Current recommendations of managing HBV infection in preconception or pregnancy

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Abstract Hepatitis B remains a leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation worldwide. Management of chronic hepatitis B during pregnancy is challenging. Transmission of hepatitis B to infants still occurs perinatally although immunoprophylaxis is widely available for infants born to mothers with chronic hepatitis B infection. The emerging data suggest that initiation of antiviral therapy in the beginning of the third trimester in highly viremic mothers can prevent immunoprophylaxis failure in their infants. The available drug safety data show that lamivudine, telbivudine and tenofovir are generally safe to be used during the pregnancy. In order to minimize the fetal exposure to the antiviral medication, antiviral therapy during the pregnancy should be limited to a selected group of patients with cirrhosis, high hepatitis B viral load, or prior history immunoprophylaxis failure. An elective Caesarean section may reduce the risk of perinatal transmission. For those females planning for pregnancy or in early stage of pregnancy, communication and follow-up among obstetrician, gastroenterologist, and primary care physician are important. In this article, we will review the features of hepatitis B infection before, during and after the pregnancy; the risk factors that increase mother-to-child transmission; safety data on antiviral drug use during pregnancy; and the potential role of Caesarean section in selected cases.

Keywords antiviral therapy; Caesarean section; cirrhosis; hepatitis B; immunoprophylaxis; mother-to-child transmission; pregnancy; prevention

Introduction

Approximately 350 million individuals worldwide are chronically infected with hepatitis B virus (HBV)[1]. Hepatitis B is a leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation worldwide. Those with chronic hepatitis B (CHB) have up to a 15% to 40% risk of cirrhosis, hepatocellular carcinoma, and hepatic decompensation in their lifetime [2]. In Africa and Asia where the HBV infection is highly prevalent, the major mode of infection is mother-to-child transmission (MTCT) [2]. In countries of low HBV endemicity such as Europe and the Unites States, most of HBV infection is transmitted horizontally among adolescents and adults through sexual behavior or intravenous drug use [3]. However, with the migration of world population from the high endemic countries to the low endemic countries, the prevalence of HBV infection increased in the previously low endemic countries like the United States.

Those individuals with chronically active hepatitis B infection should be offered for treatment because they are at an increased risk of developing advanced fibrosis and hepatocellular carcinoma. Such treatment for chronic hepatitis B infection is based on the disease stage extrapolated from HBV DNA level, serologic information, and liver injury indicated by the elevation of transaminases and/or histological evidence [4,5]. Those with advanced fibrosis or cirrhosis should be treated regardless of their HBV DNA and aminotransferase levels due to a high risk of transition to hepatic decompensation and hepatocellular carcinoma [6]. Conversely, the individuals who are in immune tolerant stage of hepatitis B (lack of histological disease) or in inactive stage (low replicative state) of CHB are not indicated for antiviral treatment [7].

There are multiple available treatment options for the treatment of CHB. These include pegylated interferon (PEG-IFN), oral nucleoside analogs such as lamivudine (LAM), telbivudine (LdT), and entecavir (ETV) and oral nucleotide analogs such as adefovir (ADV) and tenofovir (TDF) [5,7]. Entecavir and tenofovir are recommended as the first line of therapy due to their high degree of genetic barrier to
resistance compared to other agents [5–7]. ADV, LdT and LAM are not the first line of therapy due to a high rate drug resistance that can result in cross resistance with other agents [5–7]. ADV has a small but appreciable risk of causing nephrotoxicity including Fanconi syndrome [8]. LdT has potential risk of myopathy and myositis [9]. Interferon is an injectable drug and offers a finite duration of treatment but has significant adverse events compared to oral antiviral treatment [6]. Interferon treatment has been recommended as the first line treatment [4,6]. However, the efficacy in Asian patients with genotypes B and C remains suboptimal [5].

Management of HBV infection in pregnancy is difficult and challenging because of several controversial aspects involving mothers, fetus and infant development. These patients often raise important questions such as the effect of HBV infection during pregnancy, the progression of maternal disease, the indication of initiating antiviral therapy before and during pregnancy, the safety of antiviral therapy on the mothers and fetus, the need to prevent MTCT of HBV, and the approach of breast-feeding. Despite the available pregnancy safety data of using LAM or category B antiviral agents including LdT and TDF, some patients may choose to stop antiviral therapy prior to conceiving due to a fear of having fetal exposure to these drugs. In this article, we provide a systemic review on the issues relevant to CHB infected females before, during and after pregnancy.

