

REVIEW

CME CREDIT **EDUCATIONAL OBJECTIVE:** The reader will develop a plan of care for pregnant women with viral hepatitis that includes appropriate treatment of the mother and minimizes the risk of transmission to the infant.

ZHILI SHAO, MD, PhD

Department of Cellular and Molecular Medicine, and Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic

MOHAMMAD AL TIBI, MD

Section of Hepatology, Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic

JAMILÉ WAKIM-FLEMING, MD

Section of Hepatology, Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic

Update on viral hepatitis in pregnancy

ABSTRACT

Pregnant women with acute viral hepatitis are at higher risk of morbidity and death than pregnant women with chronic viral hepatitis. The risk of death is highest with acute viral hepatitis E, and the rate of transmission to the baby may be highest with hepatitis B virus (HBV) infection. Managing viral hepatitis in pregnancy requires assessing the risk of transmission to the baby, determining the gestational age at the time of infection and the mother's risk of decompensation, and understanding the side effects of antiviral drugs.

KEY POINTS

Preventing vertical transmission of HBV infection in pregnancy is key to decreasing the global burden of this infection. Universal maternal screening and passive-active immunoprophylaxis of newborns have reduced transmission of HBV, but the addition of antiviral therapy is necessary to further decrease immunoprophylaxis failure.

Tenofovir, telbivudine, and lamivudine can be used safely in pregnancy without apparent teratogenicity or other harmful effects on mother or baby. But optimal outcome requires discussion of safety and the plan of care with the patient, obstetrician, and hepatologist.

Most pregnant women with hepatitis C virus (HCV) infection have chronic disease, with no effects on the pregnancy or baby, but 3% to 5% transmit HCV to their child at the time of birth. All pregnant women at risk should be screened at the first prenatal visit. The safety and efficacy of treating pregnant women to prevent transmission to the fetus are not established; thus, treatment is not recommended for pregnant women.

VIRAL HEPATITIS AFFECTS mother and child, and pregnancy can exacerbate the disease. Vertical transmission contributes significantly to the high prevalence of viral hepatitis and compromises the well-being and the prognosis in the newborn. The indications for therapy in pregnant women may differ from those in the general population, and new therapies are available.

■ HEPATITIS A

Hepatitis A virus (HAV) infection is associated with significant morbidity and death around the world, as 1.4 million cases are reported every year worldwide.¹ However, in the United States, the prevalence has declined by 95% since HAV vaccination was introduced in 1995, and in 2013, the prevalence was 0.6 per 100,000 population.² Acute HAV infection during pregnancy is rare. As a result, the incidence during pregnancy is difficult to ascertain.³

HAV is transmitted by the fecal-oral route from person to person contact and from contamination of food and water. Vertical transmission from pregnant mother to fetus has not been reported.⁴

Clinical outcomes of HAV in pregnancy

Acute HAV infection during pregnancy is rare, and teratogenicity associated with HAV has not been reported.³ The course of the disease during pregnancy is generally similar to that in nonpregnant patients, with excellent maternal and fetal outcomes in developed nations. There have been reports in developing nations of premature contractions and labor, placental separation, premature rupture of the membranes, and vaginal bleeding.^{5,6}

doi:10.3949/cjfm.84a.15139

Diagnosis

Routine screening for HAV is not recommended, but serologic testing by detection of anti-HAV immunoglobulin M (IgM) antibodies is done in high-risk patients suspected of having acute HAV infection.

Prevention

Prevention includes adherence to sanitary practices and active and passive immunoprophylaxis.³ Universal vaccination for pregnant mothers is not recommended,^{1,2,6} but vaccination is recommended for high-risk patients and mothers—those with chronic liver disease, those receiving clotting factors, those who use illegal drugs, and travelers to areas where HAV is endemic. Immune globulin is also available for postexposure prophylaxis. HAV vaccines and immune globulin are safe in pregnancy.^{3,6,7}

Treatment

Treatment of acute HAV in pregnancy is supportive because of its benign nature; few patients require hospitalization.³

Pregnant patients with HAV can deliver vaginally, and breastfeeding is not contraindicated.⁸

■ HEPATITIS B

Hepatitis B virus (HBV) infection is a major global health problem. About 240 million people worldwide have chronic HBV infection, and more than 780,000 die every year from acute and chronic consequences.⁹

