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TOPIC HIGHLIGHT

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Individualized management of pregnant women with high hepatitis B virus DNA levels

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Abstract

Hepatitis B is a major health concern in the Asia-Pacific region, and is endemic in China, Southeast Asia, and Africa. Chronic hepatitis B virus (HBV) infection may cause hepatic cirrhosis and liver cancer. It is estimated that there are more than 350 million chronic HBV carriers worldwide, of whom approximately one quarter will die of chronic hepatitis B-related liver diseases. HBV is transmitted horizontally through blood and blood products or by sexual transmission, and vertically from mother to infant. Perinatal infection is the predominant mode of transmission in countries with a high prevalence of hepatitis B surface antigen (HBsAg) carriage, and perinatal transmission leads to high rates of chronic infection. Therefore, it is important to prevent the mother-to-child transmission (MTCT) of HBV. Research has shown that pregnant women with high HBV DNA levels have an increased risk of MTCT. However, most of the obstetrics guidelines do not make a distinction between pregnant women with high HBV DNA levels and those who are HBsAg positive only. This review addresses the management of pregnant women with high levels of HBV viremia, in terms of antiviral therapy, use of hepatitis B immunoglobulin (HBIG), the combined application of hepatitis B vaccine and HBIG, choice of delivery mode and feeding practices.

Key words: Hepatitis B virus; Hepatitis B virus DNA; High level; Management; Pregnancy

Core tip: Research has shown that pregnant women with high hepatitis B virus (HBV) DNA levels have an increased risk of mother-to-child transmission. However, most of the obstetrics guidelines do not make a distinction between pregnant women with high HBV DNA levels and those who are hepatitis B surface antigen positive only. This review addresses the management of pregnant women with high levels of HBV viremia, in terms of antiviral therapy, use of hepatitis B immunoglobulin (HBIG), the combined application of hepatitis B vaccine and HBIG, choice of delivery mode and feeding practices.

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INTRODUCTION

It is estimated that there are more than 350 million

chronic hepatitis B virus (HBV) carriers worldwide, and approximately 75% of these carriers are found in Asia[1]. In recent years, the positive rate of hepatitis B surface antigen (HBsAg) in China has decreased from 9.09% to 7.18%, however, there are still 93 million HBV carriers[2,3]. Forty to fifty percent of chronic HBV carriers are caused by vertical transmission, which ranks among the important modes of HBV infection and an important reason for so many HBV carriers[4]. The Advisory Committee on Immunization Practices recommends that all infants born to HBsAg-positive mothers should be given post-exposure immunoprophylaxis with hepatitis B vaccine and hepatitis B immunoglobulin (HBIG)[5-8]. However, this remedial prevention measure still does not completely prevent the vertical transmission of HBV. In addition, standard passive-active immunoprophylaxis with HBIG and hepatitis B vaccine in neonates has a failure rate as high as 10% to 15%[9]. One of the important causes of vaccine failure is related to intrauterine infection[9-11]. Current research shows that pregnant women with high HBV DNA levels have an increased risk of mother-to-child transmission (MTCT)[12-14]. Therefore, to reduce the risk of MTCT and the failure rate of combined immunization after birth, special attention should be paid to pregnant women with high HBV DNA levels, and the treatment of these women should be different from those with low HBV DNA levels.

PRENATAL SCREENING

Due to the high prevalence of HBV and availability of a safe and effective HBV vaccine, prenatal screening for HBV has become standard in antenatal care in most countries. However, following universal screening, as many as 50% of HBsAg-positive individuals were lost to follow-up in some populations as shown by a study from Denmark[15]. Therefore, the American Association for the Study of Liver Disease (AASLD) recommends that all pregnant women should be screened for HBsAg during the first trimester, even if previously vaccinated or tested[16]. If serum HBsAg is positive, HBV DNA levels in these pregnant women should be monitored. Based on the level of HBV DNA, antiviral treatment during pregnancy may be indicated, the combined application of hepatitis B vaccine and HBIG and mode of delivery should be carefully selected, and counseling of sexual and household contacts should be undertaken.

With regard to the cut-off value for HBV DNA level, there is no uniform definition at present. Wang *et al*[12] used 6 log copies/mL as the cut-off, and their study showed that when the HBV DNA level was < 6 log copies/mL, the failure rate of prevention of MTCT (PMTCT) was 1.9%. However, the failure rate of PMTCT was as high as 23.4% when HBV DNA level was ≥ 6 log copies/mL. Similar results were also observed in some studies which used 7 log copies/mL or 8 log copies/mL as the cut-off, respectively[13,14]. As most studies used 6 log copies/mL as the cut-off, this value is referred to in the present review. We consider that pregnant women with an HBV DNA level exceeding 6 log copies/mL require individualized management during pregnancy.

