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BRIEF ARTICLE

# A nested case-control study of maternal-neonatal transmission of hepatitis B virus in a Chinese population

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## Abstract

**AIM:** To examine the determinants of maternal-neonatal transmission of hepatitis B virus (HBV).

**METHODS:** A nested case-control study was conducted in Changsha, Hunan, People's Republic of China from January 1, 2005 to September 31, 2006. To avoid potential maternal blood contamination, we collected vein blood of newborns immediately after birth and before initial hepatitis B vaccination to determine the HBV infection status of the newborn. For each HBsAg-positive infant, one HBsAg-negative infant born to an HBsAg-positive mother was matched by hospital at birth (same), gender (same), and date of birth (within 1 mo). A face-to-face interview was conducted to collect clinical and epidemiological data. Conditional logistic regression analysis was used to estimate the independent effects of various determinants on maternal-neonatal transmission of HBV.

**RESULTS:** A total of 141 HBsAg-positive infants and 141 individually matched HBsAg-negative infants were included in the final analysis. Maternal first-degree family history of HBV infection, intrahepatic cholestasis, and premature rupture of membranes were risk factors for perinatal transmission of HBV, whereas systematic treatment and HBV immunoglobulin injections for mothers with HBV infection were protective factors for maternal-neonatal transmission of HBV, after adjustment for potential confounding factors.

**CONCLUSION:** For HBsAg-positive mothers, systematic treatment, HBV immunoglobulin administration, and controlling intrahepatic cholestasis and pregnancy complications may reduce the incidence of perinatal transmission of HBV.



**Key words:** HBsAg-positive; Hepatitis B virus; Perinatal transmission: Nested case-control study

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## INTRODUCTION

China has a high incidence of hepatitis B infection. The positive rate of serum hepatitis B surface antigen (HBsAg) is about 10%-15%, and accumulated hepatitis B virus (HBV) infection rate is 60%-70% in China[1-3]. The reported positive rate of serum HBsAg in Chinese pregnant women varies from 5.9% to 21.3%[4,5]. Perinatal transmission is the most important vertical transmission route of chronic infection by HBV. About one third of HBV infections are through perinatal transmission, and mostly occur in asymptomatic carriers[6]. There are three ways to realize perinatal transmission of HBV: (1) intrauterine transmission; (2) labor transmission; and (3) postnatal transmission. Intrauterine transmission, including infections that are blood-borne and cell, spread mainly *via* the placenta[7]. This may be because of uplink vaginal infections and other infections. Wang proposed that HBV can be integrated into placental tissue leading to the infection[8]. The mechanisms of intrauterine transmission of HBV are not fully understood. Current theories include infection through the placenta, placental leakage, peripheral blood mononuclear cells, and paternal transmission. In general, pregnant women who are HBV-DNA positive are at increased risk of perinatal transmission of HBV[9-11]. Among HBsAg-positive pregnant women, newborn infection rate in the United States is lower than 15%, while it is higher than 40% in China and Japan[12,13]. If there is TORCH infection, this may result in placental cracks, or placental barrier damage, and therefore the risk of neonatal HBV infection is increased. HIV infection will also increase the risk of HBV infection[14-16]. There is no effective prevention of intrauterine transmission. It remains controversial whether injection of three to four doses of hepatitis B immune globulin (HBIG) can prevent vertical transmission[17,18]. Labor transmission occurs mainly through the HBV contaminated maternal blood, amniotic fluid, and vaginal secretions, which are either swallowed by the fetus or get into the fetal blood circulation by placental rupture[19]. As little as $10^{-8}$ HBV per mL of contaminated maternal blood entering a fetal body can result in fetal infection[20,21]. A small proportion of perinatal transmission is attributable to postpartum transmission, through HBV contaminated maternal material such as breast milk and saliva. If mothers are positive for HBsAg, HBeAg, and anti-HBc, HBV-DNA can be detected from almost all mothers' breast milk, but if only HBsAg is positive, HBV-DNA can be detected in only 46% of the subjects[22,23].