Vertical transmission is responsible for about half of chronic HBV infections worldwide. Thus, interruption of mother-to-child transmission is important. Universal maternal screening and passive-active immunoprophylaxis of newborns have lowered the transmission rates to between 5% and 10%. The 10% failure rate is unacceptably high and has been attributed to seropositivity for hepatitis B e antigen and a high viral load in the mother (ie, HBV DNA > 10⁶ copies/mL). High viral load is an independent risk factor for failure of immunoprophylaxis.¹⁰ Therefore, antiviral therapy is suggested in pregnant women who have a high HBV viral load to further decrease the chance of mother-to-child transmission and to prevent failure of immunoprophylaxis.¹¹

Clinical outcomes of HBV in pregnancy

Acute HBV infection during pregnancy is usually benign and is not associated with increased risk of death or teratogenicity.¹² Symptomatic disease in the mother with acute hepatitis B includes nausea, vomiting, abdominal pain, fatigue, and jaundice.³ For the newborn, there is increased risk of low birth weight and prematurity.¹³

When acute HBV infection occurs early in pregnancy, the rate of perinatal transmission is about 10%, increasing to 60% if it occurs near delivery.^{12,13}

Chronic HBV infection does not usually affect the outcome of pregnancy, but it may if the woman has cirrhosis or advanced liver disease¹⁴; however, pregnancy is very rare in women with HBV cirrhosis due to anovulation, and acute HBV flares have been described during pregnancy and postpartum.¹⁵

Pregnant patients with cirrhosis and portal hypertension are at risk of hepatic decompensation, variceal bleeding, and death.¹⁶ Risk is high with a score of 10 or more on the Model for End-stage Liver Disease scale, and is low with a score of 6 or less.¹⁷ Like nonpregnant patients, pregnant patients with cirrhosis should be monitored, and upper endoscopy should be performed in the 2nd trimester to assess for varices. A beta-blocker should be given or banding of varices should be done to avoid rupture. Rates of fetal demise, premature labor, spontaneous abortion, and stillbirth are high with portal hypertension.¹⁶

Risk of mother-to-child HBV transmission

Vertical HBV transmission can occur during the antepartum, intrapartum, and postpartum periods,^{18,19} but it most often occurs during the intrapartum period at the time of delivery. Without immunoprophylaxis of the newborn, the risk of mother-to-child transmission can be as high as 90% if the mother is hepatitis B e antigen-positive and has a viral load greater than 10⁶ copies/mL. With active and passive immunoprophylaxis, the risk decreases substantially.

Screening and diagnosis

All pregnant women should be tested for hepatitis B surface antigen during the 1st trimester,²⁰ or any time thereafter if early testing was not done, even if they were vaccinated before becoming pregnant.²¹

Routine screening for HAV is not recommended

Prevention

HBV infection is best prevented before pregnancy by vaccinating the mother or, after delivery, by vaccinating the newborn. Universal vaccination of newborns has been the standard of care since the 1990s. Pregnant women should be tested early in the pregnancy; unvaccinated, uninfected women at high risk of acquiring HBV (eg, because of sexual contacts or intravenous drug use) should be vaccinated.^{2,3}

HBV vaccine and immune globulin are both approved by the US Food and Drug Administration (FDA) for prevention of HBV infection and can be given during pregnancy and breastfeeding.³ All infants should be vaccinated for HBV at birth, and all infants born to mothers who test positive for hepatitis B s antigen should receive the HBV vaccine and the immune globulin within 12 to 24 hours after delivery. The vaccine series should be completed within 6 months.^{20,21} This will decrease the rate of neonatal infection.

Treatment of HBV infection in pregnancy

The main objectives of treating chronic HBV infection in pregnancy are to maintain stable liver function in the mother and to prevent neonatal infection, which may cause cirrhosis and hepatocellular carcinoma and contribute to the global burden of the disease.²² Therefore, maternal HBV DNA and liver aminotransferase levels should be tested regularly during gestation.

The current guidelines of the American Association for the Study of Liver Diseases suggest antiviral therapy to reduce the risk of perinatal transmission of HBV in pregnant women with an HBV DNA level greater than 200,000 IU/mL or greater than 10⁶ copies/mL.^{23,24}

In a meta-analysis,²⁵ antiviral therapy with lamivudine, telbivudine, or tenofovir showed no apparent teratogenicity or safety concerns for maternal and fetal outcomes²⁶ and significantly reduced the rate of mother-to-child transmission. Of these 3 drugs, telbivudine was associated with a higher rate of normalization of liver enzymes, HBV suppression, and e-antigen seroconversion.²⁵ Lamivudine has proven the test of time in mothers co-infected with HBV and human immunodeficiency virus (HIV). However, tenofovir is considered the preferred treatment in pregnancy, owing to concerns about drug resistance to telbivudine and lamivudine and a high genetic barrier to resistance with tenofovir.²⁶ In mothers with HBV and HIV treated with tenofovir, treatment was associated with lower bone mineral density in the newborns, with a propensity for renal injury in the mothers. No safety concerns for maternal or fetal outcomes were identified in pregnant women infected only with HBV.²⁵

Many pregnant mothers choose to stop therapy around the time of conception because of safety concerns for the baby. In such situations, close monitoring is necessary to detect flares of HBV infection.

