and their safety for both the mother and the baby. This review summarizes liver diseases that are not unique to pregnancy.

INTRODUCTION

Although not unique to pregnancy, liver diseases reviewed here can have significant consequences on pregnant women and their infants.

Approach to the diagnosis of liver conditions in preg-
Table 1  Normal physiological alterations in liver tests in pregnancy

| Test                        | First trimester | Second/third trimesters |
|-----------------------------|-----------------|-------------------------|
| Albumin                     | ↓               | ↓                       |
| ALT                         | N               | N                       |
| AST                         | N               | N                       |
| Total bilirubin             | ↓               | ↓                       |
| Alkaline phosphatase        | N               | ↑                       |
| GGT                         | N               | ↓                       |
| 5'-nucleotidase             | N               | May increase in second and third trimesters |
| Fasting total bile acids    | N               | N                       |
| Prothrombin time            | N               | N                       |

N: No change; ↑: Increase; ↓: Decrease; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase.

VIRAL HEPATITIS AND PREGNANCY

**Hepatitis A virus**

Hepatitis A virus (HAV) is an RNA virus that transmits through fecal-oral route, usually through contaminated water or food. Overall incidence is 9.1 per 100000 in the United States and less than 1:1000 pregnancies. Clinical presentation ensues within 2-4 wk of exposure. Generally, HAV does not result in chronic infection. Acute hepatitis A starts with prodromal symptoms including anorexia, malaise, nausea and vomiting, and progresses into jaundice and elevated liver transaminases. Presence of HAV immunoglobulin M (IgM) antibodies confirms the acute infection. Management is supportive care including optimization of hydration and nutrition. Rarely acute hepatitis A can lead to fulminant hepatic failure. Inactivated HAV vaccine and immunoglobulin prophylaxis are safe in pregnancy. Although vertical transmission has been reported, intranatal transmission is rare. Fecal-oral transmission during birth is possible. No cases of teratogenicity were reported, but maternal complications such as preterm labor were described. Susceptible woman should receive vaccination. Breast-feeding is not contraindicated in acute hepatitis A with following appropriate hygiene measures.

**Hepatitis B virus**

Hepatitis B virus (HBV) is a DNA virus that is highly infectious and transmits through intravenous route, sexual contact, and vertically from the mother to her fetus. It can present both as an acute or chronic infection. Pregnancy does not affect the course of infection directly. Fortunately, since universal children vaccination for hepatitis B was implemented in 1992, the numbers of vertically transmitted chronic hepatitis B cases, and its complications such as hepatocellular carcinoma have dropped. Prenatal screening for HBV is standard of care in many countries including the United States. Those susceptible should be vaccinated. Pregnant women exposed to HBV should receive HBV immunoglobulins (HBIG) within 72 h of exposure in addition to the vaccination series. Infants with infected mothers should receive both immunoglobulins and vaccination series at the time of delivery. While acute infection can present with a viral syndrome and jaundice such as that of acute hepatitis A infection, chronic infection is usually asymptomatic and diagnosis can be made relying on serum serology testing. A summary of the tests used in hepatitis B diagnosis and their interpretation is displayed in Table 2.

Treatment should follow guidelines published by medical societies such as the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver, or the Asian Pacific Association for the Study of the Liver in the United States, we recommend referring infected pregnant women to the state’s perinatal hepatitis B prevention program, that is CDC-funded (centers for disease control and prevention), and to liver specialists for optimizing counseling and treatment.

There are seven Food and Drug Administration (FDA)-approved medications for the treatment of hepato-
Table 3  Food and Drug Administration approved medications for hepatitis B treatment

| Generic name                      | Trade name    | Company                        | Approved for HBV treatment |
|-----------------------------------|---------------|--------------------------------|-----------------------------|
| Interferons                       | Intron® A     | Schering Corporation/ Merck and Co | 1992                        |
| Perinterferon α-2a                | Pegasis®      | Genentech/ Roche group          | 2005                        |
| Nucleosides/nucleotides           |               |                                |                             |
| Lamivudine                        | EPIVIR-HBV®   | Gilead Sciences                 | 1998                        |
| Adefovir dipivoxil                | HEPSERA®      | Gilead Sciences                 | 2002                        |
| Entecavir                         | BARACLIDE™    | Bristol-Myers Squibb            | 2005                        |
| Telbivudine                        | TVZERA®       | Novartis                        | 2006                        |
| Tenofovir                         | Viread        | Gilead Sciences                 | 2008                        |

