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Risk factors of HBV intrauterine transmission among HBsAg-positive pregnant women

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Abstract

Little is known about the risk factors associated with hepatitis B virus (HBV) intrauterine transmission among HBsAg positive mothers. We conducted a study in Taiyuan, China including 1,133 HBsAg positive mothers and their babies. A total of 101 neonates had HBsAg and/or HBV DNA positive with an intrauterine transmission rate of 8.9%. Maternal menstrual irregularity (OR=4.95, 95%CI: 1.71, 14.33) and severe nausea during the first trimester (OR=1.86, 95%CI: 1.11, 3.09) were associated with an increased risk of intrauterine transmission, while cesarean delivery (OR=0.32, 95%CI: 0.20, 0.51) was associated with a decreased risk after adjusting for potential confounders. Maternal HBeAg positive was a strong independent predictor for intrauterine transmission (OR=2.56, 95%CI: 1.54, 4.27). A positive association between maternal HBV DNA levels and intrauterine transmission was suggested. Maternal HBIG administration during pregnancy, family history of HBV infection, and premature rupture of membranes were not associated with the risk of intrauterine transmission. The study confirmed that maternal HBeAg positive was a risk factor and cesarean delivery was a protective factor for intrauterine transmission. The new findings associated with menstrual irregularity and severe nausea during the first trimester warrant further investigation.

Keywords

China; Epidemiology; HBV; HBV DNA; HBeAg; HBsAg; intrauterine transmission

Introduction

Approximately two billion individuals worldwide have been infected with hepatitis B virus (HBV) and about 350 million live with chronic HBV infection (1). With a hepatitis B surface antigen (HBsAg) positive rate of approximately 10%, China's is one of the highest in Asia (2). Mother-to-child transmissions, including intrauterine, labor, breast-feeding, and daily contact, are major routes of HBV infection and account for approximately half of HBV carriers (3, 4). The rate of intrauterine transmission, which accounts for the majority of mother-to-child transmissions, among HBsAg positive pregnant women ranges from 5% to

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40% in different areas of China (2, 5). Understanding the risk factors of HBV intrauterine transmission will help to effectively control the spread of HBV infection.

Several studies investigating various factors (i.e., mode of delivery, history of abortion, antepartum hemorrhage, maternal HBV DNA load) related to HBV intrauterine transmission reported inconsistent findings (6–8). It has been suggested that maternal administration of hepatitis B immunoglobulin (HBIG) may prevent intrauterine infection (9), though its efficacy is controversial (10, 11).

To better elucidate these poorly understood risk factors, we conducted a study in Taiyuan, China to examine various maternal characteristics and serum markers of HBV infection during pregnancy and the risk of HBV intrauterine transmission.

Materials and methods

Eligible study subjects were HBsAg positive pregnant women who gave birth in the Third People Hospital of Taiyuan City between August 1, 2003 and August 1, 2009. A total of 2,467 pregnant women were eligible for the study and 1,133 agreed to participate. The protocol was reviewed and approved by the Human Investigation Committee at the Shanxi Medical University. Informed written consent was obtained from all participants.

Information was collected by trained interviewers using a standardized, structured questionnaire through face-to-face interviews. Maternal information included demographics and characteristics before and during pregnancy. Mode of delivery, maternal complications, and newborns' information were obtained from medical records. All participants donated peripheral blood before delivery and 5ml of femoral venous blood was collected from each infant less than 24 hours after birth and prior to inoculations of hepatitis B vaccine and HBIG. Blood samples were processed within 24 hours of being drawn. Serum samples were stored at −20°C.

HBsAg and hepatitis B e antigen (HBeAg), were measured using ELISA (Kehua Biotechnology, Shanghai, China). HBV DNA levels were tested by FQ-PCR (Da'an Gene Co., Ltd., Sun Yat-Sen University, Guangdong, China). All procedures were performed according to the manufacturers' instructions. If the levels of HBV DNA were $\leq 10^3$ copies/mL according to the fluorescent signals set by the operation manual the sample was considered negative, otherwise it was positive. Intrauterine transmission was defined as finding HBsAg and/or HBV DNA positive in the peripheral blood of newborns within 24 hours of birth and before active or passive immune prophylaxis (11).

