



Viral Hepatitis and Pregnancy

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Overview

Pregnancy is generally considered to be an immunosuppressed state; however, the impact of pregnancy on mothers with viral hepatitis (Table 1) and the impact of viral hepatitis on fetuses/infants (Table 2) are not the same for all types of hepatitis.

Pregnant women with acute hepatitis due to hepatitis E virus (HEV) or herpes simplex virus (HSV) have an increased risk of acute liver failure compared to persons who are not pregnant. Flares of chronic hepatitis B may occur during pregnancy and in the postpartum period, but hepatic decompensation is rare.

The risk of vertical transmission of hepatitis viruses is higher in pregnant women with acute versus chronic infection. In general, the risk is not increased with amniocentesis, fetal monitoring, or vaginal birth, and cesarean should not be recommended to prevent transmission of hepatitis viruses.¹ Breastfeeding is safe for women with chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV) infections—unless they have cracked nipples.^{2,3} Hepatitis A and B vaccines are safe to be administered during pregnancy.

Hepatitis A Virus

Hepatitis A virus (HAV) infection does not progress to chronic infection, and HAV is generally transmitted via fecal-oral route; therefore, maternal-infant transmission is rare. The highest risk of gestational complications such as premature rupture of membrane, placental separation, or preterm labor is during the second half of pregnancy (Table 1).

Hepatitis B Virus

Neither acute nor chronic hepatitis B virus (HBV) infection poses a risk to fetal development. Flares of chronic

hepatitis B had been reported during pregnancy and in the postpartum period. These flares are usually mild and in some instances may be accompanied by the spontaneous loss of hepatitis B e antigen (HBeAg).⁵

In the absence of prophylaxis, the risk of vertical transmission is up to 90%.⁶ The risk is higher if the mother is HBeAg-positive or has high serum HBV DNA levels.

Perinatal transmission of HBV results in chronic infection in 90% of infants; therefore, screening of all pregnant women for hepatitis B surface antigen (HBsAg) at the first antenatal visit to identify those who test positive is critical. As of 2012, 181 countries worldwide have adopted universal HBV vaccination (regardless of maternal HBsAg status) for all newborns. In most countries, babies born to HBsAg-positive mothers will additionally receive one dose of hepatitis B immune globulin (HBIG) at a different site from the first dose of HBV vaccine within 12 hours of birth. Passive-active prophylaxis reduces the incidence of maternal-infant transmission of HBV to 5% to 10%. The infant should be tested for HBsAg and antibody to HBsAg 1 to 2 months after completing the vaccine series to confirm immunity and to rule out infection.

High maternal serum HBV DNA is a major cause of prophylaxis failure. Administration of an oral antiviral to mothers with high serum HBV DNA during the third trimester of pregnancy has been shown to decrease the incidence of prophylaxis failure (Table 3). Lamivudine was used in most studies but is a pregnancy class C drug, whereas telbivudine and tenofovir are pregnancy class B drugs. Data in the anti-retroviral registry showed that the use of lamivudine and tenofovir during pregnancy, even in the first trimester, did not result in an increased incidence of birth defects. Although the antiviral drug is used for a short duration in this setting, given the high HBV DNA levels, tenofovir is

Abbreviations: anti-HCV, HCV antibody; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; NUC, nucleos(t)ide analogue; PCR, PEG-IFN, pegylated interferon.