1Pregnancy risk category C, can be used in the third trimester; 2Pregnancy risk category B. HBV: Hepatitis B virus.

tis B (Table 3) in non-pregnant patients. Interferon use is contraindicated in pregnancy. Tenofovir and Telbivudine belong to pregnancy risk category B; all others belong to category C. The choice to treat or not should be weighed in light of benefits versus risks for both the mother and her fetus. Those with higher viral load (serum HBV DNA > 10⁵ copies/mL) were at higher risk for vertical transmission in one study. Wen et al. showed recently that the adjusted odds ratio of transmission for each log10 copy/mL increase, is 3.49 (P = 0.001), with predictive rates of infection at maternal viral load levels of 7, 8, and 9-log10 copies/mL of 6.6% (P = 0.033), 14.6% (P = 0.001), and 27.7% (P < 0.001), respectively. Therefore, it is reasonable to treat those women or women with previous infected children, especially towards the end of pregnancy (from week 28 and up), with risk category B drugs or Lamivudine (increases birth defects if used in 1st trimester). In a meta-analysis, significant drop in the risk of vertical transmission was found in those who succeeded to lower HBV DNA below 10⁴ copies/mL. Telbivudine was used safely and with good efficacy in reducing transmission (0% vs 8%; P = 0.002) in a recent study.

Although cesarean section is proposed as a measure to lower the risk of transmission, particularly in women with high viral loads towards term, there is a conflicting evidence regarding choosing cesarean section versus vaginal delivery to lower the risk of vertical transmission. Breast-feeding should be encouraged for infants receiving HBIG and vaccination. On the other hand, no adequate evidence of the safety of breast-feeding in mothers receiving antiviral therapy is available and women on antiviral therapy with lamivudine, telbivudine or tenofovir should be discouraged from breast-feeding.

Hepatitis C virus

With prevalence around 1.6%, chronic hepatitis C infection continues to present a big public health concern in the United States. The majority of those patients, left untreated, will progress to cirrhosis with expected peak in prevalence around the year 2030, with expected medical cost exceeding $85 billion. Generally, all high-risk patients should be screened for hepatitis C virus (HCV) following CDC and AASLD guidelines. Those include children born to HCV infected mothers. While there is no approved medicine to treat chronic hepatitis C in pregnant women, those should be referred to liver experts for education regarding options of treatment after delivery and preventive measures to slow the progression of the disease. HCV antibodies ELISA testing is a sensitive test and carries high positive predictive value in high-risk patients. Diagnosis can be confirmed using HCV RNA polymerase chain reaction (PCR). There are several therapies for hepatitis C that are under investigation currently. Some of those could prove safe to use in pregnancy in the future. Pregnant women with hepatitis C should be educated about the mode of transmission and how to reduce the risk, smoking cessation, alcohol abstinence, and vaccination for hepatitis A and hepatitis B. They should also be screened for hepatitis B and human immunodeficiency virus (HIV) infection. Women undergoing treatment for hepatitis C, or those with partners undergoing treatment for hepatitis C, should avoid pregnancy by using at least 2 forms of barrier contraception, for the period of treatment and 6 mo after.

Infants of hepatitis C infected mothers were at higher risk for low birth weight, being small for gestational age, or requiring intensive care upon birth in one report. The risk of vertical transmission is approximately 4%. This risk increased up to 19.4% when co-infected with HIV. High viral load also increase the risk for vertical transmission. HCV transmission could occur through viral transcytosis across trophoblast cells mediated by HCV receptors expressed on trophoblasts or through some form of injury that influences the placental barrier. Although there were few reports of increased risk of transmission with premature rupture of membrane, more than 6 h before delivery, mode of delivery was not found to change the risk of hepatitis C transmission. As the new era of direct antiviral agents is evolving, treating hepatitis C during pregnancy may become an option and thus the possibility of reducing the risk of transmission.

Breast-feeding is considered safe when nipples are not cracked or bleeding according to CDC recommendations.