Since 1992, HBV vaccination for newborn infants has been implemented in China. The vaccination rate in urban areas has reached 90%, and the HBsAg-positive rate in these areas has been reduced to below 1%[24]. However, joint neonatal HBV vaccine and HBIG still have an immunization failure rate of 20%-30% in infants born to HBsAg-positive mothers[4,25]. Wu *et al* found that neonatal T cell function has not yet been fully developed, and newborns have immune tolerance to HBsAg. It is easier for them to become chronic carriers, and the younger the age infected, the higher probability of becoming chronic carriers[26]. It is important to identify the determinants of perinatal transmission of HBV in this era of immunization. Moreover, previous studies in this field have largely relied on cord blood samples to determine HBV infection status of the newborn. False positives may have occurred in the diagnosis of neonatal HBV infection in these studies where cord blood sample was used because contamination from maternal blood cannot be avoided; therefore, the validity of the study findings is compromised. The objective of this study was to assess the determinants of perinatal HBV transmission in a group of Chinese pregnant women with HBV infection, using vein blood of newborns immediately after birth and before initial hepatitis B vaccination to determine the HBV infection status of the newborn.

## MATERIALS AND METHODS

This study was conducted in Xiangya Hospital and Xiangya Second Hospital of the Central South University, Yiyang Municipal Hospital, and Yiyang Maternal and Infant Hospital in Hunan, China. This study has been approved by REB of the Central South University.

All consenting HBsAg-positive pregnant women in the participating hospitals with a singleton live-born infant during the period of January 1, 2005 to September 31, 2006 were recruited into the study. Mothers with serious mental illness were excluded.

All HBsAg-positive newborns were selected as cases of the study. For each HBsAg-positive newborn, an HBsAg-negative newborn matched for hospital at birth (same) and gender (same) and date of birth (within 1 mo) was selected as the control. A questionnaire designed specifically for this study was used to collect clinical and epidemiological data, using face-to-face interview with the mother during postpartum hospital stay after childbirth.

Elbow blood of pregnant women prior to delivery and vein blood of newborns immediately after birth and before initial hepatitis B vaccination was taken for laboratory investigations. ELISA was used to detect HBsAg; Test Kits were purchased from the Shanghai Kehua Bioengineering Technology Company, Limited. All laboratory processes were strictly followed according to the instructions provided by the company. A HITACHI 7600-automatic biochemical analyzer was used to test liver functions for HBsAg-positive pregnant women.

We first compared the baseline maternal and infant characteristics between cases and controls. Then we estimated the odds ratios (ORs) and 95% confidence intervals (CIs) of maternal-neonatal transmission of HBV. Conditional logistic regression analysis was used to estimate the independent effects of various determinants on maternal-neonatal transmission of HBV, adjusting simultaneously for several potential confounding factors. Independent variables included in the logistic regression model were maternal education, family income, maternal first-degree family history of HBV infection, liver function, systematic treatment of patients with liver function abnormality, hypertension in pregnancy, intrahepatic cholestasis, premature

**Table 1 Comparison of baseline characteristics between cases and controls (Hunan, China, 2005-2006)**

| Research factor | Cases number (%) | Controls number (%) |
|---|---|---|
| Education of mother | | |
| < College | 81 (57.45) | 57 (40.43) |
| > College | 60 (42.55) | 84 (59.57) |
| Income **(yuan/mo)** | | |
| < 1500 | 90 (63.83) | 92 (65.25) |
| > 1500 | 51 (36.17) | 49 (34.75) |
| First-degree family history | | |
| No | 69 (48.94) | 107 (75.89) |
| Yes | 72 (51.06) | 34 (24.11) |
| Liver function | | |
| Normal | 99 (70.21) | 117 (82.98) |
| Abnormal | 42 (29.79) | 24 (17.02) |
| Systematic treatment | | |
| No | 119 (84.40) | 94 (66.67) |
| Yes | 22 (15.60) | 47 (33.33) |
| EHP | | |
| No | 127 (90.07) | 133 (94.33) |
| Yes | 14 (9.93) | 8 (5.67) |
| Intrahepatic cholestasis | | |
| No | 101 (71.63) | 121 (85.82) |
| Yes | 40 (28.37) | 20 (14.18) |
| Premature rupture of membranes | | |
| No | 99 (70.21) | 119 (84.40) |
| Yes | 42 (29.79) | 22 (15.60) |
| Anti-hepatitis B immunoglobulin injection | | |
| No | 100 (70.92) | 68 (48.23) |
| Yes | 41 (29.08) | 73 (51.77) |
| Fetal distress | | |
| No | 68 (48.23) | 91 (64.54) |
| Yes | 73 (51.77) | 50 (35.46) |

EHP: Edema hypertension proteinuria syndrome.