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TABLE 1 Risks of Viral Hepatitis in Pregnant Women

Type of Viral Hepatitis	Potential Risks to Mother	Timing of Pregnancy With Highest Risk
Hepatitis A	Gestational complication; preterm labor	2nd half of pregnancy, especially 3rd trimester
Hepatitis B*	Flares of chronic hepatitis B	Can occur during pregnancy or postpartum period
Hepatitis C*	None	
Hepatitis E	Acute liver failure; eclampsia	2nd and 3rd trimester
HSV hepatitis	Acute liver failure	3rd trimester

*Data based on pregnant women with chronic infection.

preferred to minimize the risk of antiviral drug resistance. There is no consensus on when to initiate, when to discontinue, or what cutoff HBV DNA level should be used to initiate antiviral therapy. Most experts agree that antiviral therapy should be considered when maternal HBV DNA is > 7 to $8 \log_{10}$ IU/mL, and treatment should be started around week 28 to 32 of pregnancy to allow time for the virus to be suppressed. Treatment may be stopped after delivery if the goal of antiviral therapy is to decrease the incidence of perinatal transmission. Tenofovir is a prodrug, and the concentration in breast milk is 4.7% of that in serum.^{7,8} Limited data suggest that breastfeeding is permissible for mothers receiving tenofovir. Hepatitis flares may occur after antiviral therapy is discontinued, and the mothers should be closely monitored for 6 months after treatment is stopped.

Fig. 1 shows an algorithm for managing women with chronic HBV infection who are contemplating pregnancy. Prior to pregnancy, pegylated interferon (PEG-IFN) may be considered because of its finite duration. Among the oral antivirals, tenofovir is the preferred drug because of its high barrier to resistance and demonstrated safety in pregnancy.

Hepatitis C Virus

Vertical transmission of hepatitis C virus (HCV) occurs in approximately 5% of newborns born to HCV-infected moth-

ers; the risk is higher if the mother is coinfecting with HIV⁹ or has high HCV RNA level. Diagnosis of HCV infection in the infant can be performed by testing for HCV RNA. If HCV antibody (anti-HCV) is tested, it should be delayed until the infant is at least 12 months of age.¹ Approximately 60% to 80% of infected infants will develop chronic infection.

Treatment of HCV should not be offered during pregnancy because ribavirin is a pregnancy class X drug that is highly teratogenic, and interferon is a class C drug. There are no data on safety of direct-acting antiviral agents in pregnancy. Currently, there is no means to prevent maternal-infant transmission of HCV.

Hepatitis E Virus

Hepatitis E virus (HEV) is usually spread via fecal-oral route; however, ingestion of undercooked pork or exposure to boar or wild pigs had also been reported to be a source of HEV infection in developed countries.¹¹

Acute hepatitis E is self-limiting in the vast majority of cases, but hepatitis E during pregnancy can cause severe hepatitis and acute liver failure, especially when it occurs in the third trimester. Maternal fatality of 16% to 20% had been reported when hepatitis E occurs in the third trimester of pregnancy^{12,13} and is caused by acute liver failure, eclampsia, or hemorrhage. A vaccine has been developed for hepatitis E, but it is not available in most countries.

Herpes Simplex Virus

Herpes simplex virus (HSV) infection during pregnancy is rare but can cause disseminated infection, HSV hepatitis, and acute liver failure, especially when the infection occurs in the third trimester of pregnancy. Primary as well as latent HSV infection—and both HSV-1 and HSV-2—can cause hepatitis and acute liver failure. Patients typically present with fever and markedly elevated aminotransferases. Skin

TABLE 2 Risks of Viral Hepatitis on Fetus/Infant and Preventive Measures

	Potential Risks to Fetus/Infant	Preventive Measures
Hepatitis A	Fetal ascites; meconium peritonitis. Rare, mainly if mother is infected during 1st trimester	Vaccinate pregnant women who will be traveling to endemic areas Administer immune globulin to pregnant women who had contact with persons with acute hepatitis A
Hepatitis B	Perinatal infection. Risk higher if mother is HBsAg+ or has high HBV DNA	Passive/active prophylaxis. HBIG and HBV vaccination within 12 hours of birth for all newborns of HBsAg+ mothers Antiviral therapy for mothers with high HBV DNA in 3rd trimester of pregnancy
Hepatitis C	Perinatal infection. Risk higher if mother is coinfecting with HIV or has high HCV RNA	None
Hepatitis E	Spontaneous abortion; premature delivery. Risk higher if mother is infected during 3rd trimester	None
HSV hepatitis	Neonatal HSV: Skin lesions, keratoconjunctivitis, cataracts, chorioretinitis, ulcerative lesions in mouth/tongue, central nervous system disease, disseminated HSV (hepatitis, hemorrhagic pneumonitis, necrotizing enterocolitis, meningoencephalitis)	Treat mother with primary or first episode of genital HSV infection with acyclovir Consider suppressive therapy for recurrent infections at 36 weeks of pregnancy Consider cesarean section delivery if predicted risk of transmission is high