Hepatitis D virus

Hepatitis D virus (HDV) is an RNA virus that requires...
Hepatitis E virus
Hepatitis E virus (HEV) is an RNA virus that is usually transmitted through fecal-oral means, although transmission via infected blood products and vertical transmission has been reported\(^\text{[42]}\). It is usually a self-limiting disease in immunocompetent patients. Hepatitis E can cause significant disease in patients with chronic liver disease and can present in a chronic form leading to fibrosis in immunocompromised individuals\(^\text{[59]}\). Pregnant women in highly endemic areas are particularly at risk with up to 60% developing fulminant hepatic failure with a maternal death rate of up to 31%\(^\text{[44,45]}\). A review from Bangladesh suggests it is responsible for 9.8% of pregnancy-related deaths\(^\text{[46]}\). On the other hand, the severity of the disease was not different between pregnant and non-pregnant women in non-endemic places such as the United States and Europe. A report suggested that such variance in severity between endemic and non-endemic areas might be related to different genotypes of HEV\(^\text{[57]}\). Other studies suggested that pregnancy per se is not a poor prognostic factor for those who developed acute liver failure\(^\text{[48]}\). To a lesser extent, hepatitis E is prevalent in some western countries, particularly genotype 3.

Vertical transmission was described up to 78.9% with infant mortality of 40%\(^\text{[60]}\). The level of viremia appears to be associated with the severity of the disease during pregnancy\(^\text{[49]}\). Despite such high mortality, current treatment remains supportive. Pregnant woman seeking travel to endemic areas should be counseled about the risk of hepatitis E, and be advised to avoid unpurified water, uncooked fruit, vegetables, and shellfish.

Hepatitis E vaccines have been developed and evaluated in trials but has not been approved for commercial use yet. Their utility is yet to be determined\(^\text{[50-54]}\).

Herpes simplex virus
32 out of 137 cases of herpes simplex virus (HSV) hepatitis were pregnant women in one report, suggesting their susceptibility\(^\text{[56]}\). Although rare, HSV hepatitis carries a very high mortality (39%) if inappropriately treated\(^\text{[55]}\). Providers should have high index of suspicion in this patient group in the appropriate clinical setting; elevated liver transaminases usually 100 times upper level of normal with typically normal or mildly elevated bilirubin (anicteric hepatitis)\(^\text{[57-60]}\). Serology testing including anti-HSV IgM should be ordered. HSV PCR can be ordered as well to confirm diagnosis. Recent study has revealed that HSV DNA load correlated with liver transaminase levels and disease severity\(^\text{[61]}\). Although no strong evidence to support starting Acyclovir in patients with indeterminate acute liver failure, clinicians should consider empirical therapy with acyclovir when HSV hepatitis is suspected\(^\text{[62]}\). Liver biopsy with appropriate immunohistochemistry staining can be useful, but usually is avoided because of its invasive nature, coagulopathy and because of the potential delay in results/treatment.

AUTOIMMUNE HEPATITIS AND PREGNANCY
Autoimmune hepatitis is a disease characterized by elevated liver aminotransferases, hypergammaglobulinemia, and positive serum autoantibodies. Autoimmune hepatitis and pregnancy (AHP) is more common in females, especially those in childbearing ages. It can happen during pregnancy and may not follow consistent pattern. Normalization of liver aminotransferases has been described in patients with no treatment\(^\text{[63]}\). This normalization could be related to the immunotolerant state that predominates pregnancy. On the other hand, flare-ups have been reported during and after pregnancy\(^\text{[64]}\). Prematurity and fetal-loss were described in those patients\(^\text{[66]}\). A link was observed between antibodies to soluble liver antigen/liver-pancreas and ribonucleoprotein/Sjögren’s syndrome A and adverse outcomes\(^\text{[65]}\). Inadequate disease control in the year prior to pregnancy and the absence of treatment during pregnancy were associated with unfavorable outcomes in a recent study\(^\text{[59]}\).

Although the patients should be counseled about possible adverse outcomes, pregnancy appears to be safe in well-controlled AHP women\(^\text{[67]}\). Special considerations should be given to the postpartum period as flare-ups may occur frequently, and treatment should be resumed preemptively two weeks before delivery and maintained thereafter\(^\text{[68]}\). Immunosuppressive therapy with steroids and agents such as azathioprine is the mainstay for treatment of AHP. Azathioprine use during pregnancy is generally safe (despite reports of birth defects in animal models)\(^\text{[69]}\).

PRIMARY BILIARY CIRRHOSIS/PRIMARY SCLEROSING CHOLANGITIS AND PREGNANCY
There is limited data about pregnancy in patients with primary biliary cirrhosis. Reports have ranged from normal course of pregnancy and good fetal outcomes to poor prognosis for both mother and fetus\(^\text{[69,70]}\). Earlier diagnosis and the use of ursodeoxycholic acid (UDCA) in treatment, which has been used safely in pregnancy, have been linked to favorable outcomes\(^\text{[71]}\). Primary sclerosing cholangitis did not appear to reduce fertility and resulted in good outcomes, in one report. UDCA was successfully used to control pruritus in this cohort\(^\text{[72]}\).