**Impact of hepatitis B on pregnancy**

There is limited understanding of the natural history of hepatitis B and its effect on pregnancy. A recent study by Tse et al. suggested that mothers with CHB are at higher risk of pregnancy related complications such as gestational diabetes, antepartum hemorrhage, and threatened preterm labor [10]. Data are conflicting regarding fetal outcomes from such maternal CHB infection. Some studies observed that CHB in pregnant mothers was associated with preterm labor, perinatal mortality, congenital malformations, and low birth weight [11,12]. However, when Wong et al. analyzed in their study, 824 hepatitis B surface antigen (HBsAg)-positive mothers to 6281 HBsAg-negative controls, there was no statistically difference on fetal outcomes such as gestational age at delivery, birth weight, neonatal jaundice, congenital anomalies, incidence of prematurity, and perinatal mortality [13]. A case report from Japan described the negative infant outcome due to MTCT. In their report, there were two cases of fulminant hepatitis of two babies born from hepatitis B e antigen (HBeAg)-negative mothers [14].

**Impact of pregnancy on hepatitis B**

Pregnancy is an immune tolerance state marked by absence of a maternal immune response against the fetus and placenta. Apart from locally acting mechanisms that specifically delete maternal allo-reactive cells, a variety of autoimmune diseases have been found to improve during gestation in mice and humans, with a higher risk of relapse after delivery [15,16]. Hepatitis B infected females generally do well during pregnancy. Although the majority of women have relatively stable HBV DNA during pregnancy, some studies have shown that hepatitis B replication and ALT might increase during the third trimester of pregnancy or shortly after delivery. This phenomenon of increased ALT is known to be associated with spontaneous HBe-seroconversion or severe hepatitis flare-up in HBeAg-positive mothers due to a postpartum immune rebound [17,18]. Therefore, it is recommended to follow the hepatitis B virus infected mothers closely for hepatitis flare-up during and after the pregnancy.

Child bearing age women are often in the age of 18 to 35. If the mother acquired HBV infection in early childhood, the maternal disease stage is often considered to be an immune tolerant phase. In addition to the tolerance to HBV, maternal immune reaction in general will be suppressed during pregnancy. The exact mechanism for this phenomenon is unclear; however, it is possibly related to mother’s adoptive change in hormone and cytokines to tolerate genetically different fetal tissue during pregnancy [19]. The low levels of immune reaction would allow higher level of HBV replication during the early stage of pregnancy. As immune function is reinstituted at the late stage of pregnancy or during postpartum period, hepatitis B flare-up can occur during pregnancy, resulting in maternal disease progression and fetal complications. Therefore, those individuals who decide to stop the antiviral therapy in preparation for pregnancy should be monitored closely for the clinically significant flare-up using the liver injury tests and hepatitis B DNA PCR assay [20,21].

**Antiviral therapy before and after the planned pregnancy**

For females planning to get pregnant, generally, the same treatment decision algorithm applies (Figs. 1 and 2). The initiation of antiviral therapy against CHB is indicated for those in the immune clearance or immune reactivation phase manifested by high viremia, abnormal aminotransferases, and/or histologically active disease (Fig. 1) [20, 21]. HBV replication is known to be present in the oocytes and in the embryo of viremic mothers [22]. The level of HBV DNA replication is often decreased after HBeAg loss (seroconversion) for females with high viremia. It is therefore worthwhile to consider a finite duration of interferon therapy with a goal of achieving HBeAg loss before conceiving [23]. Interferon is potentially abortifacient. These patients on interferon therapy should be advised to use contraceptive measure to prevent unplanned pregnancy up to 6 months after interferon therapy is ceased [23]. Other approach is to take the category B
Mothers with chronic active hepatitis B infection

No → Cirrhosis or severe hepatitis → Yes

Monitor and check HBV DNA at week 28

HBV DNA $\leq 6 \log_{10}$ copies/ml → Monitor

HBV DNA $> 6 \log_{10}$ copies/ml or history of immunoprophylaxis failure or pre-term labor → Start treatment at the start of 3rd trimester (i.e., TDF, LAM, LdT)

Give HBIG and HBV vaccination series to infants

Continue Treatment (i.e., TDF)

Continue treatment postpartum and avoid breast feeding

If breast-feeding is planned, hold treatment at delivery and restart once breast feeding is finished except cirrhotic patients. Monitor ALT/HBV DNA every 4–6 weeks for 12 weeks after the cessation of antiviral treatment.

