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MAJOR ARTICLE

Maternal Hepatitis B Infection and Pregnancy Outcomes in the United States: A Population-Based Cohort Study

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Background. Hepatitis B virus (HBV) infection in pregnancy has been associated with risk of adverse maternal and infant outcomes in highly endemic settings, but this association is not well characterized in the United States.

Methods. We conducted a retrospective population-based cohort study in Washington State using linked birth certificate and hospital discharge records from 1992–2014. Among pregnant women with hepatitis B (n = 4391) and a hepatitis B–negative group (n = 22 410), we compared the risk of gestational diabetes, pre-eclampsia, eclampsia, placenta previa, preterm delivery, low birthweight, small for gestational age, and large for gestational age using multivariate logistic regression.

Results. Hepatitis B–infected pregnant women were more likely to be Asian (61% vs 8%, $P < .001$), foreign-born (76% vs 23%, $P < .001$), and older in age (77% vs 64% ≥26 years, $P < .001$). They were less commonly overweight or obese (33% vs 50%, $P < .001$). There was a lower risk of small for gestational age infants among HBV-infected women (adjusted RR [aRR], 0.79; 95% confidence interval [CI], 0.67–0.93). The risk of other adverse outcomes was not significantly different between hepatitis B–infected and –negative women (gestational diabetes: aRR, 1.11; 95% CI, 0.92–1.34; pre-eclampsia: aRR, 1.06; 95% CI, 0.82–1.35; eclampsia: aRR, 2.31; 95% CI, 0.90–5.91; placenta previa: aRR, 1.16; 95% CI, 0.35–3.84; preterm delivery: aRR, 1.15; 95% CI, 0.98–1.34; low birth weight: aRR, 1.08; 95% CI, 0.90–1.29; large for gestational age: aRR, 1.01; 95% CI, 0.82–1.24).

Conclusions. In a low-burden setting in the United States, hepatitis B infection was not associated with adverse pregnancy outcomes.

Keywords. eclampsia; gestational diabetes; hepatitis B infection; preterm delivery; small for gestational age.

Hepatitis B virus (HBV) is a leading cause of death globally, with chronic infection commonly causing cirrhosis and hepatocellular carcinoma [1]. Though the United States is considered a low-burden country, with routine childhood vaccination recommended since 1991 [2], a substantial number of people are HBV-infected, with estimates around 847 000 [3]. Mother-to-child transmission (MTCT) of HBV is an important mode of viral propagation. To prevent transmission, HBV screening is part of routine prenatal care in the United States, and infants born to hepatitis B surface antigen (HBsAg)–positive mothers are given HBV immune globulin and vaccination [4].

In addition to known risk of MTCT, emerging research suggests that maternal hepatitis B carrier status may contribute to other important adverse pregnancy outcomes, such as increased risk of gestational diabetes mellitus (GDM) [5–8], miscarriage [9], preterm delivery (PTD) [7, 10–12], and antepartum or postpartum hemorrhage [5, 8], but results are inconsistent across studies [13–15]. The biological basis for poor pregnancy outcomes in HBV-infected women is not fully understood, though HBV infection is recognized as a chronic inflammatory state that can precipitate acute hepatitis flares and further complications [16–18]. Limitations of published studies that could explain conflicting results include small sample sizes, heterogeneous patient populations, differences in study designs, and incomplete adjustment for important confounders.

Few data from large population samples have been published in the United States and other low-burden, developed country settings. The epidemiology of HBV infection differs between the United States and highly endemic regions like East Asia. In Asia, mother-to-child and bloodborne HBV transmission predominate [19]. In contrast, in the United States, transmission occurs most commonly through sexual exposure or intravenous drug use in young adults [20]. Due to variance in chronicity of infection related to mode of transmission, comorbid conditions, and clinical care models, we hypothesize that pregnancy-related outcomes may differ between these settings [20]. The primary purpose of our study was to determine whether there is an association between maternal HBV infection and risk of adverse

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pregnancy outcomes, including GDM, pre-eclampsia, eclampsia, placenta previa, PTD, low birth weight (LBW), small for gestational age (SGA), and large for gestational age (LGA) in the United States, using a large birth cohort from Washington State.