WILSON’S DISEASE AND PREGNANCY
Wilson’s disease is an autosomal recessive disease with
prevalence of 1:30000 to 1:50000[78]. It affects hepatic copper transport with inhibition of biliary excretion, resulting in excess circulating copper and deposition in organs such as the liver and the brain. Cases of reduced fertility and recurrent spontaneous abortions in untreated women were reported[79]. Chelation therapy using D-penicillamine or trientine, or the use of zinc to reduce intestinal absorption of copper, have been the mainstay therapy for Wilson’s disease. Zinc has been used with minimal teratogenicity during pregnancy[79]. Although teratogenic effects of D-penicillamine in humans and animals, and teratogenic effects of trientine in animals were described[80–82], therapy should not be discontinued as this can result in severe hemolysis, worsening of liver function and even death. Even though zinc dosages can be maintained during pregnancy, AASLD recommends lowering D-penicillamine and trientine to the minimum needed (usually 25%–50% of the pre-pregnancy dose)[79], particularly towards term to aid in wound healing. Baseline dosages can be resumed postnatally. The mother should be counseled, and both the mother and her fetus should be monitored closely during pregnancy. Breastfeeding is discouraged as D-penicillamine can be harmful to the infant and safety has not been established with trientene and zinc.

GALLSTONES AND PREGNANCY
Physiological changes during pregnancy particularly hormonal changes lead to decrease in contractility of the gallbladder and changes in bile content, with increase in cholesterol saturation, resulting in increase in lithogenicity of the bile[83]. Incidence of gallstones is up to 12% in pregnant women[84]. Those typically remain asymptomatic. The patient can present with biliary pain, gallstone pancreatitis, or less likely acute cholecystitis. Other manifestations such as cholelithiasis and cholangitis can also happen. Management is mostly conservative with hydration and antibiotics if indicated. In more severe cases, cholecystectomy can be indicated. Endoscopic retrograde cholangiopancreatography (ERCP) can also be used with taking precautions to minimize radiation exposure of the fetus. In general, surgical procedures are the safest in the second trimester. ERCP was reported to be associated with higher risk for preterm pregnancy and low birthweight when performed in the first trimester. Post-ERCP pancreatitis rate was higher in pregnancy than general population[85–87].

Table 4 Options for portal hypertension management in pregnancy

| Esophageal varices | Nonelective β-blockers |
|                   | Endoscopic and ligation and/or sclerotherapy |
| Aspects           | Sodium (salt) restriction, diuretics |
| Hepatic encephalopathy | Lactulose, rifaximin |

TIPS: Transjugular portosystemic shunt.

CIRRHOSIS/ PORTAL HYPERTENSION AND PREGNANCY
Pregnancy in cirrhotic women is rare, probably because of low prevalence of cirrhosis in reproductive age group (45 in 100000) and also due to amenorrhea and anovulation, likely related to metabolic and hormonal derangements[86]. The physiological increase in plasma volume during pregnancy can worsen portal hypertension, resulting in increase risk of variceal bleeding. Variceal bleeding can happen in up to 38% of cirrhotic pregnant women. This is even higher in those with known portal hypertension. Those with known varices have a 78% chance of bleeding[87]. AASLD recommends screening for esophageal varices by the second trimester, as the risk of bleeding appears to be highest at that time. Women with cirrhosis planning to become pregnant should be screened before conception by endoscopy and prophylaxis (with nonselective beta blockers) should be started as recommended by AASLD guidelines. Complications of portal hypertension in pregnancy can be as high as 50% resulting in high mortality rate of up to 18%, and higher risk for fetal loss[88]. Pregnancy should be avoided in women with previous history of variceal bleeding and liver insufficiency. Means such as early forceps delivery or vacuum extraction should be considered to prevent excessive straining during vaginal delivery. Management options of complications of portal hypertension are summarized in Table 4. All medications used during pregnancy should be checked as of which risk category they fall under according to the FDA classification before prescribing (Tables 5 and 6).

HEPATOCELULAR ADENOMA AND PREGNANCY
The incidence of hepatocellular adenoma has increased since the introduction of oral contraceptives. There is a link between pregnancy and liver adenomas secondary to higher levels of hormones[89]. Rupture of adenomas has resulted in maternal mortality of a 44% and fetal loss of 38% in one study[89]. Adenoma rupture risk increases towards the end of pregnancy[90]. Women with adenomas > 5 cm or those with previous complications with adenomas, should avoid subsequent pregnancies. Those pregnant with smaller adenomas should be monitored closely with serial ultrasound imaging. If the lesion is progressively enlarging, or 5 cm in size or bigger, surgical resection should be considered[89]. Radiofrequency ablation is another modality that can be used in the treatment of hepatic adenomas[91,92]. Close monitoring of the lesion should continue in the postpartum period as well.