MATERNAL ANTIVIRAL THERAPY

Hepatitis B antiviral drugs are classified into two kinds: interferons and nucleosides. Due to their antiproliferative effects and no available data on their safety during pregnancy, the use of interferons are not advised in pregnancy. Nucleoside analogues often cannot eliminate the virus completely; following discontinuation of treatment, the virus is likely to return to the original level or even higher, which may induce severe liver dysfunction; and long-term treatment may cause virus mutation, drug resistance and other side effects[17]. Therefore, the use of antiviral drugs during pregnancy is still controversial. Decisions on antiviral therapy during pregnancy must include the risks and benefits for both the mother and the fetus; the risk-benefit equation also depends upon the trimester of the pregnancy[18]. Safety data on HBV antiviral drugs during pregnancy are from two major sources, the Antiretroviral Pregnancy Registry (APR)[19] and the Development of Antiretroviral Therapy Study (DART)[20]. The APR interim report showed that if initial exposure to any nucleoside or nucleoside drug occurred in the first trimester compared to the second or third trimester, there was no significant difference in the rate of adverse outcomes. Three percent of congenital anomalies reported in the DART compares favorably with 2.72% reported by the Centers for Disease Control birth defect surveillance system[20].

Studies[12-14] have shown that high levels of maternal HBV DNA increase the rate of intrauterine infection. To minimize or avoid the use of medication during pregnancy and abuse of medical resources, it is necessary to select the appropriate HBV DNA level for antiviral treatment. At present, most researchers[9,21,22] believe that the management of HBV infection during pregnancy depends on disease severity and HBV DNA levels and needs to be individualized: (1) if HBV DNA levels are low (HBV DNA levels < 6 log copies/mL) and there is no significant fibrosis, it is reasonable to defer therapy until after delivery, to avoid fetal exposure to the therapeutic agent, however, periodic review of liver function and HBV DNA level is required; (2) in pregnant women with an HBV DNA level ≥ 7 log copies/mL without abnormal ALT or an HBV DNA level ≥ 6 log copies/mL with an HBV-positive infant history in a previous pregnancy, but normal ALT, treatment in the last trimester with a "B" category drug seems reasonable; (3) in pregnant women with an HBV DNA level < 5 log copies/mL combined with significant fibrosis, but no cirrhosis [fibrosis can be diagnosed during pregnancy by a rise in serum procollagen-3-peptide, type 4 collagen, laminin and hyaluronic acid, and the results of ultrasound or magnetic resonance imaging (MRI)], treatment is needed during pregnancy;

and (4) in pregnant women with cirrhosis (cirrhosis can be diagnosed during pregnancy based on clinical symptoms and the results of ultrasound and MRI), antiviral therapy should be administered from the gestation period to the postpartum period. In addition, treatment should be discontinued if resistance occurs following the administration of antiviral drugs during pregnancy. However, frequent monitoring of liver function and HBV DNA level should also be conducted. If the HBV DNA level is ⩾ 7 log copies/mL after drug withdrawal, treatment should continue by replacement of the original drug.

The Food and Drug Administration has classified telbivudine and tenofovir as category B medications, whereas lamivudine is a category C medication. In a large randomized placebo-controlled double-blind study[23] of 155 HBeAg-positive women with HBV ⩾ 1000 Meq/mL (9 log copies/mL), but mainly normal ALT, lamivudine 100 mg daily was compared with placebo. Infants in the lamivudine + vaccine + HBIG group had a significant decrease in the incidence of HBsAg seropositivity (10/56, 18% *vs* 23/59, 39%; $P = 0.014$) and in detectable HBV DNA (11/56, 20% *vs* 27/59, 46%; $P = 0.003$) compared to infants in the placebo + vaccine + HBIG group. The results of this study showed that lamivudine reduced HBV transmission from highly viremic mothers to their infants who received passive/active immunization, and no safety concerns were noted in the lamivudine-treated mothers or their infants. In the last few years, similar results were also found in other clinical trials[23-25]. A recent meta-analysis[26] systematically reviewed 15 randomized controlled trials (RCTs), which included 1693 HBV-carrier mothers. The results revealed that lamivudine treatment in HBV-carrier mothers from 28 wk of gestation may effectively interrupt MTCT of HBV, and the incidence of lamivudine-associated adverse effects was similar to that in the controls. As the effectiveness and safety of using lamivudine during pregnancy have been proved, the National Institutes of Health (NIH) proposed that lamivudine should be classified as a category B medication. Therefore, at present, first-line antiviral drugs during pregnancy include lamivudine, telbivudine and tenofovir. However, lamivudine has been associated with high levels of HBV resistance during long-term use[27], thus, attention should be paid to this antiviral agent during pregnancy.