METHODS

Study Population

We conducted a population-based retrospective cohort study using Washington State singleton birth certificates from 1992–2014 linked to the Washington Comprehensive Hospital Abstract Reporting System (CHARS), which contains maternal and infant hospital discharge data. For women who had multiple births during this period, only 1 randomly selected birth was included in the analysis.

The exposed group consisted of mothers with HBV infection ascertained from birth certificates (denoted as "hepatitis B" or "hepatitis B surface antigen positive") or relevant ICD-9 codes in CHARS (070.20–23, 070.30–33, or V02.61). The unexposed cohort was selected from the full 1992–2014 birth cohort and consisted of women without HBV by birth certificate or ICD-9 codes, frequency matched by birth year in a 5:1 ratio to HBV-infected women.

Maternal-Neonatal Outcomes and Covariates

We ascertained maternal and neonatal outcomes from birth certificates including maternal GDM, pre-eclampsia, eclampsia, placenta previa, PTD (live birth before 37 weeks' gestation determined by prenatal obstetric estimate), delivery of an LBW neonate (weighing less than 2500 grams), SGA, and LGA. Neonates were classified as SGA if they were in the lowest 10% or LGA if they were in the highest 10% of Washington State birth weight range for a given gestational age for their gender, using previously described methods [21]. We compared LBW infants with a reference category of normal birth weight infants (2500–4500 grams), SGA and LGA newborns with normal for gestational age newborns (10%–90% of the Washington State birth weight range), and PTD infants with those born after 37 weeks in our analysis. Women with preexisting diabetes were excluded from the analysis of maternal GDM.

Maternal demographics and other medical and obstetric history data were obtained from birth certificates, including data on maternal age (stratified as ≤25, 26–35, >35 years), parity (nulliparous or multiparous), level of education (<12 or ≥12 years of education), maternal race (white, black, Hispanic, Asian, Pacific Islander, or other), maternal country of birth (US or foreign born), marital status (married or not married), any tobacco use during pregnancy (no/yes), any alcohol use during pregnancy, trimester of first prenatal visit, number of prenatal visits (stratified as <6, 6–14, >14 visits), and maternal sexually transmitted infections (syphilis, gonorrhea, chlamydia, hepatitis C, and herpes simplex virus). We determined prepregnancy body mass index (BMI) combining maternal height and weight from birth certificates, available from 2003–2014. Mothers were classified as underweight (BMI < 18.5 kg/m^2), normal weight (BMI, 18.5–24.9 kg/m^2), overweight (BMI, 25.0–29.9 kg/m^2), or obese (BMI > 30.0 kg/m^2). Excess weight gain during pregnancy was defined as gaining ≥40 pounds for underweight women, ≥35 pounds for normal weight women, and ≥25 pounds for obese women [22].

Statistical Analysis

We used the chi-square test to compare baseline demographic and clinical characteristics between mothers with and without HBV. For each maternal and neonatal outcome, we calculated a crude odds ratio, adjusted odds ratio, and 95% confidence intervals (CIs) associated with maternal HBV using multivariate logistic regression. As these outcomes were rare, the odds ratios estimated crude (RR) and adjusted relative risks (aRR). Potential confounders for adjusted models were selected based on review of the literature [6, 7, 10, 23]. We considered maternal age, race, country of origin, marital status, education level, parity, gravidity prepregnancy BMI, and tobacco use as potential confounders for all outcomes. Additionally, we considered confounding by hypertension for pre-eclampsia and eclampsia outcomes and sexually transmitted diseases for PTD, LBW, SGA, and LGA outcomes. We included potential confounders in final models if they altered the effect estimate by 10% or more. Subgroup analysis included examination of the association between HBV and GDM among women with excess weight gain. We also considered country of origin as a proxy for chronicity of HBV infection and examined the potential for country of origin to modify the association between HBV status and GDM using an interaction term. Analysis was performed using STATA, version 14 (StataCorp, College Station, TX). This study was exempt from review by the Washington State Department of Health Institutional Review Board as we did not have access to personal identifiable information.

