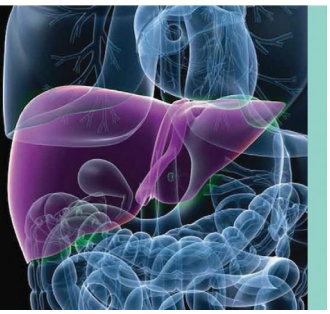

Viral Hepatitis in Pregnancy: An Update on Screening, Diagnosis, and Management

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Viral hepatitis in pregnancy is common; accordingly, there is a need for evolved best practices in the approach to treatment of this special population.[1] Historically, the major limitation to standardization of evaluation and management of pregnant patients with viral hepatitis had been the availability of high-quality evidence and consensus expert opinion. In this article, we review the updated evidence for the screening, diagnosis, and management of acute and chronic viral hepatitis in pregnancy.

Viral hepatitis in pregnancy increases the risk for pregnancy-related complications, as well as the risks associated with acute and chronic liver disease for both the mother and the infant as a result of mother-to-child transmission (MTCT) (Table 1).[1] A comprehensive and multidisciplinary approach to the management of viral hepatitis in pregnancy is necessary to reduce morbidity, mortality, and need for liver transplantation. This methodology involves early identification by screening, use of prevention techniques, encouragement of safe breastfeeding, treatment of infection, and immunoprophylaxis (Tables 1 and 2).

HEPATITIS A VIRUS

Hepatitis A virus (HAV) typically has minimal impact on pregnancy. Testing in acute illness includes serum anti-HAV

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; ALD, acute liver disease; ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVT, antiviral therapy; CI, confidence interval; CMV, cytomegalovirus; CVS, chorionic villous sampling; DAA, direct-acting antiviral agent; EASL, European Association for the Study of the Liver; EBV, Epstein-Barr virus; FDA, USFood and Drug Administration; FLD, fulminant liver disease; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgM, immunoglobulin M; ITTA, intention-to-treat analysis; IVDU, intravenous drug use; LAM, lamivudine; LTD, telbivudine; MTCT, mother-to-child transmission; OR, odds ratio; PCR, polymerase chain reaction; PPA, per protocol analysis; RCT, randomized controlled trial; RR, relative risk; STD, sexually transmitted disease; STI, sexually transmitted illness; SVR12, sustained virologic response at 12 weeks; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; VZV, varicella zoster virus.

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Potential conflict of interest: Nothing to report.
Received September 13, 2020; accepted November 25, 2020.

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TABLE 1. APPROACH TO THE MANAGEMENT OF HEPATITIS A, B, C, AND E IN PREGNANCY[2]

	HAV	HBV	HCV	HEV
MTCT (*in utero* and perinatal transmission)	Uncommon.	Increased risk if mother has chronic HBV, $HBeAg^+$, HBV DNA > 200,000 IU/mL, or amniocentesis. Up to 90% of HBV infections acquired as a result of MTCT develop into chronic HBV.[1] Treatment reduces the risk for MTCT from 10% to 1%-2%.	Increased risk with maternal viral load, HIV coinfection, prolonged rupture of membranes, and fetal scalp monitoring.[1] In the absence of these factors, risk is approximately 5%, and chronic HCV develops in 3% of infants.	Increased risk with acute HEV in third trimester (range, 30%-100%). Reports of MTCT in chronic HEV are absent.[1]
Screening	No routine screening of the mother is recommended.	Standard routine test with HBsAg in all pregnant women (<12-14 weeks) is recommended.	Routine universal testing with anti-HCV antibody at first antenatal visit is recommended. If antibody positive, HCV RNA level and testing for STI (HIV, syphilis, HBV, gonorrhea, chlamydia) should be considered.	No routine screening of the mother is recommended.
Prevention (of viral transmission to mothers)	By observing hygienic practices. HAV vaccine and passive immunization can be considered in mothers at risk.	By observing hygienic and safe sex practices and avoiding sharing of personal items. Hospitals should follow safe blood/organ donation practices. MTCT is reduced by avoiding use of fetal scalp electrodes, fetal blood sampling, assisted delivery, and vigorous airway suctioning of infant at birth.	By observing safe sex practices and avoiding sharing of personal items and needles. Attempts to reduce MTCT include avoiding use of fetal scalp electrodes and episiotomy. Amniocentesis is preferred to CVS.	By observing hygienic practices, use of safe drinking water (boiling and chlorination may inactivate HEV), and avoiding uncooked or poorly cooked meat. Advise against traveling to highly endemic areas.
Breastfeeding	No contraindication to breastfeeding and should be encouraged (even during the acute infectious period).	Recommended after the HBIG and first dose of HBV vaccine are administered. Breastfeeding is not contraindicated during AVT.	Low risk for transmission. Avoid in high viral loads, HIV/HCV coinfection, and if nipples are cracked, damaged, or bleeding.[3] Anti-HCV antibody and HCV RNA are present in colostrum at very low levels.	Generally considered safe with low risk for transmission despite the known presence of anti-HEV antibody and HEV RNA in breast milk.

