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Cesarean section reduces the risk of early mother-to-child transmission of hepatitis B virus

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ABSTRACT

Aims: To evaluate the effects of cesarean section (CS) on the prevention of mother-to-child transmission (MTCT) of hepatitis B virus (HBV) among hepatitis B surface antigen (HBsAg) positive pregnant women.
Methods: A prospective cohort study was performed on HBsAg-positive pregnant women who delivered from June 2012 to March 2017 at Wuhan Medical Care Center for Women and Children in Wuhan, China. Logistic regression models were used to examine the associations between mode of delivery and the presence of HBV MTCT.
Results: A total of 1384 women paired with 1407 infants were enrolled. Our study showed that the incidence of HBV MTCT was 1.0% (14/1407) in infants born to HBsAg-positive pregnant women. We observed that the infants born by CS had a smaller percentage of HBV infection than those born by vaginal delivery (VD) (0.5% *vs* 1.7%, $P = 0.043$). In the fully adjusted model, CS was significantly associated with a decreased risk of HBV MTCT (OR = 0.26; 95% CI: 0.07–0.95; $P = 0.042$).
Conclusion: Our data confirmed that CS has a protective effect on early MTCT of HBV. CS for HBeAg-positive mothers with high viral load could reduce risk of MTCT and may become a new preventive measure of HBV MTCT through research on its risk-benefit assessment.

1. Introduction

Chronic hepatitis B virus (HBV) infection is a major public health problem [1–3]. With approximately 2 billion HBV-infected individuals worldwide, more than 350 million persons have chronic HBV infection. Most importantly, one million per year die from HBV-related liver disease, such as chronic hepatitis, cirrhosis and hepatocellular carcinoma [4–6]. The published data suggest that most HBV infection occur in the perinatal period or in early childhood, especially in highly endemic areas [7]. According to previous studies, after HBV infection, 90% of infants versus less than 5% of the adult population, will develop into chronic carriers [8]. As a result, mother-to-child transmission (MTCT) of HBV becomes the predominant mode of HBV transmission, which can account for 35–50% of HBV infections [9]. Despite appropriate passive and active immunization, MTCT remains a concern; it has been reported in approximately 5–10% of infants born to hepatitis B surface antigen (HBsAg)-positive mothers, and is even higher in infants with high viral DNA or hepatitis B e antigen (HBeAg)-positive mothers [10].

MTCT of HBV occurs in different stages of pregnancy, including the antepartum, intrapartum and postnatal stages. To date, some interventions have been taken to prevent HBV transmission at the antepartum stage, for instance, injection of hepatitis B immunoglobulin (HBIG) and antiviral therapy in late pregnancy [11–13]. In addition, combined application of hepatitis B vaccine and HBIG in infants can successfully block most MTCT after birth [14]. Cesarean section (CS) is considered a method of preventing HBV transmission in the peripartum stage; however, its action remains controversial. Some reports have elucidated that the HBV infection rate in infants born by CS was significantly lower than that of other infants born by vaginal delivery (VD) [15,16]. However, other studies have demonstrated that CS did not reduce the likelihood of HBV infection in infants [17–19]. Consequently, we performed a prospective cohort study to determine whether CS, compared with VD, prevented the transmission of HBV from infected mothers to their infants.

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2. Materials and methods

2.1. Study populations

From June 2012 to March 2017, we conducted a prospective cohort study at Wuhan Medical Care Center for Women and Children in Wuhan, China. All pregnant women who visited this hospital underwent a routine screening for HBsAg status and for the antibodies to hepatitis C virus (HCV), human immunodeficiency virus (HIV) and Treponema pallidum (TP) before labor. All enrolled participants had to fulfill the following criteria: (i) positivity for HBsAg, (ii) no evidence of HCV infection (anti-HCV negative), (iii) the absence of HIV infection (anti-HIV negative) and TP infection (anti-TP negative), (iv) the exclusion of a husband with HBV infection, and (v) the absence of preexisting chronic diseases such as diabetes mellitus, hypertension, or heart diseases. All HBsAg-positive pregnant women who met the criteria mentioned were invited to participate in this study.

The present study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from all subjects. The methods were carried out in accordance with the principles of the Declaration of Helsinki.

2.2. Data collection and specimen collection

Participants were asked to complete a questionnaire once informed consent had been obtained. The questionnaires were used to collect data on maternal characteristics (age, medical history, HBsAg status, and the use of antiviral drug). Other information was obtained from medical records, including maternal demographics, complications during pregnancy or delivery, neonatal administration of HB vaccine and HBIG at birth, and mode of delivery. Based on mode of delivery, the participators were classified as subjects in the CS group or the VD group.

