

Chronic hepatitis B infection in pregnancy

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Abstract

There are no standard guidelines to follow when a patient with chronic hepatitis B infection becomes pregnant or desires pregnancy. Topics to consider include which patients to treat, when to start treatment, what treatment to use and when to stop treatment. Without any prophylaxis or antiviral therapy, a hepatitis B surface antigen and E antigen positive mother has up to a 90% likelihood of vertical transmission of hepatitis B virus (HBV) to child. Standard of care in the United States to prevent perinatal transmission consists of

administration of hepatitis B immune globulin and HBV vaccination to the infant. The two strongest risk factors of mother to child transmission (MTCT) of HBV infection despite immunoprophylaxis are high maternal HBV viral load and high activity of viral replication. The goal is to prevent transmission of HBV at birth by decreasing viral load and/or decreasing activity of the virus. Although it is still somewhat controversial, most evidence shows that starting antivirals in the third trimester is effective in decreasing MTCT without affecting fetal development. There is a growing body of literature supporting the safety and efficacy of antiviral therapies to reduce MTCT of hepatitis B. There are no formal recommendations regarding which agent to choose. Tenofovir, lamivudine and telbivudine have all been proven efficacious in decreasing viral load at birth without known birth defects, but final decision of which antiviral medication to use will have to be determined by physician and patient. The antivirals may be discontinued immediately if patient is breastfeeding, or within first four weeks if infant is being formula fed.

Key words: Chronic hepatitis B infection; Pregnancy; Hepatitis B immune globulin; Hepatitis B virus vaccine; Antivirals

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Core tip: In pregnant patients chronically infected with hepatitis B, determining which patients require treatment is not well understood. In this concise review, we discuss four important questions to consider when faced with this patient population: who to treat, when to treat, what medication in which to treat and when to stop treatment.

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) is a relatively well-understood and manageable disease process. With current available medications, suppression of the virus can be achieved in most patients. Practice guidelines are available for beginning medical therapy in chronic HBV infection. However, in certain specific circumstances, treatment of HBV infection becomes less clear. One of those circumstances is chronic HBV infection in pregnancy. In fact, of the 50 million people newly infected with hepatitis B every year worldwide, the majority of this transmission occurs from mother to child transmission (MTCT)^[1]. In this concise review, we discuss four important questions to consider when faced with this patient population: who to treat, when to treat, what medication in which to treat and when to stop treatment.

WHO TO TREAT?

It is first important to note the difference between acute and chronic HBV infection in pregnancy. Generally, patients acutely infected with HBV during pregnancy should be monitored closely and managed conservatively. Unless the pregnant mother develops evidence of acute liver failure, antivirals are not generally indicated^[2].

Although MTCT is not the most common transmission route of HBV infection in the United States, it remains extremely high risk if the mother and child are not managed properly. Without any prophylaxis or antiviral therapy, a hepatitis B surface antigen (HBsAg) and E antigen (HBeAg) positive mother has up to a 90% likelihood of vertical transmission of HBV to child^[3]. Standard of care in the United States to prevent perinatal transmission consists of administration of hepatitis B immune globulin (HBIG) and HBV vaccination to the infant^[4,5]. Despite receiving immunoprophylaxis, up to 10%-15% of infants develop chronic HBV infection through MTCT.

There are two indications to treat chronic hepatitis B in a pregnant mother; chronic liver disease in mother and prevention of MTCT. We will not discuss chronic liver disease in the mother in detail in this review.

Risk factors that increase the risk of perinatal transmission of HBV to the infant have been determined. The two strongest risk factors are high maternal HBV viral load and high activity of viral replication^[6,7]. Other risk factors including amniocentesis, preterm premature rupture of membranes and breast feeding carry a much lower risk for MTCT of HBV^[8].

Not every pregnant woman with chronic HBV infection needs antiviral therapy due to concern of drug related adverse events^[9]. The decision to start antivirals must be discussed in detail between patient and physician. However, it should be strongly considered in HBsAg positive pregnant patients with high viral load and/or active viral disease.

High viral load is defined as $> 10^6$ or $> 10^8$ copies

per milliliter (20 million IU/mL) in previous studies^[10,11]. High activity of viral replication can be defined in several different manners and has been proposed with positive HBeAg (prior to seroconversion) or elevated alanine aminotransferase level and viral load of > 20000 IU/mL^[9].

WHEN TO TREAT?

Again, immunoprophylaxis is given to all infants born to HBsAg positive mothers. The passive immunization, the HBIG, is given to the infant within 12 h of birth. The active immunization, which is the first dose of HBV vaccine, is also given in these first few hours of life. The remainder of the dosing for HBV vaccine follows standard protocol; the second dose is given at 1 mo and the last dose is given at 6 mo of age and no later than 9 mo of age^[5].