TABLE 2. IMMUNIZATION SCHEDULE TO REDUCE THE RISK FOR MTCT IN PREGNANCY[4]

Immunization Schedule	Mother	Infant
HAV (weigh risks of vaccine against the risk for infection in pregnant women)	HAV vaccine is recommended in women with risk factors: history or current IVDU, travel to endemic regions, residence in high-prevalence regions, close contact with HAV-infected primates, chronic HBV, or liver transplant recipient. If exposed, HAV immunoglobulin and inactivated HAV vaccine are administered.	Inactivated HAV vaccine for all at 12 months and 18 months. If maternal HAV infection occurs within 2 weeks of delivery: HAV immunoglobulin injection to the neonate.
HBV (risk for infection outweighs the risks of vaccine: vaccination prevents 80%-95% cases)	HBV vaccine is recommended in women with risk factors (>1 sexual partner in 6 months, history of STD, IVDU, $HBsAg^+$ sexual partner) and those with chronic HCV, cirrhosis, FLD, ALD, AIH, and AST/ALT >2× ULN. If exposed, HBIG (within 72 hours of exposure) and HBV vaccine (within 7 days, at 1 and 6 months) are administered.	HBV vaccine and HBIG within 12 hours after birth.
HCV	No vaccine or immunoglobulin for preexposure or postexposure prophylaxis is available.	
HEV	No FDA-approved vaccine is available. In 2012, a recombinant HEV vaccine was approved for use in China.[2]	

immunoglobulin M (IgM) antibody. Treatment is supportive for mild hepatitis, and rarely, hospitalization may be indicated for severe hepatitis or in the uncommon case of fulminant hepatitis. Prevention is the key through the practice of universal precautions (Table 1) and by following the recommended vaccination schedule (Table 2).

HEPATITIS B VIRUS

The World Health Organization aims to reduce hepatitis B surface antigen (HBsAg) in infants to 0.1% in their goal to eliminate hepatitis B virus (HBV) by 2030 as a public threat.[5] Hence the prevention of MTCT is a critical step in the elimination strategy (Tables 1 and 2). The recommended approach to management of HBV in pregnancy is described in Table 3. Treatment is guided by disease progression, and options include tenofovir, lamivudine (LAM), and telbivudine (LTD). Numerous studies have emerged in recent years that favor the use of tenofovir disoproxil fumarate (TDF) because of its high efficacy and safety profile in addition to its high barrier to resistance (Table 4).[6–12] Patients who become pregnant while already maintained on HBV treatment should be assessed for both the appropriateness of the drug therapy and their response to treatment. Patients should be continued on HBV antiviral therapy (AVT) throughout the pregnancy and after delivery in the long term.

HEPATITIS C VIRUS

Both the American Association for the Study of Liver Diseases (AASLD) in 2018 and the Centers for Disease Control and Prevention in April 2020 updated their recommendation to include hepatitis C virus (HCV) screening in all pregnant women during each pregnancy (except in regions where the prevalence rate is <0.1%).[2,3] Whenever feasible, HCV diagnosis and treatment prior to becoming pregnant is preferred to reduce the risk for MTCT. HCV treatment during pregnancy is not yet US Food and Drug Administration (FDA) approved; however, treatment options include interferon, ribavirin, and the newer direct-acting antiviral agents (DAAs). Ribavirin is contraindicated in pregnancy because of its teratogenic effects.[3] Animal studies have failed to demonstrate evidence of fetal harm with use of DAAs (except simeprevir) during pregnancy; however, the data in humans are limited (Table 5). Universal screening is preferred to recruit mothers with chronic HCV into health care for postpartum treatment, prevent future MTCT, guide management during pregnancy, testing and monitoring in infants, and overall cost-effectiveness. Testing in infants includes HCV-RNA polymerase chain reaction (PCR) or anti-HCV antibody (≥18 months).[1] There is no FDA-approved treatment for infants and children 0 to 3 years old.