Newborns with intrauterine transmission of HBV were considered cases, those without were considered controls. In univariate analyses, Chi-squire tests were used for categorical data and student t-tests were used for continuous variables. Odds ratios (OR) and 95% confidence interval (CI) were estimated using unconditional logistical regression to measure the association between maternal characteristics and intrauterine transmission. All analyses were performed using SAS software Version 9.3 (SAS Institute).

Results

The study detected 101 newborns with serum HBsAg or HBV DNA positive (8.9%). The mean levels of HBV DNA were higher among mothers than infected infants (Figure 1). As shown in Table 1, distributions of maternal and newborn characteristics were similar across cases and controls.

In univariate analyses (Table 2), menstrual regularity (P=0.0004), maternal HBeAg positive (P<0.0001), maternal HBV DNA positive (P=0.0004), pregnancy reaction (severe nausea/vomiting during the first trimester) (P=0.02), and cesarean section (P<0.0001) were significantly associated with HBV intrauterine transmission.

After adjusting for important covariates (Table 3), women who had irregular menstruation experienced increased risk of HBV intrauterine transmission (OR=4.95, 95%CI: 1.71–14.33). Pregnancy reaction was associated with 86% increased risk (95%CI: 1.11–3.09). Cesarean delivery was associated with a reduced risk compared to vaginal delivery (OR=0.32, 95%CI: 0.20–0.51). HBeAg positive women had more than twice the risk of intrauterine transmission compared to HBeAg negative women (OR=2.56, 95%CI: 1.54–4.27). Being HBV DNA positive was not significantly associated with intrauterine transmission (OR=1.44, 95%CI: 0.86–2.41), although risk of transmission increased with increasing levels of maternal HBV DNA (P for trend=0.032).

Discussion

We observed an increased risk of intrauterine transmission associated with HBeAg positive women and those with high HBV DNA levels, which was consistent with the majority of early studies (8, 12–14). Both HBeAg and HBV DNA positive indicate active viral replication. Dwivedi et al. (14) found that combination of HBeAg and HBV DNA was a more sensitive marker of intrauterine transmission than HBeAg alone; we observed no such association.

Maternal HBIG administration during pregnancy may neutralize HBV in the maternal body and subsequently reduce HBV viremia and risk of intrauterine transmission (9). A recent meta-analysis found that maternal HBIG injection significantly reduced the risk of intrauterine transmission (15), however heterogeneity between included studies makes the validity questionable. We found no association between maternal administration of HBIG and HBV intrauterine transmission. Recent Chinese chronic hepatitis B prevention guidelines did not advocate HBIG use for women in advanced stages of pregnancy to prevent intrauterine transmission (16). The World Health Organization, World Gastroenterology Organization, and the U.S. Centers for Disease Control and Prevention do not endorse any schedule of HBIG injections in pregnant HBV carriers (17–19).

Cesarean delivery has the least placental contraction and has been speculated to have the least maternal-fetal transfusion (20). It also limits direct contact of the fetus with infected secretions or blood in the maternal genital tract. The finding that cesarean delivery was protective for HBV intrauterine transmission from the current study was consistent with most earlier studies (14, 21–23) but not all (8).

The study found that menstrual irregularity and severe nausea/vomiting during the first trimester were associated with an increased risk of HBV intrauterine transmission, which had not been previously reported. Although the underlining mechanisms are unclear, diseased liver caused by HBV infection may lead to impaired metabolism, inactivation of estrogens, and accumulation of estrogens in the body (24). Abnormal estrogen levels could cause menstrual irregularity and severe nausea/vomiting during the first trimester. Although many women at this age are less likely to have severe liver disease, we found that women who were HBsAg positive before pregnancy were slightly more likely to experience menstrual irregularity and/or severe nausea during the first trimester compared with women who were HBsAg negative before pregnancy (result not shown). Future studies should examine of the effect of comorbid liver diseases in order to understand these associations.

A major strength of the study was that vein blood samples from newborns were used for serological markers of HBV infection; many previous studies used cord blood increasing the chance of false positive diagnosis of neonatal HBV infection. However, obtaining vein blood samples from newborns was difficult and invasive, resulting in lower participation (45.9%).

