Journal of Infection (2013) **66**, 447–452

BIA British Infection Association

www.elsevierhealth.com/journals/jinf

Identification of risk factors associated with immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus

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Accepted 7 December 2012
Available online 31 December 2012

KEYWORDS
Hepatitis B virus infection;
Vertical transmission;
Immunoprophylaxis failure;
Risk factor analysis

Summary *Objective:* To determine the potential risk factors associated with the immunoprophylaxis failure to prevent hepatitis B virus (HBV) vertical transmission.
Methods: A total of 1360 newborn infants from $HBsAg^+$ women were included. Some pregnant women were vaccinated with anti-HBs immunoglobulins (HBIG) monthly for three months beginning at 7 months post pregnancy. All newborns received HBIG injection immediately after birth and were vaccinated with recombinant hepatitis B vaccine. Neonates were followed up for one year and their HBV-related parameters were tested longitudinally.
Results: There were 21 cases (1.54%) with immunoprophylaxis failure ($HBsAg^+$ and/or HBV DNA^+ in 12-month old). Infants with immunoprophylaxis failure were associated with $HBeAg^+$ or HBV DNA^+ in their mother, particularly for those with high titers ($\geq 10^7$ IU/ml) of HBV DNA. The HBV vertical transmission rates in those infants were associated with feeding modes, but not with the HBIG vaccination in their mothers or delivery method of these babies. Serum $HBeAg^+$ (RR, 31.740; 95%CI, 3.884–259.381; $p < 0.001$) and HBV DNA $\geq 10^7$ IU/ml in pregnant women (RR, 22.583; 95%CI, 4.749–107.397; $p < 0.000$) after adjusted other tested factors were independent risk factors of the immunoprophylaxis failure in infants.
Conclusions: Our results suggest that maternal serum $HBeAg^+$ and high HBV load are potential predictors of immunoprophylaxis failure to prevent HBV vertical transmission.

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0163-4453/$36
http://dx.doi.org/10.1016/j.jinf.2012.12.008

Introduction

Infection with hepatitis B virus (HBV) is a serious public health problem worldwide, because HBV infection can progress into chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).[1,2] It has been estimated that 120 million Chinese people are carriers of HBV and have positive detection of serum hepatitis B surface antigen (HBsAg).[3] Approximately, half of those obtain HBV infection through vertical transmission.[4] Although the current immunoprophylaxis of infants with passive vaccination of hepatitis B immunoglobulin (HBIG), and active immunization with HBV vaccine is effective in the prevention of HBV infection,[5] some infants born from HBV^+ mothers still suffer from HBV infection.[6–9] Therefore, the discovery of risk factors for the failure of immunoprophylaxis in these infants is of great significance.

Previous studies have shown that the failure of HBV immunoprophylaxis is significantly associated with maternal HBeAg seropositivity, HBV DNA seropositivity, vaginal delivery, feeding mode, and the nucleotide changes at certain alleles in the genome of maternal HBV.[4,10–12] However, this issue remains controversial.[13–15] These discrepancies may be due to the different cohorts studied or the limited sample size examined.

To determine the potential risk factors associated with the failure of immunoprophylaxis to prevent HBV vertical transmission, 1355 $HBsAg^+$ mothers were recruited in Guangzhou, China, and their 1360 newborn infants were studied for the infection of HBV up to one year of age. We found that maternal HBeAg and high levels of serum HBV DNA were risk factors associated with HBV vertical transmission. Therefore, the levels of HBeAg and HBV DNA need to be evaluated prior to childbirth to identify those children at high risk of immunoprophylaxis failure.

Materials & methods

Subjects

A total of 1360 newborn infants were recruited from 1355 $HBsAg^+$ mothers who received prenatal care and delivered their babies at the Department of Obstetrics and Gynecology, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China between June 2006 and March 2010. Individual pregnant women were included if they met the following criteria: (1) $\geq$20 years old; (2) pregnancy at 20–42 weeks of gestation; and (3) positive for serum HBsAg test. Subjects with severe liver dysfunction or having an HBsAg-positive spouse were excluded. Subjects who received treatment with antiviral agents, immuno-modulatory agents, cytotoxic drugs during gestation, or long term administration of glucocorticoids were also excluded. Written informed consent was obtained from all mothers, and the study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University.

Vaccination

Individual $HBsAg^+$ pregnant women were offered intramuscular injections of 200 IU HBIG (Sichuan Yuanda Shuyang Pharmaceutical, Chengdu, China) monthly for three months beginning at 7 months post pregnancy. All newborns received a passive immunization intramuscularly with 200 IU HBIG within 6 h after birth. Subsequently, these babies were vaccinated intramuscularly with 10 μg recombinant hepatitis B vaccine (HBVac, Beijing Tiantan Biological Products, Beijing, China) at 1 day, 30 days, and 6 months of age, according to the standard immunization protocol.

Virological assays

Venous blood samples were obtained from individual pregnant women at the first time of prenatal care visiting. The concentrations of serum HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc were examined by enzyme-linked immunosorbent assay (ELISA), according to the manufacture's instructions (Intec Productshepatitis B vaccine, Xiamen, China). The levels of serum HBV DNA were determined before the administration of HBIG to the mothers, and the contents of HBV DNA in breast milk were measured after delivery. Moreover, 2 ml of peripheral venous blood samples were collected from individual newborns within 24 h post birth before immunoprophylaxis, and in 7 and 12 months of age for evaluating the levels of serum HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, and HBV DNA. Total DNA was extracted from blood samples, and the contents of HBA DNA in individual samples were assessed by real-time quantitative polymerase chain reaction (qPCR) using a specific kit (Daan Gene, Guangzhou, China). Individual samples with HBV DNA $< 1.0 \times 10^3$ IU/ml were considered as negative, while those with $\geq 1.0 \times 10^3$ IU/ml were positive.

Follow up study

Individual women and children were followed up for one year in the outpatient service of our hospital. These women were interviewed by filling out questionnaires about the feeding mode, the history of immunoprophylaxis, and the complications of individual babies.

Data collections

Detailed obstetrical and perinatal history of individual pregnant women was obtained by reviewing the medical records, including age, gestational age at birth, mode of delivery, birth history, HBIG treatment, feeding mode, pregnant complications, liver function, kidney function, coagulation function, laboratory testing results of HBV markers, and HBV DNA loads in blood and breast milk. Similarly, the gender and birth weight, the laboratory testing results of HBV markers, and contents of serum HBV DNA loads of individual infants were recorded. Individual children at 12 months of age with $HBsAg^+$ and/or HBV DNA^+ were considered as positive vertical transmission of HBV.

Statistical analysis

Quantitative data were analyzed by Student *t*-test, and qualitative data were analyzed by Chi-square test, rank sum test, or Fisher exact test, respectively. The potential risk factors of the immunoprophylaxis failure to prevent HBV vertical transmission from pregnant mothers to