HEPATITIS D VIRUS

Hepatitis D virus (HDV) is an incomplete virus and requires HBV for its replication. Infection can occur in $HBsAg^+$ women only as a coinfection or superinfection. The risk for MTCT and severe hepatitis increases with elevated HBV DNA levels, especially in the third trimester of pregnancy. Testing includes HDV RNA by PCR. Treatment is supportive; however, interferon/PEGylated interferon-alpha or liver transplant are considered when lifesaving measures are needed. Preventive strategies used for HBV are applicable to HDV (Table 1). Breastfeeding is encouraged.

TABLE 3. APPROACH TO HBV INFECTION DURING PREGNANCY[13,14]

Indication	Approach to Management
Screening	Screen all pregnant women at first encounter with HBsAg. If HBsAg$^+$, obtain HBeAg, HBV DNA, ALT, and imaging. Hepatology consult at the time of diagnosis (for staging, guidance, and monitoring during pregnancy) and subsequently for postpartum continuity of care.
Management in pregnant mother	Patients with cirrhosis who are receiving AVT should remain on AVT during pregnancy and after delivery. In patients with chronic HBV not previously on AVT: 1. Pregnant women who otherwise meet the standard indications for treatment of HBV infection, including HBV flare, should be treated as nonpregnant women. 2. Treatment with AVT is recommended in the third trimester in HBsAg$^+$ pregnant women when maternal HBV DNA is >200,000 IU/mL to reduce the risk for MTCT. Treatment is usually started at 28-32 weeks of gestation with tenofovir (preferred) or LTD. 3. Consensus treatment decisions for HBV during pregnancy for DNA levels >20,000 and <200,000 have not been reached in society guidelines. 4. Treatment is indicated for acute HBV in pregnancy when ALT >5× the ULN.
Discontinuation of AVT	At delivery or in the 4- to 12-week postpartum period in women: 1. Without ALT flares 2. Without preexisting advanced liver fibrosis or cirrhosis 3. As indicated for the clinical benefit of the woman 4. After discontinuation, continue close monitoring every 3 months for 6 months; subsequently, follow routine management protocol as for chronic HBV infection in nonpregnant patients
Immunoprophylaxis of the infant	In infants born to HBsAg$^+$ mothers (or unknown status): first dose of HBV vaccine and HBIG should be administered within 12 hours of delivery and two additional doses of vaccine within 6- to 12-month period
Pregnancy and lactation labeling rule conversion for AVT using the Antiretroviral Pregnancy Registry:	1. Entecavir: Contraindicated in pregnancy because of carcinogenic potential in animal studies. 2. LTD: The available data show no increase in the overall risk for major birth defects. Its presence in breast milk or the effects on the breastfed infant are unknown. 3. LAM: The available data do not suggest an increase in the overall risk for birth defects. It is present in human breast milk; however, its effect on the breastfed infant is unknown. 4. Tenofovir: For TDF, the available data show no significant effect on the overall risk for major birth defects. It is present in human breast milk; however, its effect on the breastfed infant is unknown. TDF is associated with loss of bone mineral density in infants and renal injury in mothers, requiring close monitoring. TAF has an improved safety profile on bone mineral density and renal function; however, currently, there is no clinical recommendation guiding its use in pregnancy.

HEPATITIS E VIRUS

Hepatitis E virus (HEV) infection is more common in developing countries, such as in South East Asia, and less common in developed countries, including the United States and Europe.[2] HEV in pregnancy is typically a subclinical, self-limiting acute illness. However, the risk for fulminant hepatitis and acute liver failure (ALF) is increased in the second and third trimesters (Table 1). Testing includes anti-HEV IgM or HEV RNA by PCR in serum or stool. Supportive care is provided in acute infection, while hospitalization with urgent liver transplantation evaluation is necessary in severe cases. Prevention with universal safety precautions is the key (Table 2).