In conclusion, we confirmed that HBeAg positive and vaginal delivery were independent risk factors for intrauterine transmission. New findings of menstrual irregularity and severe nausea during the first trimester warrants further investigation.

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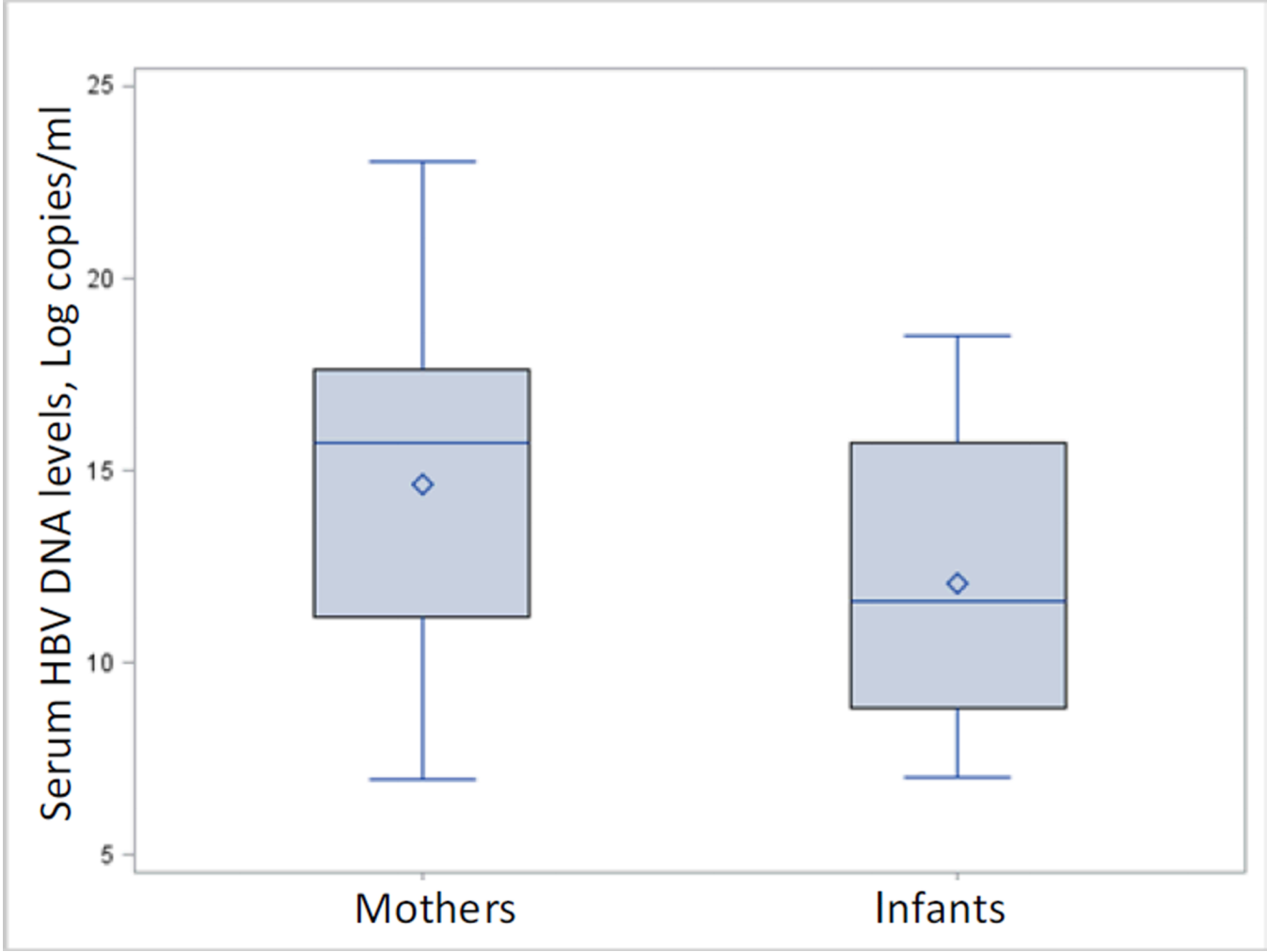

Figure 1.
HBV DNA levels of mothers and infected infants. Mean levels of mothers and infected infants were 1.9×10^8 and 1.0×10^7 copies/ml, respectively.

