REVIEW

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Prevention strategies of mother-to-child transmission of hepatitis B virus (HBV) infection

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ABSTRACT
Chronic hepatitis B virus (HBV) infection caused by mother-to-child transmission (MTCT, also known as vertical transmission) during the perinatal period is a major public health problem worldwide. Despite the availability of the combined active-passive immunization with a hepatitis B vaccine and hepatitis B immunoglobulin after birth, about 9% of newborns are still infected with HBV, especially those born to hepatitis B e antigen (HBeAg)-positive mothers. Currently, the management of HBV infection during pregnancy remains controversial. This article briefly reviews the recent advances in the epidemiology of HBV, immunization against it, and management strategies in the third trimester.

KEYWORDS
Hepatitis B virus, Mother-to-child transmission, Immunization, Antiviral therapy

Epidemiology of hepatitis B virus infection

Hepatitis B virus (HBV) infection is a major public health concern worldwide. Chronic HBV infection is extremely harmful and is closely associated with the development of cirrhosis, hepatocellular carcinoma (HCC), and liver failure. Globally, HBV infection is found in 30% and 45% of patients with liver cirrhosis and HCC, respectively.[1,2] In China, the incidence of HBV infection is 60% and 80% in these patients, respectively.[3] According to the World Health Organization, about two billion people are infected with HBV worldwide, more than 240 million of whom are chronically infected.[4,5] In most cases, these infections are acquired during the perinatal period or in infancy or childhood, especially in countries and regions with a high prevalence of HBV.[6-8] Even in countries and regions with low prevalence of HBV infections, the number of individuals infected with HBV during the perinatal period or infancy may account for more than one third of the total number of infections.[4,5,9] The risk of chronic infection is related to the age at infection, and approximately 90% of infections acquired in the perinatal period or infancy become chronic,[4] compared with 50% of those acquired under 3 years of age[6] and 5% of those acquired in adulthood.[10] The prevalence of chronic hepatitis B is high in China. A seroepidemiological survey of hepatitis B in 2006 showed that the prevalence of hepatitis B surface antigen (HBsAg) among the general population aged 1–59 years in China was 7.18%.[11,12] It was estimated that there were about 93 million HBV carriers in China, including about 20 million patients with chronic hepatitis B.[13] The Chinese Center for Disease Control and Prevention undertook a seroepidemiological survey of hepatitis B in the general population aged 1–29 years in 2014, which showed that the HBsAg prevalence rates in the subpopulations aged 1–4 years, 5–14 years, and 15–29 years were 0.32%, 0.94%, and 4.38%, respectively.[14]

Preventing mother-to-child transmission (MTCT) is the key to controlling HBV infection and reducing the

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incidence of related complications. The major routes of HBV infection are blood contact, MTCT, and sexual contact.[15] With improvements in detection methods and the standardization of medical procedures, HBV transmission through blood transfusions and blood products has become less common. In contrast, MTCT has become a major transmission route—more than half of existing hepatitis B patients were infected through MTCT.[14] An epidemiological survey showed that the prevalence of HBsAg among pregnant women in China was 5.49%. In the newborn infants of HBsAg- and hepatitis B e antigen (HBeAg)-positive mothers, the incidence of MTCT reached 7.1% despite the administration of a hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) at birth.[16]

There are three main MTCT routes: in utero, during labor, and during close contact with the mother after birth. Among these, transmission in utero and during labor are the commonest routes, and this explains the high failure rate of immunizing newborns to after birth.[10,17,18] Preventing the MTCT of HBV infection should be based on its transmission mechanism, and the main measures taken are the antiviral treatment of mothers during pregnancy and the immunization of newborns after delivery.

Postnatal immunization

Hepatitis B vaccination within 24 hrs of birth can dramatically reduce perinatal HBV transmission.[19] Since China introduced the hepatitis B vaccine into its national vaccination program in 1992, the prevalence of HBsAg has dropped significantly.[20] Meta-analyses have suggested that the dual immunization of newborns born to HBsAg-positive mothers with a hepatitis B vaccine and HBIG can reduce the incidence of HBV infection and effectively prevent the MTCT of HBV infection.[21-24] For newborns of HBsAg-positive mothers, especially those who are HBsAg- and HBeAg-positive, HBIG should be injected as early as possible within 24 hrs of birth (preferably within 12 hrs), at a dose of ≥ 100 IU. The first dose of a human hepatitis B vaccine (10 mg) from recombinant yeast should be administered at different locations and the second and third doses are administered at 1 and 6 months after the initial dose, which will effectively prevent MTCT.[14,25-27]