Fig. 1 Active CHB during pregnancy.

Mothers with chronic inactive hepatitis B infection or at immune tolerance phase

Immune tolerant

Monitor and test HBV DNA at week 28

HBV DNA $> 6 \log_{10}$ copies/ml, Start treatment at the start of 3rd trimester (i.e., TDF, LAM, LdT)

Give HBIG and HBV vaccination series to infants

Inactive hepatitis B

Monitor and test HBV DNA at week 28

If HBV DNA $\leq 6 \log_{10}$ copies/ml, continue monitoring without treatment

If breast-feeding is planned, hold treatment at delivery and restart once breast feeding is finished. If no breast-feeding is planned, stop treatment at 4 week postpartum. Monitor ALT/HBV DNA q 4–6 weeks for 12 weeks after the cessation of antiviral treatment.

Fig. 2 Non-active CHB during pregnancy.
Antiviral treatment to suppress HBV replication prior to conceiving, and then consider stopping the medication during the pregnancy if there is no evidence of advanced maternal disease or hepatitis flare. Mothers in immune clearance or reactivation stage of CHB can restart on antiviral treatment postpartum unless there is a need to use antiviral at the third trimester for the prevention of MTCT.

Those patients in immune tolerant phase or in inactive (low replicative) state of CHB can be monitored without treatment until the beginning of the third trimester (Fig. 2) [24]. Antiviral therapy should be offered at the beginning of the third trimester if the week 28 viral load is greater than 10^6 copies/ml; there is a history of a child with immunoprophylaxis failure; or the mother has evidence of preterm labor [24]. In such case a monotherapy with TDF is the preferred agent of choice. If TDF is not available, either LdT or LAM is an acceptable alternative. The antiviral therapy can be stopped at week 4 of postpartum if no breast-feeding is desired or at delivery if breast-feeding is planned (Figs. 1 and 2). Maternal transaminases and HBV DNA levels are required to be monitored closely within 3 months of treatment cessation. Patients with hepatitis flare should be followed up continuously and evaluated for the treatment need.

It is important to understand that mothers with CHB and cirrhosis are at a high risk of maternal and perinatal complications including fetal death and maternal liver decompensation. In general, antiviral therapy should be provided to all patients with CHB and cirrhosis regardless of their viral load or aminotransferase levels [6]. In cirrhotic mothers antiviral therapy is recommended to be continued throughout the entire pregnancy in order to reduce the risk of hepatic decompensation related to viral flare-up [6,23]. For pregnant females with acute hepatitis B flare (ALT > 10 × upper limit of normal or 5 × baseline values) with or without hepatic decompensation, TDF is the preferred agent to be used throughout the pregnancy [21,23]. The potential safety concerns of feral exposure to the antiviral therapy should not prevent starting the antiviral therapy which could be lifesaving to both mothers and fetus.

### The safety of using antiviral therapy during pregnancy

The safety of medication during pregnancy is often started with the strategy of minimizing the drug exposure. Mothers in the immune tolerant phase can be monitored without treatment until the beginning of the third trimester [24]. If the mother is highly viremic ( > 6 log_{10} copies/ml), antiviral should be considered to prevent the immunoprophylaxis failure in the infant [24]. Cirrhotic patients should continue the antiviral therapy since they are at an increased risk of flare-up and hepatic decompensation during the pregnancy [6]. Current available data on safety of antiviral therapy during pregnancy are mostly from trials evaluating the use of antiviral therapy in the prevention of MTCT [23]. In May 2008, the FDA implemented a system to designate each drug into one of 5 categories based on the safety data for pregnancy (Table 1). Generally, pregnancy category B drugs are safe to use during pregnancy. LdT and TDF are classified as FDA pregnancy risk category B. All other antiviral drugs are classified as FDA pregnancy risk category C and are not recommended to use except for LAM which is classified as FDA pregnancy category C but has been widely used in mothers based on the extensive safety data involving than 4600 women exposed to LAM during their second or third trimesters of pregnancy (Table 1) [25]. Antiretroviral Pregnancy Registry (APR) data confirmed that birth defect rates from LAM and TDF were comparable to those seen in the general population [25]. According to APR data, LAM is associated with a risk of birth defects (2.2% to 2.4%) that is no higher than the background birth defect rate [25]. A study of TDF in 606 pregnant women in their first trimester and 336 in their second trimester showed that the rates of birth defects