TABLE 3 Clinical Studies of Oral Antiviral Therapy in HBsAg+ Pregnant Women to Decrease Risk of Perinatal Transmission of Hepatitis B

Author, Year, Country (ref)	Study Design	No. of Pregnant Women	Maternal HBV DNA	Antiviral Drug and Start Time During Pregnancy	% Infants HBsAg+Ve Treated vs Control (time of assessment)	P Value
WM Xu et al, 2009, China ¹⁵	Randomized double-blinded, placebo controlled	56 treatment vs 59 placebo	> 10 ⁹ cp/ml	Lamivudine week 32	18% vs 39% (52 week)	0.014 (intention to treat analysis) vs 0.37 (per protocol analysis)
GR Han et al, 2011, China ¹⁶	Prospective, not randomized	135 treatment vs 94 untreated control	> 10 ⁷ cp/ml	Telbivudine weeks 20-32	0% vs 8% (28 week)	0.001
CQ Pan et al, 2012, China ¹⁷	Prospective, open-label	53 treated vs 35 untreated control	> 10 ⁶ cp/ml	Telbivudine weeks 12-30	0% vs 8.6% (28 week)	0.03
MK Celen et al, 2013, Turkey ¹⁸	Retrospective	45 treatment vs 24 controls	> 10 ⁷ cp/ml	Tenofovir weeks 18-27	0% vs 8% (28 week)	0.022

*All pregnant women were HBeAg+ and all newborns received HBIG + HBV vaccine

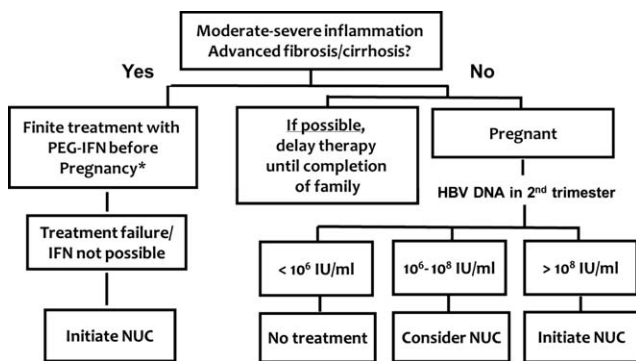


Figure 1 Management of HBV in women contemplating pregnancy. *Effective contraceptive indicated. Abbreviation: NUC, nucleos(t)ide analogue.

lesions may be seen in 30% of patients. Diagnosis can be made by PCR testing for HSV DNA. Treatment is with acy-

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clovir or valacyclovir, which are pregnancy class B drugs. Clinical vigilance, prompt diagnosis, and treatment are critical because treated patients have lower rates of liver transplantation or death compared to untreated patients (55% vs 88%).¹⁴ Risk of vertical transmission is highest in women who have a primary infection at the time of delivery (40%-44%), followed by having a first episode of genital nonprimary infection (24%-31%) and recurrent infections (1.3%-3%). Intrauterine infection is rare (1 in 250,000). Eighty-five percent of infection occurs in the perinatal period and 10% in the postnatal period. Invasive fetal monitoring, prolonged duration of ruptured membrane, and vaginal delivery increase the risk of vertical transmission. Cesarean is recommended in select cases. ■

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