Maternal HBsAg is checked during early pregnancy and again in the third trimester of pregnancy. If the HBsAg status of mother is unknown at the time of birth, the infant should receive first dose of HBV vaccine. If confirmatory testing is positive for HBsAg in the mother, then HBIG should be administered to the infant as well, and the HBV vaccine should be completed^[12].

If the decision is made to treat with antivirals, due to either maternal high viral load and/or evidence of active disease, the timing of administration of these medications is noteworthy. The goal is to prevent transmission of HBV at birth by decreasing viral load and/or decreasing activity of the virus. Although it is still somewhat controversial, most evidence shows that starting antivirals in the third trimester is effective in decreasing MTCT without affecting fetal development. Starting medication earlier in the pregnancy is not necessary to decrease MTCT and puts the fetus at higher risk due to the longer exposure to a non-approved medication. In fact, many studies have shown the efficacy of starting antivirals well into the third trimester, such as 29 wk, 32 wk or even 34 wk^[13-15].

WHAT MEDICATION IN WHICH TO TREAT?

As previously mentioned, MTCT accounts for more than one-third of all HBV transmission worldwide. With the use of HBV vaccination and HBIG, the rate of MTCT may be reduced from 90% to 10%^[16]. The greatest risk exists in children born to mothers with high viral loads. In this particular population, there are several studies examining the use of antiviral agents to further reduce the risk of MTCT. The following paragraphs will review the data surrounding the use antiviral agents available for the treatment of chronic hepatitis B during pregnancy.

Currently, there are six therapies approved for the treatment of chronic HBV infection. None is approved for use during pregnancy (Table 1). Current registry data does not suggest any increased risk of major

Table 1 Food and Drug Administration pregnancy categories for nucleos(t)ide analogues for hepatitis B

Drug	Pregnancy category
LdT	B
TDF	B
LAM	C
Entecavir	C
Adefovir	C
(Pegylated) interferon	C

LdT: Telbivudine; TDF: Tenofovir; LAM: Lamivudine.

birth defects in women exposed to tenofovir (TDF) or lamivudine (LAM) during pregnancy compared with large population controls^[17].

In early studies of LAM in pregnancy, 8 women with HBV DNA levels $> 1.2 \times 10^9$ copies/mL were treated with 150 mg daily beginning at 34 wk of gestation. Viral serologies of their offspring were measured at 0, 3, 6, and 12 mo. Twenty-five children born to untreated women served as controls. All children received active and passive immunization at birth. At 12 mo of age, only 1 of the 8 children (12.5%) in the treatment group remained HBsAg positive with measurable HBV DNA levels. In the control group, MTCT occurred in 7 of 25 children (28%)^[15]. No adverse events were noted. A double blind, randomized control trial examined the use of LAM 100 mg daily and active-passive immunization vs placebo and active-passive immunization in Chinese women from a gestational age of 32 wk to 12 wk after delivery. All women had an HBV DNA level $> 10^9$ copies/mL. At week 52, infants in the LAM group had a significant decrease in HBsAg positivity (18% vs 39%) and HBV DNA compared with placebo. With sensitivity analyses to account for dropouts in the placebo group, these differences were not statistically significant. One congenital anomaly was noted in the LAM group^[18].

Telbivudine (LdT) has also been studied for the prevention of MTCT of HBV. In an open label study, 135 women with HBV DNA levels $> 10^7$ copies/mL received LdT 600 mg daily from week 20 to week 32 of gestation. Ninety-four women served as controls. All infants received standard active-passive immunization. Seven months after delivery, MTCT was significantly lower in the infants born to the LdT treated mothers than to controls (0% vs 8%). No congenital abnormalities were identified^[14]. Similar efficacy and safety data has been provided by other studies, wherein the rate of MTCT was 8.6% in the placebo group vs 0% in the treated group^[19]. In a larger Chinese study, 648 women with high viral load were randomized to receive LAM, LdT, or placebo from 28 wk gestation until 4 wk postpartum. On treatment analysis indicated 0% of HBsAg positive infants in the treated group vs 2.84% in the placebo group. There were no safety concerns identified in this large study^[20].

The utility of TDF for the prevention of MTCT was first demonstrated in a small case series, in which

women with greater than 10^7 copies/mL of HBV DNA were given TDF 300 mg daily in the third trimester. The median duration of TDF use was 10 wk. All infants received active-passive immunization; all infants were HBsAg negative 28-36 wk after birth^[13]. A larger multicenter prospective study demonstrated that MTCT was reduced to 2% in a group of high viral load women treated with TDF 300 mg daily for a mean of 58 d before delivery. Within the same study population, the rate of MTCT was 20% in the controls and 0% in the LAM cohort^[21]. Although there have been limited studies regarding TDF and hepatitis B in pregnancy, there is significant safety data within human immunodeficiency virus/HBV coinfection cohorts supporting safe use of TDF in pregnancy^[22].