When the decision to treat is made, treatment should begin at 28 to 30 weeks of gestation, when organogenesis is complete and to allow enough time for HBV DNA levels to decline.

Breastfeeding is not contraindicated because antiviral drugs are minimally excreted in breast milk and are unlikely to cause toxicity. However, data are insufficient as to the long-term safety for the newborn when the mother took these drugs during pregnancy and while breastfeeding.^{23,27}

Alanine aminotransferase and HBV DNA levels should be monitored postpartum because of the possibility of a hepatitis flare. In this setting, any of the three drugs can be used.²⁸ For mothers on therapy because of cirrhosis or an advanced histologic feature, antiviral therapy should be continued throughout pregnancy to prevent disease progression and decompensation.^{19,22,27}

No drug therapy is necessary for pregnant carriers of HBV.

Delivery and breastfeeding

The mode of delivery does not appear to have a significant effect on the interruption of vertical transmission of HBV.²⁹ Cesarean delivery is not recommended by the US Centers for Disease Control and Prevention (CDC)² or the American College of Obstetricians and Gynecologists.⁶ Breastfeeding is encouraged if the infant has received appropriate immunoprophylaxis.⁶

Coinfection with hepatitis D

Coinfection with hepatitis D virus (HDV) and HBV is associated with severe acute hepatitis^{30,31} and increases the risk of death by a factor of 10. The World Health Organization

Test all pregnant women for hepatitis B surface antigen, even if they were vaccinated before becoming pregnant

recommends testing for HDV in pregnant women who are HBV-positive.⁸

Prevention of HDV infection requires prevention of HBV. The treatment of HDV in pregnancy is supportive. Pegylated interferon is successful outside pregnancy but is contraindicated during pregnancy.³² In patients with fulminant hepatic failure and end-stage liver disease, liver transplant can be lifesaving.

Take-home points

- HBV infection during pregnancy is usually benign and not severe but can be associated with an increased risk of mother-to-child transmission and progression of liver disease in the pregnant mother.
- Prevention of vertical transmission of HBV is important to reduce the burden of chronic HBV infection. Universal maternal screening early in pregnancy and passive-active immunoprophylaxis of newborns are usually sufficient to prevent vertical transmission of HBV, but antiviral therapy is needed for highly viremic mothers to further reduce the risk.
- Antiviral therapy is also indicated for pregnant women with moderate to severe hepatitis or cirrhosis to prevent disease progression and liver failure.
- Telbivudine, tenofovir, or lamivudine can be used during pregnancy, but more data are needed on the long-term safety of fetal exposure to these agents.

■ HEPATITIS C

The global prevalence of hepatitis C virus (HCV) infection is 2% to 3%, with 130 to 170 million HCV-positive people, most of whom are chronically infected.³³ The incidence of HCV during pregnancy is 1% to 2.4%, but 3% to 5% of infected mothers transmit HCV to their child at the time of birth.^{6,34} Women coinfect with HIV and HCV have twice the risk of perinatal HCV transmission compared with women who have HCV infection alone.^{6,34}

HCV infection is usually asymptomatic and is discovered either by screening high-risk patients or during evaluation of persistently elevated aminotransferase levels. Acute HCV infection during pregnancy has been reported only rarely, and most pregnant women who

are infected have chronic disease with no effect on the pregnancy or the infant.^{6,34}

Treatment

The CDC recommends that all adults (including pregnant women) born between 1945 and 1965 undergo 1-time testing for HCV without prior ascertainment of HCV risk (strong recommendation, with moderate quality of evidence).³⁵ The most important risk factor for HCV infection is past or current injection drug use.³³ Additional risk factors are similar to those for nonpregnant patients.