The passive-active immunization of newborns with an HBV vaccine and HBIG can lower the HBV infection rate and effectively prevent vertical transmission. However, up to 25%–30% of newborns are still infected with HBV as a result of HBIG or vaccination failure, which may be related to intrauterine infections.[10,28,29] The transplacental transmission of and intrauterine infection with HBV mainly occur in the third trimester, and the risk of MTCT correlates positively with maternal HBV-DNA levels.[30,31] One study reported that when the serum HBV-DNA level in pregnant women exceeded 1.0×10^8 copies/mL, the incidence of intrauterine infection was as high as 9%, despite postnatal active and passive immunization of the newborns.[32] MTCT is more likely to occur in newborns born to mothers with an HBV-DNA level of $> 1.0 \times 10^6$ copies/mL than in those born to mothers with than an HBV-DNA level of $< 1.0 \times 10^6$ copies/mL. The risk of HBV infection is 8%–30% higher in the former.[16,33-35] Therefore, preventing measures that are based on the combination of a hepatitis B vaccine with HBIG cannot fully meet clinical requirements. Pregnant women have abnormal immune elimination and liver function, which are harmful to themselves and their fetuses. Therefore, appropriate measures must be taken at the appropriate time in high-risk pregnant women.

Antiviral therapy during pregnancy for HBsAg-positive mothers

The maternal HBV-DNA level and HBeAg positivity are important factors affecting the MTCT of HBV infection. Without any intervention, the incidence of HBV infection in babies delivered to HBeAg-positive mothers is up to 95%. In contrast, if combined active-passive immunization with a hepatitis B vaccine and HBIG is given to newborns of HBeAg-positive mothers at birth, the incidence of MTCT is reduced to 3%–7%.[22,36,37] In contrast, for newborns of HBeAg-positive mothers with high HBV-DNA loads, the incidence of MTCT can reach 8%–32% despite the application of combined active-passive immunization with a hepatitis B vaccine and HBIG at birth.[31,32,38] Therefore, lowering the mother's HBV-DNA level during pregnancy is particularly important in preventing MTCT.

A large number of clinical studies have explored the use of nucleosides as an antiviral treatment for mothers with high HBV-DNA viral loads during the second and third trimesters of pregnancy, in addition to combined active-passive immunization with a hepatitis B vaccine and HBIG.[39-41] Nucleoside analogues currently approved by the U.S. Food and Drug Administration for anti-HBV therapy include telbivudine, tenofovir, and lamivudine.[42-44] Telbivudine and tenofovir are class B drugs. Lamivudine is a class C drug and was the first nucleoside analogue approved in China. Animal experiments have shown that it has adverse effects on embryos, but it is safe and tolerated well in HIV-infected pregnant women.[45]

Yu et al conducted a study of the efficacy and safety of lamivudine in preventing MTCT in 100 HBeAg-positive mothers whose HBV-DNA levels were $> 1.0 \times 10^7$ copies/mL (6.3 $\log_{10}$ IU/mL) between weeks 24 and 32 of pregnancy. Newborns in both groups (lamivudine group and placebo group) received combined hepatitis B vaccine and HBIG immunization after birth. The results showed that the MTCT rates were 0% and 7% in the lamivudine group and placebo group, respectively ($P < 0.05$).[46]

An Australian observational study suggested that lamivudine has a low resistance barrier and that its use should be initiated in the third trimester of pregnancy and discontinued immediately after delivery. Twenty-one mothers with HBV viral loads of > 1.0×10^7 IU/mL received lamivudine for an average of 53 days, and after treatment, their viral loads decreased by an average of 2.6 $\log_{10}$ IU/mL, although the HBV-DNA levels in four patients were still > 1.0×10^7 IU/mL. Viral mutations and reduced lamivudine sensitivity were observed in four mothers (19%).[47] Therefore, the use of lamivudine in the third trimester of pregnancy may not be very effective and there is a risk of selective resistance. Lamivudine is no longer used as a first-line antiviral therapy in chronic hepatitis B patients because of its high resistance rate. Therefore, the use of lamivudine as an antiviral therapy during the third trimester of pregnancy requires careful evaluation.