PRENATAL USE OF HBIG

HBIG is purified from highly effective plasma or serum taken from healthy individuals following administration of the HBV vaccine, contains a high titer of antibody to HBsAg, and was first introduced in 1974 for passive immunization shortly before or soon after exposure to HBV[28]. Zhu *et al*[29] reported the intramuscular administration of 2000 IU HBIG at 1-mo intervals during the last three months before delivery in asymptomatic HBsAg positive women in 1995. The results of this study confirmed that this regimen significantly and safely reduced the rate of intrauterine infection. However, whether HBIG administration during pregnancy can interrupt HBV intrauterine transmission is still controversial. Other research claims that the half-life of HBIG is short, therefore, its neutralization efficacy is limited and transitory[30]. Following the administration of HBIG in HBV carrier mothers during pregnancy, none of their newborns were positive for HBsAb[31]. Even when HBsAb was detected in newborns, there was no difference in newborn HBsAb seropositivity between women who had received HBIG treatment during pregnancy and those who had not[32]. During replication in HBV carriers, HBV production may approach 10 (11) molecules/d, although during peak activity this rate may increase by 100 to 1000-fold[33]. The concentration of HBsAg in serum is 1-100 thousand times higher than HBV. Therefore, administration of 200-400 IU HBIG at 1-mo intervals during the third trimester could not reduce HBV viral load sufficiently[34]. However, a recent meta-analysis[35] systematically reviewed 37 RCTs, which included 5900 newborns of asymptomatic HBsAg seropositive mothers. The results revealed that multiple injections of HBIG in HBV carrier mothers with a high degree of infectiousness in late pregnancy effectively and safely prevented HBV intrauterine transmission. Similar results have also been reported in China[36,37]. Consistent RCTs, cohort studies and the clinical decision rule validated in different populations belong to level A evidence of the evidence-based medicine (EBM), which indicates good scientific evidence and suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients. Studies[12-14] have shown that a high level of maternal HBV DNA can increase the rate of intrauterine infection. Although the effect and mechanism of HBIG administration during pregnancy remain unclear, we believe that after an adequate explanation of the benefits and limitations of HBIG treatment to the pregnant women with high HBV DNA levels, clinicians could suggest HBIG administration during pregnancy in order to prevent HBV intrauterine infection.

There is still controversy concerning the dosage of HBIG during pregnancy. In patients undergoing liver transplantation, after the HBV-producing liver has been replaced by a healthy liver, it requires a continuous blood concentration of 100-500 IU/L of HBIG to neutralize HBV in the blood[38]. There are no reports of HBV mutation in patients treated with HBIG at a total dosage less than 20000 IU within two months[35]. In our previous study[39] HBIG administration in late pregnancy did not cause HBV S gene mutation. As HBV intrauterine transmission mainly occurs during the third trimester, and most fetal organs have developed by that time, medication during late pregnancy would have minimal effects on the fetus[40]. Therefore, HBIG administration in late pregnancy at higher doses (400 IU or more) or shorter intervals (twice a week) and for a limited duration may be more effective in preventing HBV intrauterine transmission. This issue requires confirmation in multicenter RCTs and systematic reviews.

