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REVIEW

Management of chronic hepatitis B in pregnancy

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Abstract

Pregnancy associated with chronic hepatitis B (CHB) is a common and important problem with unique challenges. Pregnant women infected with CHB are different from the general population, and their special problems need to be considered: such as the effect of hepatitis B virus (HBV) infection on the mother and fetus, the effect of pregnancy on replication of the HBV, whether mothers should take HBV antiviral therapy during pregnancy, the effect of these treatments on the mother and fetus, how to carry out immunization of neonates, whether it can induce hepatitis activity after delivery and other serious issues. At present, there are about 350 million individuals with HBV infection worldwide, of which 50% were infected during the perinatal or neonatal period, especially in HBV-endemic countries. Currently, the rate of HBV infection in the child-bearing age group is still at a high level, and the infection rate is as high as 8.16%. Effective prevention of mother-to-child transmission is an important means of reducing the global burden of chronic HBV infection. Even after adopting the combined immunization measures, there are still 5%-10% of babies born with HBV infection in hepatitis B e antigen positive pregnant women. As HBV perinatal transmission is the main cause of chronic HBV infection, we must consider how to prevent this transmission to reduce the burden of HBV infection. In this population of chronic HBV infected women of childbearing age, specific detection, intervention and follow-up measures are particularly worthy of attention and discussion.

Key words: Chronic hepatitis B; Hepatitis B virus; Mother-to-child transmission; Perinatal transmission; Pregnancy; Vertical transmission; Antiviral therapy

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INTRODUCTION

Chronic hepatitis B (CHB) in pregnancy is an important and pervasive issue with unique challenges. However, for pregnant women with chronic hepatitis B virus (HBV) infection, unlike the general population, many special

problems need to be considered, such as the influence of HBV infection on the mother and fetus, influence of pregnancy on HBV replication, effects of antiviral treatment on maternal and neonatal outcomes, immunization of newborns and the possible flare of hepatitis after delivery. Approximately 350 million people are infected with HBV worldwide and 50% of them have acquired their infection in the perinatal or neonatal period, especially in countries where HBV has a high prevalence[1,2]. In these countries, women of childbearing age have a higher hepatitis B e antigen (HBeAg)-positive rate and a higher probability of mother-to-infant transmission, the younger they are when infected with HBV, the higher the risk of developing CHB[1,3,4]. The rate of HBV infection among women of childbearing age is still at a high level (7.18%) in China[5-7], which leads to an increased risk of HBV vertical transmission and damage due to CHB in the mother and fetus in pregnancy. Therefore, the effective prevention of vertical transmission of HBV is an important approach in reducing the global burden of CHB. Specific hepatitis B immunoglobulin (HBIG) is available for passive protection and is normally used in combination with hepatitis B vaccine to confer immediate cover (passive immunity) and long-lasting protection (active immunity) in newborns, which is administered as an effective prophylactic measure to prevent mother-to-infant transmission of HBV, however, 5%-10% infants of HBeAg-positive mothers are still infected with HBV[8-10].

PREGNANCY AND CHRONIC HBV INFECTION

Overall, no severe effects due to CHB are found in pregnancy. Studies have shown that chronic HBV infection is associated with gestational diabetes mellitus, antepartum hemorrhage, threatened premature labor and lower Apgar score. Mothers with seriously abnormal liver function complications are prone to postpartum hemorrhage, puerperal infection, low body weight infants, fetal distress, premature birth, fetal death and neonatal asphyxia[11-21]. A series of physiological changes occur during pregnancy, including vigorous metabolism and increased nutrient consumption. These changes occur to promote the metabolic needs of the mother as well as the needs of the growing fetus. Abundant sex hormone produced by the mother needs to be metabolized and inactivated in the liver, and metabolism and detoxification in the fetus also depend on the mother's liver, which correlates with aggravation of pre-existing liver diseases and exacerbation of liver damage[22,23]. Alanine aminotransferase (ALT) in late pregnancy and the postpartum period shows an increasing tendency, however, HBV replication in the gestational period is not noticeably different[24-28]. Some women appear to undergo HBeAg seroconversion in the initial months after delivery if immune activation occurs, with a seroconversion rate of 12.5% to 17%, which is correlated with an obvious decrease in adrenal cortex hormone[29,30]. Although HBV infection during pregnancy can often be tolerated, severe hepatitis and hepatic failure induced by perinatal hepatic flare reactions still occur, and can have an unfavorable outcome[29].

PERINATAL MANAGEMENT OF CHB

As relatively safe assays for the diagnosis of HBV infection are available and effective treatment strategies for CHB have been developed, the screening of HBV infection in the perinatal period has become standard care, which can identify newborns that require prophylaxis with hepatitis B vaccine and HBIG as well as pregnant women who require antiviral therapy. In addition, it is beneficial to advise patients with hepatitis B about sexual and family contacts. Screening and vaccination are key factors in the successful prevention and control of HBV infection.