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) hepatitis in pregnancy is rare. MTCT occurs as a result of direct viral contact in secretions (HSV-1 is more common than HSV-2). The characteristic mucocutaneous vesicular lesions are uncommon. Testing includes HSV-DNA PCR, IgM antibodies, and HSV antigen/culture. The risks for high mortality and poor prognosis are outweighed by the benefits of empiric treatment with acyclovir when HSV is suspected.[19] Cesarean section is performed if active genital lesions are noted on the day of delivery. After delivery, the neonate is empirically treated until HSV testing results. Prevention includes handwashing and avoiding unprotected sexual intercourse with new partners in the peripartum period and contact with vesicles. Breastfeeding is safe (if no lesions are on the nipple and breast).

VARICELLA ZOSTER VIRUS

Varicella zoster virus (VZV) hepatitis is rare, and the risk for MTCT is low. Fetal complications include congenital varicella (MTCT before 20 weeks: presents with intrauterine growth retardation, limb hypoplasia, chorioretinitis, cataracts, microphthalmia, microcephaly, cutaneous scarring) and neonatal varicella (MTCT between 5 days before and 2 days after delivery: wide clinical presentation). Maternal zoster infection alone without hepatitis is not associated with viremia or fetal complications. Treatment options include anti-VZV immunoglobulin and acyclovir. Vaccination *during* pregnancy is contraindicated (live attenuated virus). Prevention includes avoiding sick contacts and vaccination

TABLE 4. CLINICAL STUDIES OF ORAL AVT IN PREGNANT WOMEN WITH HBV TO PREVENT PERINATAL TRANSMISSION (UPDATES SINCE 2016)

Author (Year), Country	Study Design	No. of Pregnant Women	Maternal HBV Status	Antiviral Drug and Time During Pregnancy	% Infants $HBsAg^+$ (MTCT) Treated Versus Control
C.Q. Pan et al. (2016), China[6]	Multicenter, open label, RCT	100 TDF versus 100 placebo	$HBsAg^+$, $HBeAg^+$, HBV DNA > 200,000 IU/mm	TDF from 30-32 weeks of gestation to 1 month postpartum	5% versus 18%; $P = 0.007$ (ITTA) and 0% versus 7%; $P = 0.01$ (PPA) (at postpartum week 28)
G. Jourdain et al. (2018), Thailand[7]	Phase 3, multicenter, double-blind, placebo-controlled RCT	168 TDF versus 163 placebo	$HBsAg^+$, $HBeAg^+$, HBV DNA 8.0 log10 IU/mm	TDF in mother from 28 weeks of gestation to 2 months postpartum	0% versus 2%; $P = 0.12$ (ITTA) (at postpartum 6 months)
R.S. Brown et al. (2016), USA[8]	Systematic review and meta-analysis	26 studies (10 RCTs, 16 non-RCTs), 3622 pregnant women	Chronic HBV infection, average HBV DNA 7.63 log10 IU/mL	Second to third trimester	Overall RR, 0.3; 95% CI: 0.2-0.4; $I^2 = 63.9\%$ at 6-12 months - LAM versus control (11.7%; RR, 0.3) - LTD versus control (15.8%; RR, 0.2) - TDF versus control (15.8%; RR, 0.2)
J. Song et al. (2019), China[9]	Meta-analysis	59 studies (32 RCTs, 27 non-RCTs), 9228 pregnant women	Chronic HBV infection	AVT (LAM, LTD, or TDF)	Overall RR, 0.51; 95% CI: 0.45-0.57 - AVT initiation in second versus third trimester: RR = 0.46 versus 0.53; $P = 0.596$
X. Yang et al. (2020), China[10]	Systematic review and meta-analysis	9 studies (observational cohort studies), 1502 pregnant women	Chronic HBV infection, average HBV DNA 8 log10 copies/mL	AVT (LAM, LTD, or TDF) to 761 women in second trimester versus 741 women in third trimester	0% versus 0.98%; $P = 0.08$
F. Jia et al. (2020), China[11]	Meta-analysis	75 studies, 12,740 pregnant women	Chronic HBV infection	AVT (LAM, LTD, or TDF)	RR, 0.16; 95% CI: 0.02- 1.28, $I^2 = 0\%$ - LAM (OR, 0.15; 95% CI: 0.09-0.25; $I^2 = 0\%$ - LTD (OR, 0.07; 95% CI: 0.05-0.10; $I^2 = 0\%$) - TDF (OR, 0.07; 95% CI: 0.04-0.13; $I^2 = 0\%$) - TDF (96.83%) was more effective than the other two AVTs
Y. Wu et al. (2020), China[12]	Systematic review and meta-analysis	35 studies (3 RCTs and 32 non-RCTs), 6738 patients	Chronic HBV infection	AVT (LAM, LTD, or TDF)	AVT in early (RR, 0.0076), middle (RR, 0.0015), or late (RR, 0.10) pregnancy showed significant reduction in MTCT: - AVT in second trimester had more effect than in third trimester (RR, 0.015); $P > 0.05$ - LTD and TDF showed a stronger trend toward significance among LAM, LTD, and TDF