### Table 1: FDA pregnancy risk categories for anti-HBV drug

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<tr>
<th>Category</th>
<th>FDA description</th>
<th>Anti-HBV drug</th>
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<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal studies, which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks</td>
<td>Entecavir</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks</td>
<td>Adefovir</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits</td>
<td>Interferon</td>
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Abbreviation: FDA: US Food and Drug Administration.
associated with TDF were 1.5% (second-trimester) to 2.3% (first-trimester), which is similar to the background birth defect rate [25]. Telbivudine received its pregnancy risk category B rating based on few and limited human pregnancy registry data [25]. Adefovir, entecavir, and interferon are classified as FDA pregnancy risk category C, therefore are not recommended to use during the pregnancy (Table 1) [21].

**Treatment as prevention for the mother to child transmission**

The MTCT is the most common route of HBV transmission worldwide [21]. The overall rate of transmission of HBV from an infected HBsAg-positive mother to her neonate during the perinatal period can be as high as 70% to 90% in the absence of immunoprophylaxis [26]. The risk of HBV perinatal transmission was reduced from 70% to 90% to approximately 5% to 10% when the infants received postnatal immunoprophylaxis with both hepatitis B immune globulin (HBIG) and hepatitis B vaccine series [26]. However, studies have shown that up to 30% of infants born to highly viremic mothers may fail immunoprophylaxis and develop CHB [27]. Recent studies have shown that the maternal HBV DNA levels are an independent risk factors for immunoprophylaxis failure [28–30]. Xu et al. showed that those mothers with positive HBeAg status had a viral transmission rate of 70%–90%, whereas those with a negative HBeAg test have a rate of transmission less than 10% which is likely due to low viremic state in HBeAg negative CHB [28]. Although controlled trials have not been performed with HBeAg-negative women, post-exposure prophylaxis with HBIG and vaccination is widely used in belief that the practice would reduce the risk of vertical transmission of the virus.

Zou et al. have demonstrated that there was a linear correlation between immunoprophylaxis failure rates and maternal HBV DNA levels [29]. When maternal pre-delivery DNA levels were stratified to < 6 log10 copies/ml, 6 to 6.99 log10 copies/ml, 7 to 7.99 log10 copies/ml, and > 8 log10 copies/ml, the corresponding rates of immunoprophylaxis failure were 0%, 3.2%, 6.7%, and 7.6%, respectively (P < 0.001). The study has suggested that MTCT occurs (reduced prophylaxis effective rate (PER)) when the maternal HBV DNA was > 6 log10 copies/ml [29]. A recent study by Yi et al. observed high MTCT rates from mothers who underwent amniocentesis with HBV DNA levels above 7 log10 copies/ml when compared to those without the procedure [31]. However, further studies are needed to confirm these findings and investigate if antiviral treatment prior to the amniocentesis can reduce the MTCT rate. Based on this data, if the pregnant mother is HBsAg positive, an assessment of hepatitis B viral load of > 6 log10 copies/ml at week 28 of gestation should be used as the reduced PER and the antiviral therapy should be offered to prevent MTCT. The MTCT risk increases with the maternal HBV DNA > 6 log10 copies/ml or other factors such as threatened preterm labor, prolonged labor, or a prior child with passive-active immunoprophylaxis failure are present [7,29,30]. At the First International Symposium on Hepatitis B Infection in Special Population, it was recommended that pregnant women with HBV DNA > 6 log10 copies/ml or > 200 000 IU/ml at week 28 of gestation should be offered for antiviral therapy [7]. Recent published studies suggested that the use of LAM, LdT or TDF at the third trimester could safely reduce MTCT rates in mothers with HBV DNA levels above 6 log10 copies/ml or 200 000 IU/ml [23]. Han et al. showed in their study of 229 HBeAg positive pregnant females who received LdT 600 mg a day from week 20 to 32 of gestation (n = 135) or served as untreated control (n = 94) that the incidence of perinatal transmission rate was lower in the infants born to the LdT-treated mothers than to the control (0% vs. 8% respectively; P = 0.002) [32]. Zhang et al. enrolled in their prospective control trial, 648 pregnant females with HBV DNA > 6 log10 copies/ml who received LdT (n = 257), lamivudine (n = 51), and control with no treatment (n = 352) from gestation week 28 to postpartum week 4 [33]. 35% of mothers in the treatment group achieved HBV DNA < 500 copies/ml compared with 0% of those in the untreated group (P = 0.001). At an infant age of week 52, HBV transmission rate was significantly reduced in the treatment group based on-treatment analysis (0% vs. 2.84%, P = 0.002) and by intention to treat analysis (2.2% vs. 7.6%, P = 0.001). There was no significant difference between LdT and LAM treated groups in the MTCT rate. Both LdT and lamivudine treatments were well-tolerated without safety concerns. A comprehensive discussion and counseling of risks and benefits should be offered to the treatment candidates.