**Table 2 Determinants of perinatal transmission of hepatitis B virus (Hunan, China, 2005-2006)**

| Research factor | OR (95% CI) | |
|---|---|---|
| | Single factors analysis | Adjust |
| Education of mother | | |
| < College | Reference | Reference |
| > College | 0.50 (0.31-0.81) | 1.17 (0.56-2.45) |
| Income **(yuan/mo)** | | |
| < 1500 | Reference | Reference |
| > 1500 | 1.06 (0.65-1.73) | 1.16 (0.72-1.87) |
| First-degree family history | | |
| No | Reference | Reference |
| Yes | 3.28 (1.98-5.46) | 2.84 (1.47-5.48) |
| Liver function | | |
| Normal | Reference | Reference |
| Abnormal | 2.07 (1.17-3.65) | 1.11 (0.48-2.55) |
| Systematic treatment | | |
| No | Reference | Reference |
| Yes | 0.36 (0.21-0.66) | 0.36 (0.17-0.76) |
| EHP | | |
| No | Reference | Reference |
| Yes | 1.83 (0.74-4.52) | 0.88 (0.28-2.75) |
| Intrahepatic cholestasis | | |
| No | Reference | Reference |
| Yes | 2.40 (1.32-4.36) | 2.71 (1.01-7.27) |
| Premature rupture of membranes | | |
| No | Reference | Reference |
| Yes | 2.29 (1.28-4.10) | 2.25 (1.08-4.68) |
| Anti-hepatitis B immunoglobulin | | |
| No | Reference | Reference |
| Yes | 0.38 (0.23-0.62) | 0.27 (0.12-0.59) |
| Fetal distress | | |
| No | Reference | Reference |
| Yes | 1.95 (1.21-3.15) | 1.70 (0.93-3.10) |

OR: Odds ratios; CI: Confidence intervals; EHP: Edema hypertension proteinuria syndrome.

rupture of membranes, maternal administration of HBIG, and fetal distress. Definition of systematic treatment in this study followed the Chinese national guideline for chronic hepatitis B prevention and treatment, which included using drugs to reduce enzyme levels, to protect the liver, and to enhance immune function in mothers with HBV infection and liver function abnormality[27]. All analyses were performed using Statistical Analysis System, Version 9.1 (SAS Institute Inc., Cary, North Carolina, United States).

## RESULTS

A total of 590 HBsAg-positive mothers were recruited into the study, of which 151 HBsAg-positive newborns were defined as cases. Ten cases were excluded because no suitable controls could be identified. A total of 141 HBsAg-positive newborns and 141 individually matched HBsAg-negative newborns were included in the final analysis.

Compared with HBsAg-negative newborns, HBsAg-positive newborns tended to be born to mothers with lower education level, or with abnormal liver function, or with intrahepatic cholestasis, or with premature rupture of membranes, or who less frequently received systematic treatment for abnormalities of liver function, or who were less likely to receive HBIG (Table 1). HBsAg-positive newborns were also more likely to develop fetal distress or to be born from mothers with first-degree family history of HBV (Table 1).

The result of the conditional logistic regression analysis showed that maternal first-degree family history of HBV, intrahepatic cholestasis, and premature rupture of membranes were risk factors for perinatal transmission of HBV, whereas antiviral treatment for maternal HBV and maternal administration of HBIG were protective factors for maternal-neonatal transmission of HBV, after adjustment for potential confounding factors (Table 2).

## DISCUSSION

Our nested case-control study, based on 141 pairs of HBsAg-positive and HBsAg-negative infants born to mothers with HBV infection in China, found that maternal first-degree family history of HBV, intrahepatic cholestasis, and premature rupture of membranes were associated with an increased risk of maternal-neonatal

transmission of HBV, whereas systematic treatment for mothers with HBV and maternal HBIG injection at late gestation were associated with decreased risk, after simultaneous adjustment for several potential confounding factors. The main strength of our study is that we used vein blood obtained from the newborns for laboratory tests of markers of HBV infection. Previous studies have largely relied on cord blood samples to determine HBV infection in the newborn. Because contamination from maternal blood cannot be avoided when cord blood samples are used, false positives can occur in the diagnosis of neonatal HBV infection, which therefore will compromise the validity of the study findings.