PRENATAL USE OF HEPATITIS B VACCINE AND HBIG

Since the development of the recombinant HBV vaccination in 1982, several health authorities, including the World Health Organization (WHO) and the AASLD, recommend its use in neonates born to HBV carrier mothers, in addition to other high-risk groups such as pregnant women and unvaccinated individuals whose parents were born in areas of high HBV endemicity[41]. Gupta *et al*[42] randomly divided 99 HBsAg negative pregnant women into two groups. Group I was given two doses of recombinant hepatitis B vaccine (dose 20 μg, first dose at around 24 wk, and at 4-6 wk intervals), and group Ⅱ was given three doses of the vaccine. Their babies were followed until 4 mo after delivery. They found that HBsAb levels in the newborns at birth were significantly higher following the three dose schedule (100%) compared with the two dose schedule (66%). Thus, it was concluded that hepatitis B vaccination during pregnancy could transfer antibodies passively to the newborn through the placenta. Duan *et al*[43] treated HBsAg and/or HBeAg positive pregnant women with three doses of hepatitis B vaccine and HBIG (hepatitis B vaccine 30 μg + HBIG 200 IU, starting from 20 wk, at 4 wk intervals). The results showed that the rate of HBV infection in newborns in the treatment group (3/42, 7%) was significantly lower than that in the non-intervention group (14/38, 37%). The authors suggested that combination immunoprophylaxis during pregnancy could effectively prevent HBV intrauterine transmission. However, administration of hepatitis B vaccine combined with HBIG during pregnancy did not completely prevent HBV intrauterine transmission. Further study on whether HBIG influences the effect of active immunization by hepatitis B vaccine is necessary. In pregnant women with high HBV DNA levels, whether the interval between HBIG administration and hepatitis B vaccine (*e.g.*, one or two weeks) would further improve the effect of preventing HBV intrauterine transmission is worthy of more RCTs.

MODE OF DELIVERY

With regard to MTCT of HBV during delivery, it is still controversial as to whether different modes of delivery [mainly cesarean section (CS) *vs* vaginal delivery] affect the vertical transmission rate of HBV. Wang *et al*[44] divided 301 babies born to HBsAg positive mothers into three groups according to the mode of delivery (vaginal delivery group, instrument assisted delivery group and CS group). All of the infants received active and passive immunizations after birth, and HBsAg and HBsAb levels were monitored annually. They found no significant difference between these three modes of delivery in the interruption of HBV MTCT, and CS did not reduce the incidence of immunoprophylaxis failure. However, a meta-analysis[45] which included 4 randomized trials involving 789 infants showed strong evidence that elective cesarean section (ECS) *vs* vaginal delivery effectively reduced the rate of MTCT of HBV. The rate of intrauterine infection following ESC was 10.5% and was 28.0% following vaginal delivery. The difference between the two groups was statistically significant (RR = 0.41, 95%CI: 0.28-0.60, $P < 0.000001$). Another meta-analysis which included seven controlled trials and cohort studies involving 1819 infants (353 in the CS group *vs* 1466 in the vaginal delivery group) showed similar results[46]. It is known that part of the MTCT of HBV occurs during the intrapartum period. The most likely route causing intrapartum HBV infection is transplacental leakage of HBV-positive maternal blood, which is induced by uterine contractions during delivery and the disruption of placental barriers[45]. Whether ECS can effectively reduce MTCT of HBV requires confirmation by high quality multicenter RCTs. In addition, most obstetric guidelines do not endorse the routine use of CS as a measure of preventing perinatal HBV transmission[17,47]. In pregnant women with high HBV DNA levels, high viremia would certainly increase the risk of neonatal HBV infection due to maternal blood exposure. The probability of maternal blood infiltrating the fetal blood circulation is correlated with the length of labor. ECS before onset of labor may avoid or reduce the risk of intrapartum HBV transmission. Therefore, an antepartum level of HBV DNA ⩾ 8 log copies/mL may be an important factor when considering selection for CS. In women with an antepartum level of HBV DNA > 11 log copies/mL, CS should be recommended[48].

BREASTFEEDING

HBsAg, HBeAg and HBV DNA can be detected in colostrum, and higher HBsAg and HBeAg titers were found in mothers with high serum HBV DNA, suggesting that breast milk may be an important vehicle for HBV transmission[49,50]. Hill *et al*[51] studied 369 vaccinated infants born to HBV carrier mothers, and found that the prevalence of HBsAg was not significantly different between breast-fed infants (0/101, 0%) and formula-fed infants (9/268, 3%). A recent meta-analysis indicated that breast milk is infectious; yet, breastfeeding, even by mothers with high infectivity, is not associated with a demonstrable risk of infantile CHB infection, provided the infants have been vaccinated against HBV at birth[52]. These results may be associated with lactoferrin (a major human milk protein) which has bacteriostatic and bactericidal activities[49,53]. Another study found that lactoferrin could inhibit HBV[54]. In view of the multiple benefits of breastfeeding, the WHO recommends breastfeeding for infants of HbsAg-positive mothers even in endemic areas where HBV vaccination may not be readily available[41,55]. With regard to pregnant women with high HBV DNA levels, more RCTs with larger samples are required to determine whether breastfeeding is recommended.

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