**Modes of delivery: Caesarean section vs. vaginal delivery**

MTCT rates in different delivery modes have been studied previously with conflicting results. Pan et al. recently showed that elective Caesarean section is effective in reducing MTCT of hepatitis B viral infection [34]. In the study, 1409 infants born to HBsAg positive mothers through vaginal delivery (n = 673), elective Caesarean section (ECS) (n = 496), or urgent Caesarean section (UCS) (n = 240), were included. Infants born by ECS had a lower rate of MTCT than those born by non-ECS (1.4% vs. 3.6%; P = 0.593). Women with HBV DNA < 10^6 copies/ml did not transmit the infection regardless of the methods of delivery [30]. Based on the study, one might consider ECS a potential way to further reduce MTCT risk, especially those patients whose HBV DNAs are greater than 6 log10 copies/ml in spite of using antiviral therapy or missing the opportunity to use antiviral at the third trimester. Further study is needed to validate this data.
Passive and active immunoprophylaxis

A prospective study by Han et al. showed that the administration of three doses of HBIG during the last trimester pregnancy does not reduce the MTCT. In addition, serum anti-HBs from the injected HBIG before delivery do not transfer to the newborns [35]. In this study, blood samples were obtained before and after injection of three doses of HBIG, and serum HBV DNA levels were detected in 10 non-pregnant and 23 pregnant women with chronic hepatitis B infection. Serum anti-HBs were tested by an enzyme-linked immunoassay in 28 infants born to chronic HBV carrier mothers who received three doses of HBIG during the last trimester pregnancy. The serum HBV DNA levels in 10 non-pregnant and 23 pregnant women of HBV carrier state were not statistically different before and after injection of three doses of HBIG. Moreover, none of the 28 newborns were positive for anti-HBs.

The most important intervention for MTCT is to provide immunoprophylaxis to infants born to mothers with CHB. The risk of HBV perinatal transmission was reduced from 70% to 90% to approximately 5% to 10% when the infants received postnatal immunoprophylaxis with both hepatitis B immune globulin (HBIG) and hepatitis B vaccine series [26]. Lee et al. showed in their meta-analysis of 26 randomized controlled trials that compared with placebo or no intervention, hepatitis B vaccination significantly decreased the risk of hepatitis B occurrence (relative risk 0.28, 95% confidence interval 0.20 to 0.40; four trials) [36]. Recombinant vaccine and plasma derived vaccine showed no significant difference in hepatitis B occurrence (1.00, 0.70 to 1.42; four trials). Hepatitis B immunoglobulin (HBIG) significantly decreased the risk of hepatitis B transmission in infants (0.52, 0.44 to 0.63; 11 trials). Compared with vaccination, vaccination plus HBIG significantly reduced hepatitis B occurrence (0.54, 0.41 to 0.73; 10 trials). Multiple HBIG plus plasma derived vaccine versus single HBIG injection plus plasma derived vaccine did not significantly reduce the risk of hepatitis B occurrence (0.87, 0.30 to 2.47; two trials, $F = 0\%$). Lee et al. concluded that there was no significant differences were found in hepatitis B occurrences among different vaccination schedules, different recombinant vaccines, and different plasma derived vaccines [36]. Therefore, salvage vaccination should still be given if the infants failed to get or in a case of unplanned pregnancy as soon as possible. Recommendations for preventive treatment of exposed infants include administration of HBIG at a dose of 0.5 ml or 100 IU intramuscularly and hepatitis B vaccine (Engerix-B®) (20 μg) within 12 h of birth, a second dose of vaccine at 1 month of age and a third dose at 6 months of age [5]. Post-vaccination testing for HBsAg and anti-HBs between 12 and 15 months of age is also recommended for the determination of vaccination response.