Women with CHB should actively plan their pregnancy and undergo baseline evaluations, such as hepatitis B surface antigen (HBsAg), HBeAg, antibody to HBeAg (anti-HBe), HBV DNA, severity of liver disease and the presence of other viral infections, are suggested before pregnancy. The ability to sustain pregnancy and the risk of vertical transmission of HBV in women with CHB should also be evaluated. All pregnant women should be screened for HBV infection at the first prenatal examination, and HBsAg-positive patients should be transferred to hospitals with experience in the management of CHB for easier monitoring of mothers in pregnancy, delivery and the postpartum period as well as newborns, and appropriate prevention of mother-to-infant transmission of HBV based on an individual's condition should be conducted.

PREVENTION AND TREATMENT OF CHRONIC HBV INFECTION IN PREGNANCY

The treatment goals for CHB in pregnancy are to achieve stabilization of liver function in mothers and prevent HBV infection in newborns. Regular monitoring of liver function and HBV DNA level should be performed in the gestational period to determine whether liver disease is progressing and antiviral therapy is needed in mothers. Sinha *et al*[11] from India made several suggestions aimed at Asian HBV carriers when planning a pregnancy: First, in patients with lower HBV DNA level at baseline (HBV DNA $< 10^6$ copies in HBeAg-positive patients and HBV DNA $< 10^5$ in HBeAg-negative patients) and no obvious fibration, antiviral therapy may be delayed, but monitoring should be performed during pregnancy. In patients with HBV DNA $> 10^7$ copies/mL repeated in the late trimester of pregnancy, or prior delivery history of a HBV-positive infant and HBV DNA $> 10^6$ copies/mL, antiviral therapy should be administered; Second, in patients with higher HBV DNA level at baseline and obvious fibration, but without liver cirrhosis, antiviral

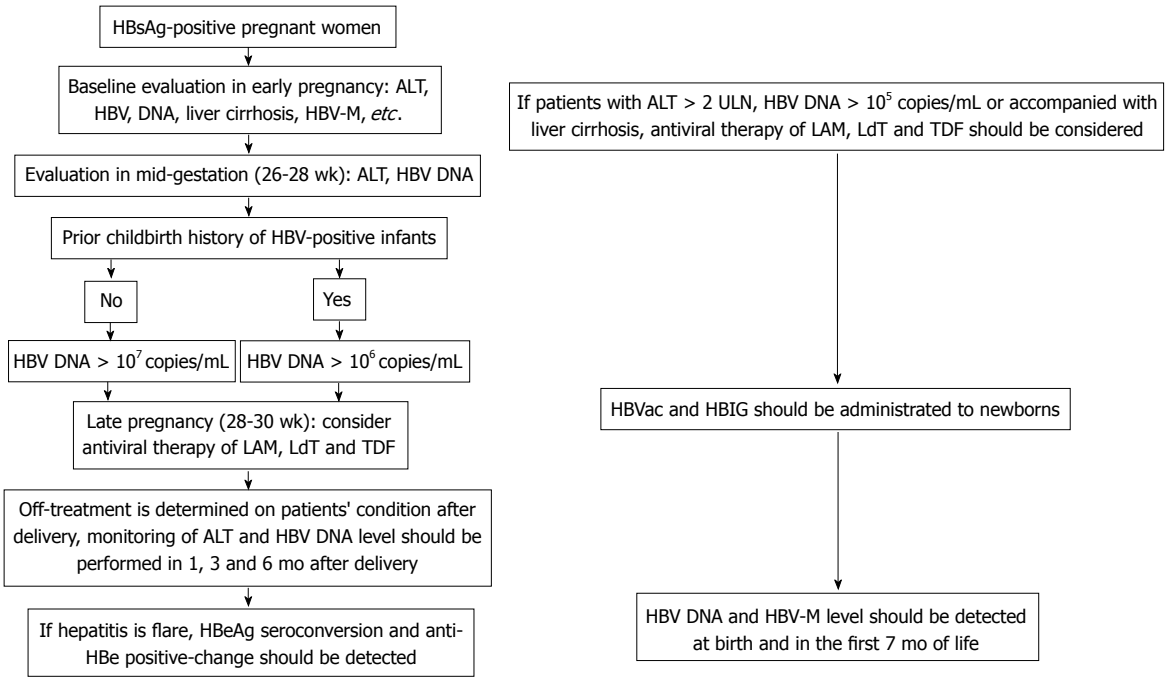

Figure 1 Management of chronic hepatitis B in pregnancy. HBsAg: Hepatitis B surface antigen; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; LAM: Lamivudine; LdT: Telbivudine; TDF: Tenofovir; HBeAg: Hepatitis B e antigen; Anti-HBe: Antibody to HBeAg; ULN: Upper limits of normal; HBVac: Hepatitis B vaccine; HBIG: Hepatitis B immunoglobulin.

therapy is suggested. If a response is sustained after off-treatment, pregnancy is feasible, monitoring should be performed, and management is the same as that outlined in the first scenario; If a response is not sustained after drug withdrawal, management is the same as the third scenario; Third, If patients have liver cirrhosis before pregnancy, antiviral therapy [lamivudine (LAM), tenofovir (TDF) or telbivudine (LdT)] is suggested first, and one of these drugs should be continued during pregnancy, and monitoring should also be conducted.