Because of the benign effect of HCV on the pregnancy, treatment is not recommended. To decrease the risk of maternal-child transmission, it is prudent to avoid amniocentesis, scalp instrumentation, and prolonged rupture of membranes.⁶

There is no vaccine or immune globulin for prevention. HCV infection should not influence the mode of delivery, and it is not a contraindication to breastfeeding.^{34,36,37}

■ HEPATITIS E

Every year, 20 million cases of hepatitis E virus (HEV) infection are recorded worldwide. These numbers include 3.3 million symptomatic cases and 56,600 deaths.³⁸ HEV infection is most common in developing countries, and pregnant women traveling to these areas are at high risk of acquiring this infection, of developing fulminant hepatitis, and of death.³⁹ Sporadic cases not associated with travel are increasingly reported in developed countries and are attributed to immunocompromised status (due to HIV or solid-organ transplant).^{38,40}

Modes of transmission of HEV are mainly via fecal-oral contamination and by vertical transmission.⁴¹

Diagnosis

HEV infection can be diagnosed either by detecting IgM antibody with an enzyme-linked immunosorbent assay or by detecting HEV RNA in the blood using reverse transcription polymerase chain reaction testing.⁴²

Treatment and prevention

Hospitalization should be considered for pregnant women. Ribavirin or pegylated interferon alpha or both are effective but are contraindicated in pregnancy because of the risk of

The goals of treating chronic HBV infection in pregnancy: stabilize liver function in the mother, prevent infection in the newborn

teratogenicity.^{41,42} Urgent liver transplant can be a successful option in acute liver failure.

Prevention relies primarily on good sanitation, clean drinking water, and avoiding raw

pork and venison. Boiling and chlorination of water inactivate HEV.^{39,40} Pregnant women should be advised to avoid travel to highly endemic areas.