For all HBsAg-positive women, a venous blood sample was collected in the third trimester. Before the administration of immune prophylaxis, blood samples were drawn from the infants' femoral vein. After blood collection, the newborns received a dose of HBIG intramuscularly (200 IU, within 24 h of birth) and 3 doses of yeast-derived recombinant HB vaccine (10 μg, at 0, 1 and 6 months). Neonates who tested positive for HBsAg at birth were asked to undergo a recheck for HBsAg at 7 months. Blood samples were processed within 24 h of being drawn. Serum samples were stored at −20 °C.

2.3. Laboratory test methods

All serum samples from HBsAg-positive women and their neonates were used to examine viral load. The hepatitis B viral load was quantified by fluorescence quantitative polymerase chain reaction (FQ-PCR) with a linear range between 10^3 and 10^8 copies/ml (equivalent to 10^3–10^8 IU/ml) (Da'an Gene Co. Ltd., Sun Yat-Sen University, Guangdong, China). If HBV DNA levels exceeded 10^3 copies/ml, the sample was considered positive, otherwise, it was considered negative. HBV DNA levels were also log10-transformed for subsequent analyses. For statistical comparisons, we assigned a value of 1000 copies/ml, the lower detection limit of the quantification assay, to samples with HBV DNA levels less than 1000 copies/ml. Similarly, a value of 100,000,000 copies/ml was assigned to samples with HBV DNA levels higher than 100,000,000 copies/ml.

In addition, maternal blood samples were used to test HBeAg status by enzyme-linked immune sorbent assay (Kehua Biotechnology, Shanghai, China). Serum HBsAg levels of infant blood samples were measured by a chemiluminescent microparticle immunoassay (Architect HBsAg; Abbott Laboratories). A concentration higher than 0.05 IU/ml was considered HBsAg positive. All procedures were performed strictly following the manufacturer's instructions.

2.4. Definition of HBV infection

This study used the seropositivity of HBsAg in infant blood as a biomarker of HBV transmission in infants. The newborns were tested for HBsAg at birth. If a neonate tested HBsAg positive, HBsAg testing was repeated 7 months later to confirm chronic infection.

2.5. Statistical analysis

All analyses were performed using SPSS software version 18.0 (SPSS, Chicago, IL, USA). Statistical significance was assessed at the 5% level (two-tail test). Descriptive values were expressed as the mean ± standard deviation (SD) or percentages. Continuous variables were analyzed by Student's t-tests and categorical data were compared by chi-square tests or Fisher's exact test. Subsequently, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate logistic regression.

3. Results

3.1. Study population

The profile of the participant selection is shown in Fig. 1. During the study period, 1476 HBsAg-positive pregnant women who met the inclusion criteria were identified. Due to two reasons, parental unwillingness to let their children undergo painful blood sampling and lost to follow-up, 92 mothers (6.2%) were excluded from the study. However, there was no significant difference in maternal age, HBeAg status, viral load, ALT levels, and delivery mode between the mothers included in this study and the mothers who dropped out of the study (shown in Supplementary Table 1). Of the total 1384 HBsAg-positive pregnant women enrolled, 62.6% (n = 867) delivered by cesarean section and were assigned to the CS group. The remaining 37.4% (n = 517) delivered by vaginal delivery and were assigned to the VD group. There were 888 infants born to 867 paired mothers in the CS group (21 pairs of twins) and 519 infants born to 517 paired mothers in the VD group (2 pairs of twins). MTCT occurred in 1.0% of infants (14 of 1407) in the entire cohort.

The maternal and neonatal characteristics of the two groups are presented in Table 1. Compared with the mothers in the VD group, the mothers in CS group had a significantly higher age, a higher proportion of premature rupture of membranes and placenta praevia. However, there was no difference in the maternal HBeAg status, HBV DNA levels, ALT levels, hyperemesis, threatened premature labor, antiviral therapy, vaccine injection at birth and administration of HBIG in infants between two groups.

3.2. HBV markers in infants at birth and during follow-up

Through comparison of HBV markers in infants at birth between the two groups, we observed that there was no significant difference in the proportion of positive HBV DNA neonates between the CS group *vs* the VD group (0.7% *vs* 1.7%, $P = 0.066$) (Table 2). There were 108 neonates who were positive for HBsAg at birth: 43 of them were delivered by cesarean section, and 65 were delivered by vaginal delivery. By contrast, a higher proportion of infants who were positive for HBsAg at birth was seen in the VD group compared with that in the CS group (12.5% *vs* 4.8%, $P < 0.001$). After follow-up, 0.6% infants (5 of 888) in the CS group and 1.7% infants (9 of 519) in the VD group were identified as having chronic hepatitis B infection.

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