Postpartum antiviral therapy and breast-feeding

Antiviral therapy can be stopped at week 4 postpartum for those patients who are in immune tolerant phase or right after delivery if breast-feeding is planned. Once the antiviral therapy is stopped, close monitoring of liver injury test and viral loads are required for the duration of 3 to 6 months [23]. HBsAg can be found in breast milk [37]. The current available data before and after the introduction of hepatitis B vaccine showed that breast-feeding was not associated with an increased risk of viral transmission compared to bottle-feeding [38–40]. Zhang et al. recently showed in his study of 1186 HBsAg-positive mothers that different feeding patterns did not increase the MTCT of hepatitis B [41]. Most experts agree that if the infant has received appropriate immunoprophylaxis, breast-feeding is safe and should be encouraged if desired. In addition, there is no need to delay breast-feeding until the infant is fully immunized with the remaining hepatitis B vaccine series [4]. Such breast-feeding can be started as long as the infant has received HBIG and the first dose of hepatitis B vaccination at birth. For those females who decide to remain on antiviral therapy in their postpartum period, breast-feeding is generally not recommended [23]. A previous study has shown that breast milk from mothers taking TDF contained low level of TDF [40]. Since the drug safety profile for infants has not been well studied and established, the breast-feeding practice should be discouraged to use. For those mothers who decided to stop the antiviral therapy in their postpartum period in effort to breast-feed their infants, clinicians should monitor for maternal CHB disease flare-up or hepatitis flare from medication withdrawal in the postpartum period. If the patients develop active CHB disease, the clinicians should counsel and offer the antiviral therapy to the mothers.

Conclusions

Management of HBV infection in females before, during and after pregnancy is challenging and requires an individualized approach to assess for the risks of antiviral drug exposure to the fetus and infants weighed against the benefits of the treatment. Those patients with cirrhosis should continue the antiviral therapy throughout the pregnancy. If TDF is not available, LAM or LdT is an acceptable alternative choice. The patients should be monitored for disease flare-up if they decide to stop the antiviral therapy in anticipation of pregnancy. Approximately 5%–10% infants fail postnatal immunoprophylaxis and this failure rate goes up to 30% of infants born to highly viremic mothers. To reduce the MTCT rate, the HBV DNA level should be assessed at week 28. If the HBV DNA level is $> 6 \log_{10}$ copies/ml (or $> 200 \, 000$ IU/ml), antiviral therapy should be offered throughout the
third trimester. Universally, all infants born to the mothers with CHB should be offered passive and active immunoprophylaxis using hepatitis B immunization and HBIG infusion within 12 h of the birth, respectively. Breast-feeding is safe with a negligible risk of MTCT in infants who had received appropriate immunoprophylaxis; however, breast-feeding should be avoided if mothers decide to remain on antiviral therapy. One might consider ECS to reduce MTCT if the mother HBV DNA is greater than $7 \log_{10}$ copies/ml in spite of using antiviral therapy, or missing the opportunity to start antiviral therapy at the third trimester. Further study is needed to validate this approach.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tr>
<td>CHB</td>
<td>chronic hepatitis B infection</td>
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<tr>
<td>ETV</td>
<td>entecavir</td>
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<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
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<tr>
<td>HBeAb</td>
<td>hepatitis B e antibody</td>
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<td>HBeAg</td>
<td>hepatitis B e antigen</td>
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<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<tr>
<td>HBsAb</td>
<td>hepatitis B surface antibody</td>
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<td>IFN</td>
<td>interferon</td>
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<td>LAM</td>
<td>lamivudine</td>
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<td>LdT</td>
<td>telbivudine</td>
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<td>TDF</td>
<td>tenofovir</td>
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<tr>
<td>MTCT</td>
<td>mother-to-child transmission</td>
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<tr>
<td>PER</td>
<td>prophylaxis effective rate</td>
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**Compliance with ethics guidelines**

James S. Park and Calvin Pan declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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