To effectively prevent HBV infection in infants, delivery methods are also believed to be potential risk factors for mother-to-infant transmission[31,32], however, there is no clear evidence to show that delivery methods are correlated with reduced vertical transmission of HBV[33-35]. Immediate vaccination with HBVac in combination with HBIG in infants born to CHB mothers can effectively prevent infection in the labor and postnatal period, but has no effect on intrauterine infection[36-38], which is the primary cause leading to failure of vaccination. As both HBV intrauterine and perinatal transmission is significantly correlated with HBV DNA level in pregnant women[39-45], currently most attention is focused on oral antiviral drugs in late pregnancy, which reduce HBV intrauterine transmission by decreasing HBV DNA titers in peripheral blood before delivery[46-48].

PROBLEMS CORRELATED WITH ANTIVIRAL THERAPY DURING PREGNANCY

The current difficulty in preventing mother-to-infant transmission of HBV is the prevention of intrauterine transmission. High HBV DNA level is the most important independent risk factor for intrauterine transmission, thus pregnant woman can take oral antiviral drugs in late pregnancy to reduce HBV DNA titers in peripheral blood before delivery and decrease HBV intrauterine transmission.

Selection of antiviral drugs

Due to inhibition of cell proliferation, interferon is contraindicated in pregnant women. For patients using interferon, pregnancy is practicable after discontinuation of interferon for 6 mo. LdT and TDF are authorized category B antiviral drugs by the Food and Drug Administration for use in pregnancy. After reviewing the increasing safety data on LAM in clinical practise[49-52], LAM was elevated to a category B antiviral drug in pregnancy by NIH, that is, the category B antiviral drugs in pregnancy include LAM, LdT and TDF[33,53].

Indication for antiviral therapy

For HBsAg-positive pregnant women by screening, baseline evaluation, such as HBV-M (HBsAg, HBeAg, anti-Hbe), HBV DNA, hepatitis activity and severity of hepatic fibrosis/liver cirrhosis, are suggested in early pregnancy[54-56]. In patients with higher HBV DNA level and hepatitis activity (ALT > 2 upper limit of normal, HBV DNA > 10^5 copies/mL) at baseline or accompanied by liver cirrhosis, antiviral therapy should be administered during early pregnancy. For patients with normal liver function, ALT and HBV DNA level should be reevaluated in mid-gestation (26-28 wk). For patients with HBV DNA > 10^7 copies/mL or prior delivery his-

tory of HBV-positive infants and HBV DNA > 10^6 copies/mL, antiviral therapy (LAM, TDF or LdT) should be given at 28-30 wk until 4 wk after delivery, then it should be determined whether the above therapy is to be continued on the basis of the patient's condition; otherwise antiviral therapy should not be given[57]. ALT and HBV DNA level should be monitored in all HBsAg-positive pregnant women at 1, 3 and 6 mo after delivery. In a hepatitis flare, HBeAg seroconversion and anti-Hbe positive-change should be detected[58]. Active-passive immunization should be performed in all newborns on schedule; HBV-M (HBsAg, HBeAg, anti-HBe) and HBV DNA level should also be detected at birth and in the first 7 mo of life in newborns[59]. In patients with liver cirrhosis before pregnancy, antiviral therapy (LAM, TDF or LdT) are suggested first, one of these drugs should be continued during pregnancy, and monitoring should also be conducted (Figure 1).

Individualized management of CHB in pregnancy

For women with an unplanned pregnancy during the course of antiviral therapy for CHB, individualized management is performed according to the actual condition of the patient. There are two options for patients: one is temporal off-treatment and whole course monitoring of HBV DNA and ALT level, in addition, antiviral therapy is based on the patient's actual condition after pregnancy, which is suitable for patients with mild hepatitis and a lower risk of recurrence and disease progression; the other option is sequential use of LAM, TDF or LdT as antiviral therapy during the whole course[11,36]. Although active-passive immunity should be given to all newborns of HBsAg-positive pregnant women, breast feeding does not increase the risks of HBV infection. However, there is not enough safety data on these drugs with regard to newborn exposure during breast feeding to assess whether patients receiving antiviral therapy should breastfeed their children [57].

Overall, HBV perinatal transmission is a major cause of chronic HBV infection. To reduce the burden of HBV infection, we must consider how to prevent HBV transmission. For women of childbearing age, HBV detection and intervention deserves special attention and investigation.

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