Table 1

Distributions of selected maternal and newborn characteristics among cases and controls

Characteristics	Cases (N=101) Number (%)	Controls (N=1032) Number (%)	P
Maternal Characteristics			
Age (years)			
Mean (SD)	27.27(5.05)	26.53(4.54)	0.16
Highest educational levels			
<High school	53(52.5)	564(54.7)	
≥High School	48(47.5)	468(45.3)	0.68
Newborn Characteristics			
Birth weight (g)			
<2500	1(1.0)	22(2.1)	
2500–3999	92(91.1)	908(88.0)	
≥4000	8(7.9)	102(9.9)	0.59
Gestational weeks			
<37	1(1.0)	43(4.2)	
37–41	98(97.0)	953(92.3)	
>41	2(2.0)	36(3.5)	0.20
Gender			
Girl	48(47.5)	470(45.5)	
Boy	53(52.5)	562(54.5)	0.70
Apgar1 score			
0–3	3(3.0)	18(1.7)	
4–7	31(30.7)	283(27.4)	
8–10	67(66.3)	731(70.8)	0.51

Table 2

Univeriate analyses of associations between maternal characteristics and intrauterine HBV infection

Characteristics	Cases		Controls		
	No Number (%)	Yes Number (%)	No Number (%)	Yes Number (%)	P-value
Pregregnancy					
HBV vaccine injection	93(93.0)	7(7.0)	924(91.1)	90(8.9)	0.53
Menstrual regularity	6(6.0)	94(94.0)	13(1.3)	1016(98.7)	0.0004
History of abortion	53(53.0)	47(47.0)	548(53.6)	474(46.4)	0.91
Family history of HBV infection	82(81.2)	19(18.8)	790(76.6)	242(23.4)	0.29
Pregnancy					
Maternal HBeAg positive	36(38.7)	57(61.3)	597(62.8)	353(37.2)	<0.0001
Maternal HBV DNA positive	32(33.3)	64(66.7)	496(52.2)	454(47.8)	0.0004
HBIG injection	27(27.3)	72(72.7)	317(31.0)	707(69.0)	0.45
HBV vaccine injection	97(99.0)	1(1.0)	1008(99.2)	8(0.8)	0.56
Medication use during pregnancy	96(96.0)	4(4.0)	994(96.7)	34(3.3)	0.71
Pregnancy reaction	76(75.2)	25(24.8)	867(84.3)	162(15.7)	0.02
Pregnancy-induced hypertension	95(94.1)	6(5.9)	981(95.7)	44(4.3)	0.44
Antepartum hemorrhage	100(99.0)	1(1.0)	1008(97.7)	24(2.3)	0.38
Delivery					
Cesarean section	72(71.3)	29(28.7)	477(46.2)	555(53.8)	<0.0001
Premature rupture of membranes	64(63.4)	37(36.6)	691(69.7)	301(30.3)	0.19
Amniotic fluid pollution	84(83.2)	17(16.8)	790(77.9)	224(22.1)	0.22
Abnormality of umbilical cord	66(65.3)	35(34.7)	701(67.9)	331(32.1)	0.60
Praevia placenta	101(100.0)	0(0.0)	1025(99.3)	7(0.7)	1.00

Table 3

Multivariate analysis of associations between maternal characteristics and intrauterine HBV infection

Characteristics	Cases	Controls	OR*(95%CI)
Pregregnancy menstrual regularity			
Yes	94	1016	1.00
No	6	13	4.95(1.71–14.33)
HBeAg positive			
No	36	597	1.00
Yes	57	353	2.56(1.54–4.27)
HBV DNA load			
Negative	32	496	1.00
Positive	64	454	1.44(0.86–2.41)
$\leq 10^6$ copies/ml	15	162	1.31(0.67–2.53)
$>10^6$–$\leq 10^8$ copies/ml	41	255	1.48(0.82–2.67)
$>10^8$ copies/ml	8	37	1.82(0.72–4.62)
P for trend			0.032
Pregnancy reaction			
No	76	867	1.00
Yes	25	162	1.86(1.11–3.09)
Cesarean section			
No	72	477	1.00
Yes	29	555	0.32(0.20–0.51)

*Adjusted for the variables listed in the table.