In summary, there is a growing body of literature supporting the safety and efficacy of antiviral therapies to reduce MTCT of hepatitis B. This is especially efficacious in women with known risk factors for MTCT as discussed elsewhere in this paper. There are no formal recommendations regarding which agent to choose. As listed in Table 1, LdT and TDF are the United States Food and Drug Administration (FDA) pregnancy category B medications (animal studies without demonstrable risk to the fetus), while LAM is a category C medication (adverse risk to fetus in animal studies). Table 2 further summarizes the articles that report on medication options discussed above. Based on available evidence, the previously mentioned drugs have minimal reported side effects to mothers or newborns, but have not yet been approved for standard use in pregnancy. Interferon is contraindicated during pregnancy and the safety of entecavir (a FDA category C medication) is unknown. If indicated, antiviral therapy should be initiated in the early third trimester as previously discussed.

WHEN TO STOP TREATMENT?

The dosing and administration of immunoprophylaxis has been previously discussed, the third and last dose of HBV vaccine should be completed by 9 mo of age^[5].

Concerning mothers that began antiviral medication due to above listed indications during the third trimester, discontinuation of the antivirals is not necessarily intuitive. If the initial indication for antivirals was due to high viral load or active disease, then the medication can be continued, following the current guidelines for treatment of chronic HBV infection^[23,24]. If the indication for therapy was to simply reduce MTCT, the antivirals may be discontinued immediately if patient is breastfeeding, or within first four weeks if infant is being formula fed^[9].

At this time, HBsAg positivity is not a contraindication to breastfeeding as evidence has shown that the risk of transmission is low^[25]. Although the active metabolite of most antivirals is not expressed in breast milk, breastfeeding on antiviral medication is not recommended^[12].

Pregnancy that occurs in women on long term

Table 2 Landmark study results of nucleos(t)ide analogues in hepatitis B virus infection and pregnancy

Ref.	Medication	Treatment timing	Major adverse events	% of transmission	
				Treatment group	Control group
Han <i>et al</i> ^[14]	LdT 600 mg daily	20 to 32 wk	0%	0%	8%
van Zonneveld <i>et al</i> ^[15]	LAM 150 mg daily	34 wk	0%	12.5%	28%
Pan <i>et al</i> ^[19]	LdT 300 mg daily	23 wk	0%	0%	8.6%
Zhang <i>et al</i> ^[20]	LdT 600 mg daily or LAM 100 mg daily	28 wk	0%	0%	2.8%
Greenup <i>et al</i> ^[21]	TDF 300 mg daily	32 wk	0%	1.1%	20%

LAM: Lamivudine; LdT: Telbivudine; TDF: Tenofovir.

treatment for chronic HBV infection is a topic not yet discussed in this review. Due to concern for adverse events from antiviral therapy early in pregnancy, consideration to stop the medication during the first two trimesters must be made. However, if the patient that has become pregnant has significant chronic liver disease due to HBV infection, risk of discontinuation of antiviral is of larger concern and thus antiviral is typically continued throughout pregnancy^[25].

There is a theoretical risk of a postpartum HBV flare with the withdrawal of antiviral therapy. This flare is typically defined as a significant rise in transaminases above upper limit of normal. Nguyen *et al*^[26] studied the effects of continuing antivirals two weeks after delivery vs twelve weeks after delivery, compared to patients that opted out of antiviral therapy altogether. In this study, there was no significant difference in occurrence of postpartum flares among the three groups and spontaneous resolution of the flare occurred equally among the groups as well. Another retrospective cohort study revealed similar findings^[27]. It can therefore safely be concluded that the decision to start or stop antiviral therapy should not be made based on concern for possible postpartum HBV flare. Nonetheless, it is important to monitor postpartum mothers closely for at least 6 mo, especially those who are HBeAg-positive or have stopped antiviral therapy^[28].

CONCLUSION

In conclusion, it is important to remember that patients chronically infected with HBV that become pregnant will need additional care and consideration. All infants in the United States should receive active and passive immunization at birth, as recommended by the Centers for Disease Control and Prevention^[5]. Pregnant women with chronic HBV infection that have high viral loads or elevated transaminases suggesting active viral replication are at risk of MTCT despite immunoprophylaxis. This patient population should consider taking antiviral medication in the third trimester of pregnancy to decrease risk of MTCT. TDF, LAM and LdT have all been proven efficacious in decreasing viral load at birth without known birth defects, but final decision of which antiviral medication to use will have to be determined by physician and patient.

Despite its prevalence and the availability of safe treatment, there are no current consensus guidelines

regarding prevention of MTCT. Large randomized studies should be conducted to further characterize the most effective method to minimize the transmission of HBV to future generations. In the interim, although it is not a frequent scenario for most gastroenterologists to encounter, with these brief recommendations; management of chronic HBV in pregnancy should be less daunting.

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