Compared with lamivudine, telbivudine is a newer nucleoside analogue with better efficacy and a lower resistance rate. It specifically inhibits the DNA polymerase of HBV without any effect on the activity of human DNA polymerases and other human viruses. Many clinical studies have investigated the role of telbivudine in preventing MTCT.

An open study with a large sample size was conducted in 229 HBeAg-positive pregnant Chinese women whose HBV-DNA load was > 1.0×10^7 copies/mL. These mothers received telbivudine from week 20 to week 32 of gestation (n = 135) or were untreated controls (n = 94). All the infants in both arms received combined active-passive immunization after birth. Before delivery, the HBV-DNA loads decreased by 1.0×10^3 copies/mL in the telbivudine-treated group, but showed no significant change in the control group. Seven months after delivery, the rate of HBsAg positivity was 0% in the babies born to the telbivudine-treated mothers and 8% in those born to the untreated mothers (P = 0.002).[48]

A meta-analysis included data from six clinical studies (a total of 576 pregnant women as subjects). The results showed that antiviral treatment with telbivudine in the third trimester of pregnancy safely and effectively prevented MTCT. However, it promoted the negative conversion of HBV-DNA and the normalization of alanine aminotransferase in HBV-infected mothers, at least to some extent.[49]

In an observational study in China, 252 HBeAg-positive pregnant women with HBV-DNA loads of > 1.0×10^6 copies/mL commenced telbivudine treatment in gestational week 28 and continued until 4 weeks after delivery. The other 345 pregnant women, with similar baseline data, were not treated with antiviral therapy (and were the control group). The results showed that the MTCT rates were 0% and 2.84% in the telbivudine-treated group and control group, respectively (P = 0.0002).[50] Other studies have also suggested that telbivudine significantly and safely prevents the MTCT of HBV infection.[51,52]

Tenofovir is a potent anti-HBV agent with a low incidence of drug resistance. It is recommended as the first-line anti-HBV drug in European and American guidelines. Many studies have reported the use of tenofovir for preventing MTCT. A retrospective study included 45 pregnant patients with HBeAg-positive chronic hepatitis B and HBV-DNA levels > 1.0×10^7 copies/mL, some of whom received tenofovir disoproxil fumarate (TDF) from week 18 to week 27 of gestation (n = 21). The untreated pregnant patients acted as the controls (n = 24). All infants received HBIG and recombinant HBV vaccine as active-passive immunization after birth. The MTCT rate was 0% and 8.3% in the TDF group and control group, respectively (P = 0.002). No adverse events were observed in the TDF group.[53]

The study of Greeup et al included 58 pregnant women who used TDF from gestational week 32 to 4–12 weeks after delivery. The control group contained 20 pregnant women who received no intervention. The results showed that TDF effectively reduced the maternal HBV viral load by (3.64 ± 0.9) $\log_{10}$ IU/mL and markedly lowered the MTCT of HBV infection, which was 2% and 20% in the TDF group and untreated group, respectively.[54]

The efficacy and safety of maternal TDF treatment in reducing perinatal HBV transmission were also evaluated in a prospective, multicenter trial that enrolled 118 HBsAg- and HBeAg-positive pregnant women with HBV-DNA > 7.5 $\log_{10}$ IU/mL. The mothers received no medication (control group, n = 56) or TDF (TDF group, n = 62) from week 30–32 of gestation until 1 month postpartum. At delivery, the TDF group had lower maternal HBV-DNA levels than the controls [(4.29 ± 0.93) versus (8.10 ± 0.56) $\log_{10}$ IU/mL, respectively, P < 0.0001]. The TDF group infants had lower rates of HBV-DNA positivity at birth than the controls (6.15% versus 31.48%, respectively, P = 0.0003) and HBsAg positivity at 6 months old (1.54% versus 10.71%, respectively, P = 0.0481).[55]

In another study, tenofovir monotherapy was effective and safe when used as a rescue therapy in pregnant women resistant to lamivudine or telbivudine.[56]

Based on the results of currently available clinical studies, the guidelines released by the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APSAL), and the Chinese Society of Hepatology recommend that in addition to combined active-passive immunization for newborns, antiviral therapy with tenofovir or telbivudine for pregnant women with high HBV viral loads, beginning

at gestational week 28–32, is an effective and safe strategy for preventing MTCT.[14,25,27,57]

CONFLICT OF INTEREST

None.

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