HEPATOCELULAR CARCINOMA AND PREGNANCY
Although rare, hepatocellular carcinoma has been reported during pregnancy. Fibrolamellar variant of hepatocel-
Table 5  The Food and Drug Administration pregnancy risk categories of medicines

| Pregnancy category | Definition |
|--------------------|------------|
| A                  | Controlled studies show no risk |
| B                  | Animal studies show no risk, and there are no human controlled studies. Or animal studies may have revealed an adverse effect that was not reproduced in human controlled studies |
| C                  | No human studies and either animal studies show an adverse effect or there are no studies available. Use if the risk is justified |
| D                  | Positive evidence of risk in human studies, only if the potential benefits outweigh the risk |
| X                  | Contraindicated in pregnancy: Risk is confirmed in animal and human studies and outweighs any advantage |

Table 6  Food and Drug Administration pregnancy risk categories of some liver disease medications

| Medicine                  | Pregnancy category | Medicine                  | Pregnancy category |
|---------------------------|--------------------|---------------------------|--------------------|
| Nadolol                   | C                  | Ribavirin                 | X |
| Propranolol               | C                  | Telaprevir                | B |
| Rifaximil                 | C                  | Boceprevir                | B |
| Lactulose                 | B                  | Tenofovir                 | B |
| Furosemide                | C                  | Entecavir                 | C |
| Spironolactone            | C                  | Telbuvudine               | B |
| Corticosteroids           | B                  | Adeovir                   | C |
| Azathioprine              | D                  | Lamivudine                | C |
| Cyclosporin               | C                  | Acyclovir                 | B |
| Mycophenolate mofetil     | D                  | Ursodeoxycholic acid      | B |
| Tacrolimus                | C                  | Penicillamine             | D |
| Sirolimus                 | C                  | Trientine                 | C |
| Antithymocyte globulin    | C                  | Zinc sulfate              | C |
| Pegylated interferon      | C (contraindicated in pregnancy) | Interferon alpha 2b | C (contraindicated in pregnancy) |

Hepatic carcinoma (HCC) was also reported\(^\text{[94-96]}\). Pregnant women with HCC can have shorter median survival than those non-pregnant. Higher levels of estrogen and immune suppression during pregnancy can play a role with HCC progression\(^\text{[97]}\). Modalities such as surgical resection and radiofrequency ablation can be used in selected patients. Limited data are available about the management of hepatocellular carcinoma in pregnancy.

HEPATIC VEIN THROMBOSIS/PORTAL VEIN THROMBOSIS AND PREGNANCY

Budd-Chiari syndrome (BCS) is rare in pregnancy but can have grave consequences for both the mother and her fetus. The physiological hypercoagulable state can contribute in BCS development in pregnancy. Other predisposing factors are factor V Leiden mutation and prothrombin gene mutations. BCS entails thrombosis of the hepatic vein resulting in passive congestion of the hepatic sinusoids leading to ischemia and portal hypertension. Low molecular weight heparin should be started if no contraindications. Extreme measures such as portacaval shunting and liver transplantation during pregnancy were reported\(^\text{[98,99]}\). Subsequent pregnancies are not absolutely contraindicated with appropriately treated disease. The mother should be counseled about the possible maternal and fetal unfavorable outcomes.

Portal vein thrombosis (PVT) is rare and can also occur during pregnancy. Local causes such as cirrhosis, intra-abdominal infections, or malignancies may predispose to PVT. Systemic disorders resulting in hypercoagulable state such as factor V Leiden mutation, anti-phospholipid syndrome, or myeloproliferative disorders should be also excluded. In acute portal vein thrombosis, anti-coagulation should be used for 3 mo at the least. Patients with chronic portal vein thrombosis should be screened for gastroesophageal varices and should be treated accordingly\(^\text{[100]}\).

CONCLUSION

Pregnant women can have a variety of liver diseases with different incidences. Clinicians should be aware of the clinical presentations and be able to manage those conditions with special attention to the peculiarities in relation to the mother and her infant. In this review we have summarized several of the liver diseases that can happen during pregnancy and offered an overview of their management.

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