before pregnancy. Breastfeeding is encouraged unless there are active lesions on the nipple or breast.

EPSTEIN-BARR VIRUS

Epstein-Barr virus (EBV) hepatitis in pregnancy presents similarly in pregnant and in nonpregnant patients. Diagnosis is established by the presence of lymphocytosis, atypical mononuclear cells, and antiviral capsid antigen IgM antibodies.[19] Mild illness is self-limited and treated symptomatically. In severe EBV hepatitis or ALF, treatment includes steroids, acyclovir, and multidisciplinary care.[19] Breastfeeding is encouraged.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) hepatitis presents with flu-like symptoms, acute hepatitis, ALF, or hemolysis, elevated

TABLE 5. CLINICAL STUDIES OF DAA IN PREGNANT WOMEN WITH HCV TO PREVENT PERINATAL TRANSMISSION

Author (Year), Country	Study Design	No. of Pregnant Women	Antiviral Drug and Time During Pregnancy	Neonatal Outcomes
Chappell et al. (2016), USA[15]	Phase I clinical trial	9 (genotype 1a)	Ledipasvir/Sofosbuvir at 24 weeks for 12-week duration	Results awaited (preliminary results show 100% SVR12 in 8/8 women)
Mandimika et al. (2019), USA[16]	Case report	1 (30-year-old woman with HCV genotype 2b and concomitant HIV infection)	Sofosbuvir alone at 34 weeks for 6 weeks followed by sofosbuvir/velpatasvir postpartum for 6 weeks	HCV negative at birth, no teratogenicity at 2 years
Yattoo et al. (2018), India[17]	Retrospective cohort study	15	Ledipasvir/sofosbuvir	SVR12
El-Sayed et al. (2019), Egypt[18]	Retrospective cohort study	8	Sofosbuvir/daclatasvir	No teratogenicity and 1/8 infants had low-level viremia at 18 months

liver enzymes, low platelet count (HELLP) syndrome.[19] Testing includes anti-CMV IgM antibodies. CMV-DNA PCR is reliable after 21 weeks of pregnancy and 6 weeks after presumed date of infection. The risk for MTCT is high when infection occurs during the first trimester, ranging from 30% to 40% in primary infection and 2% to 3% in reinfection. Mild CMV infection is self-limited with supportive care. In severe cases, hyperimmunoglobulin and AVT with ganciclovir or valacyclovir are used.[19] Breastfeeding is encouraged; however, care should be observed because viral transmission can occur in breast milk.

CONCLUSION

The clinician should have a low threshold to suspect viral hepatitis in a pregnant woman because of the increased risk for maternal and fetal complications associated with MTCT. Multidisciplinary care, including obstetrics, maternal-fetal medicine, hepatology, and pediatrics, is crucial for optimizing outcomes for both mother and child. Universal screening for HBV and HCV is recommended in all pregnant women. If needed in HBV infection in pregnancy as already described, preferentially AVT with TDF and LTD may be considered as per the AASLD, European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver current guidelines, and LAM may be considered as per the AASLD and EASL recommendations (Table 3). As we gain more knowledge surrounding the safety and efficacy of the DAAs in HCV infection in the peripartum period and await FDA approval for the use of DAAs in pregnancy, clinical outcomes for both mother and infant are expected to improve.

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