REFERENCES

1. **World Health Organization (WHO).** Hepatitis A fact sheet. www.who.int/mediacentre/factsheets/fs328/en/. Accessed December 7, 2016.
2. **US Centers for Disease Control and Prevention (CDC).** Viral hepatitis—statistics & surveillance. www.cdc.gov/hepatitis/statistics/2013surveillance/commentary.htm#hepatitisA. Accessed December 7, 2016.
3. **Rac MW, Sheffield JS.** Prevention and management of viral hepatitis in pregnancy. *Obstet Gynecol Clin North Am* 2014; 41:573–592.
4. **Workowski KA, Bolan GA; Centers for Disease Control and Prevention (CDC).** Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015; 64:1–137.
5. **Elinav E, Ben-Dov IZ, Shapira Y, et al.** Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology* 2006; 130:1129–1134.
6. **American College of Obstetricians and Gynecologists.** ACOG Practice Bulletin No. 86: Viral hepatitis in pregnancy. *Obstet Gynecol* 2007; 110:941–956.
7. **Advisory Committee on Immunization Practices.** Guidelines for Vaccinating Pregnant Women. www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html. Accessed December 7, 2016.
8. **Daudi N, Shouval D, Stein-Zamir C, Ackerman Z.** Breastmilk hepatitis A virus RNA in nursing mothers with acute hepatitis A virus infection. *Breastfeed Med* 2012; 7:313–315.
9. **World Health Organization (WHO).** Hepatitis B fact sheet. www.who.int/mediacentre/factsheets/fs204/en/. Accessed December 7, 2016.
10. **Zou H, Chen Y, Duan Z, Zhang H, Pan C.** Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. *J Viral Hepat* 2012; 19:e18–e25.
11. **Pan CQ, Lee HM.** Antiviral therapy for chronic hepatitis B in pregnancy. *Semin Liver Dis* 2013; 33:138–146.
12. **Sookoian S.** Liver disease during pregnancy: acute viral hepatitis. *Ann Hepatol* 2006; 5:231–236.
13. **Jonas MM.** Hepatitis B and pregnancy: an underestimated issue. *Liver Int* 2009; 29(suppl 1):133–139.
14. **Wong S, Chan LY, Yu V, Ho L.** Hepatitis B carrier and perinatal outcome in singleton pregnancy. *Am J Perinatol* 1999; 16:485–488.
15. **Rawal BK, Parida S, Watkins RP, Ghosh P, Smith H.** Symptomatic reactivation of hepatitis B in pregnancy. *Lancet* 1991; 337:364.
16. **Aggarwal N, Negi N, Aggarwal A, Bodh V, Dhiman RK.** Pregnancy with portal hypertension. *J Clin Exp Hepatol* 2014; 4:163–171.
17. **Westbrook RH, Yeoman AD, O'Grady JG, Harrison PM, Devlin J, Heneghan MA.** Model for end-stage liver disease score predicts outcome in cirrhotic patients during pregnancy. *Clin Gastroenterol Hepatol* 2011; 9:694–699.
18. **Cheung KW, Seto MT, Wong SF.** Towards complete eradication of hepatitis B infection from perinatal transmission: review of the mechanisms of in utero infection and the use of antiviral treatment during pregnancy. *Eur J Obstet Gynecol Reproduct Biol* 2013; 169:17–23.
19. **Pan CQ, Duan AP, Bhamidimarri KR, et al.** An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. *Clin Gastroenterol Hepatol* 2012; 10:452–459.
20. **Mast EE, Margolis HS, Fiore AE, et al; Advisory Committee on Immunization Practices (ACIP).** A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep* 2005; 54:1–31.
21. **US Centers for Disease Control (CDC).** Prevention of perinatal transmission of hepatitis B virus: prenatal screening of all pregnant women for hepatitis B surface antigen. *MMWR Morb Mortal Wkly Rep* 1988; 37:341–346, 351.
22. **Han GR, Xu CL, Zhao W, Yang YF.** Management of chronic hepatitis B in pregnancy. *World J Gastroenterol* 2012; 18:4517–4521.
23. **Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases.** AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; 63:261–283.
24. **Tran TT, Ahn J, Reau N.** ACG clinical guideline: liver disease and pregnancy. *Am J Gastroenterol* 2016; 111:176–194.
25. **Brown RS Jr, McMahon BJ, Lok AS, et al.** Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. *Hepatology* 2016; 63:319–333.
26. **Brown RS Jr, Verna EC, Pereira MR, et al.** Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: findings from the antiretroviral pregnancy registry. *J Hepatol* 2012; 57:953–959.
27. **Lamberth JR, Reddy SC, Pan JJ, Dasher KJ.** Chronic hepatitis B infection in pregnancy. *World J Hepatol* 2015; 7:1233–1237.
28. **Potthoff A, Rifai K, Wedemeyer H, Deterding K, Manns M, Strassburg C.** Successful treatment of fulminant hepatitis B during pregnancy. *Z Gastroenterol* 2009; 47:667–670.
29. **Yang J, Zeng XM, Men YL, Zhao LS.** Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus—a systematic review. *Virol J* 2008; 5:100.
30. **Price J.** An update on hepatitis B, D, and E viruses. *Top Antivir Med* 2014; 21:157–163.
31. **World Health Organization (WHO).** Global alert and response. Hepatitis Delta. www.who.int/csr/resources/publications/hepatitis/who_cds_csr_ncs_2001_1/en/. Accessed December 7, 2016.
32. **Abbas Z, Memon MS, Mithani H, Jafri W, Hamid S.** Treatment of chronic hepatitis D patients with pegylated interferon: a real-world experience. *Antivir Ther* 2014; 19:463–468.
33. **Baldo V, Baldovin T, Trivello R, Floreani A.** Epidemiology of HCV infection. *Curr Pharm Des* 2008; 14:1646–1654.
34. **Floreani A.** Hepatitis C and pregnancy. *World J Gastroenterol* 2013; 19:6714–6720.
35. **US Centers for Disease Control and Prevention.** Viral hepatitis—CDC recommendations for specific populations and settings. www.cdc.gov/hepatitis/populations/1945-1965.htm. Accessed December 7, 2016.
36. **World Health Organization (WHO).** Hepatitis C fact sheet. www.who.int/mediacentre/factsheets/fs164/en/. Accessed December 7, 2016.
37. **Moyer VA; US Preventive Services Task Force.** Screening for hepatitis C virus infection in adults: US Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2013; 159:349–357.
38. **World Health Organization (WHO).** Hepatitis E fact sheet. www.who.int/mediacentre/factsheets/fs280/en/. Accessed December 7, 2016.
39. **Velosa M, Figueiredo A, Gloria H, et al.** Fulminant hepatitis E in a pregnant woman. *GE Port J Gastroenterol* 2013; 20:210–214.
40. **US Centers for Disease Control and Prevention (CDC).** Viral hepatitis—hepatitis E information. Hepatitis E FAQs for health professionals. www.cdc.gov/hepatitis/hev/hevfaq.htm. Accessed December 7, 2016.
41. **Peters van Ton AM, Gevers TJ, Drenth JP.** Antiviral therapy in chronic hepatitis E: a systematic review. *J Viral Hepat* 2015; 22:965–973.
42. **Kamar N, Bendall R, Legrand-Abravanel F, et al.** Hepatitis E. *Lancet* 2012; 379:2477–2488.

ADDRESS: Jamilé Wakim-Fleming, MD, Section of Hepatology, Department of Gastroenterology and Hepatology, A51, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; flemingj1@ccf.org