Our study showed that maternal first-degree family history of HBV was an independent risk factor of perinatal HBV transmission[28]. This may be caused by gene polymorphisms which result in familial aggregation of HBsAg carriers. In order to reduce perinatal HBV transmission, enhanced surveillance and additional interventions may be needed for newborns born to mothers with a first-degree family history of HBV. Intrahepatic cholestasis was an independent risk factor of perinatal transmission of HBV. This finding makes biological sense. When there is an intrahepatic cholestasis in pregnancy, bile salt deposition can cause pathological changes in placental villi, weakening the protective effect of the immune system or causing abnormal immune response[29], which may lead to increased risk of perinatal transmission of HBV. Premature rupture of membranes was associated with increased risk of perinatal transmission of HBV, which was similar to the findings of the study by Yue *et al*[7]. HBV infection of the fetus may happen through HBV contaminated vaginal secretions by premature rupture of membranes. Our results show that systematic treatment of HBsAg-positive mothers whose liver function was abnormal protected their offspring from HBV infection (*OR* = 0.36), suggesting that active and systematic treatment can improve and stabilize liver function, leading to reduction in perinatal transmission of HBV. Firstly, the risk of perinatal HBV transmission increases as the mother's viral load increases[30]; treatments such as lamivudine can reduce HBV load and thus transmission from mothers to their infants[16,31]. Secondly, improving and stabilizing maternal liver function can also reduce the risk of perinatal HBV transmission[32].

Previous studies have found that HBIG can combine with HBsAg, forming antigen-antibody complexes, and promptly mobilizing the immune system to remove HBV[33]. Our study showed that prenatal injection of HBIG had a strong protective effect on perinatal transmission of HBV (*OR* = 0.38). The Chinese chronic hepatitis B prevention guidelines published in 2005 do not advocate the use of HBIG for pregnant women in advanced stages of pregnancy to prevent mother-to-infant transmission of HBV[27]. This is contrary to what happens in France, where after 6 mo of pregnancy every pregnant woman must be tested for HBsAg, and HBIG injection is mandated for all HBsAg-positive pregnant women[34].

In summary, our study found that maternal first-degree family history of HBV, intrahepatic cholestasis, and premature rupture of membranes were risk factors for perinatal transmission of HBV, whereas systematic treatment for pregnant women with HBV infection and maternal HBIG administration were protective factors. Except for maternal first-degree family history of HBV, other factors are modifiable, suggesting that there are large areas for improvement in terms of reducing maternal-neonatal transmission of HBV.

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## COMMENTS

### Background

Hepatitis B is endemic in China and other parts of Asia. Most people in the region become infected with HBV during childhood and perinatal transmission is the most common route of HBV transmission.

### Research frontiers

Maternal screening programs and universal vaccination in infants with active and passive immunoprophylaxis have reduced perinatal HBV transmission rates dramatically. However, perinatal transmission may still be occurring despite the use of effective active and passive immunoprophylaxis. More studies are needed to assess the potential risk reduction associated with treatment of high maternal-neonatal transmission during pregnancy.

### Innovations and breakthroughs

Previous studies have largely relied on cord blood samples to determine HBV infection in the newborn in which contamination from maternal blood cannot be avoided and false positives can occur. The authors' study used vein blood obtained from the newborns for laboratory tests of markers of HBV infection, and found maternal first-degree family history of HBV infection, intrahepatic cholestasis, and premature rupture of membranes were risk factors for perinatal transmission of HBV, whereas systematic treatment and HBV immunoglobulin injection for mothers with HBV infection were protective factors for maternal-neonatal transmission of HBV.

### Applications

According to the findings, the authors suggest that clinicians consider risk factors and protective factors when a pregnant woman's HBsAg test is positive in order to prevent maternal-neonatal transmission of hepatitis B virus.

### Terminology

The nested case-control study design is used here. In the nested case-control study, cases of a disease that occur in a defined cohort are identified and, for each, a specified number of matched controls is selected from among those in the cohort who have not developed the disease by the time of disease occurrence in the case.

### Peer review

The authors' investigation was to identify the determinants of perinatal transmission of HBV in the era of immunization using venous blood of newborns immediately after birth and before initial hepatitis B vaccination to determine HBV infection status. The study design and methods seem appropriate.

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