RESULTS

Compared with women without HBV, women with HBV were more likely to be Asian (61% vs 8%, $P < .001$), foreign born (76% vs 23%, $P < .001$), and older in age (77% vs 64% ≥26 years, $P < .001$). They were less likely to be overweight or obese (33% vs 50%, $P < .001$). Women born in Vietnam and China comprised half of all Asian mothers with HBV. Other baseline demographic and clinical characteristics were generally similar between exposure groups (Table 1). Baseline hypertension, alcohol use in pregnancy, and hepatitis C infection were uncommon (≤2% each).

HBV-infected women had a similar risk of GDM (GDM prevalence, 9%) compared with HBV-negative women (GDM prevalence, 5%) after adjustment for mother's age, race, country of origin, and prepregnancy BMI (adjusted relative risk [aRR], 1.11; 95% confidence interval [CI], 0.92–1.34) (Table 2). In the

Table 1. Demographic and Clinical Characteristics of Women With and Without Hepatitis B, Washington State 1992–2014

	Hepatitis B Positive (n = 4391)[a]		Hepatitis B Negative (n = 22 410)[a]		
	No.	%	No.	%	*P* Value
Age, y					<.001
≤25	1038	24	8262	37	
26–35	2572	59	11 776	53	
>35	781	18	2372	11	
Race					<.001
White	995	23	15 990	73	
Black	419	10	1013	5	
Hispanic	151	4	2423	11	
Asian	2634	61	1805	8	
Asian Indian	69	3[b]	276	15[b]	
Chinese	598	23	230	13	
Filipino	271	10	291	16	
Japanese	25	1	103	6	
Korean	223	8	151	8	
Vietnamese	711	27	266	15	
Other Asian	737	28	488	27	
Pacific Islanders	59	1	140	1	
Other	43	1	518	2	
Country of origin					<.001
United States	1054	24	16 930	77	
Foreign born	3288	76	5188	23	
Education, y					.89
≤12	2249	55	11 927	56	
>12	1806	45	9529	44	
Marital status					<.001
Married	3187	73	15 326	69	
Unmarried	1191	27	7047	31	
Parity					<.001
0	1935	45	9249	42	
≥1	2388	55	12 790	58	
Prepregnancy BMI,[c] kg/m^2					<.001
<18.5	174	7	359	3	
18.5–24.9	1449	60	5834	46	
25.0–29.9	482	20	3291	26	
≥30	312	13	3069	24	
Hypertension					.49
Yes	47	1	270	1	
No	4330	99	22 103	99	
Any alcohol use[d]					.43
Yes	20	1	84	1	
No	1560	99	7886	99	
Any tobacco use					<.001
Yes	339	8	2465	11	
No	3970	92	19 571	89	
Hepatitis C[c]					<.001
Yes	44	2	29	<1	
No	2684	98	13 816	>99	

Abbreviation: BMI, body mass index.

[a]Numbers may not equal total due to missing data.

[b]Percentages for Asian subcategories calculated with the total Asian population as the denominator.

[c]Data available from 2003–2014.

[d]Data available from 1992–2002.

Table 2. Risk of Maternal and Infant Outcomes in Hepatitis B–Positive Mothers Relative to Hepatitis B–Negative Mothers

	HBV Positive (n = 4391)[a]		HBV Negative (n = 22 410)[a]		Crude RR (95% CI)	Adjusted RR (95% CI)
	No.	%	No.	%		
Maternal outcomes						
GDM[b]	389	9	1109	5	1.88 (1.66–2.12)	1.11 (0.92–1.34)
Pre-eclampsia[b]	1299	5	177	4	0.73 (0.62–0.85)	1.06 (0.82–1.35)
Eclampsia[c]	9	0.5	25	0.3	1.86 (0.87–3.99)	2.31 (0.90–5.91)
Placenta previa[d]	7	0.4	17	0.2	2.12 (0.88–5.12)	1.16 (0.35–3.84)
Neonatal outcomes						
PTD[c] (<37 wk)	320	7	1457	7	1.13 (1.00–1.28)	1.15 (0.98–1.34)
LBW[c] (<2500 g)	236	5	1040	5	1.16 (1.00–1.34)	1.08 (0.90–1.29)
SGA[e, f]	533	13	2115	10	1.28 (1.16–1.42)	0.79 (0.67–0.93)
LGA[b, f]	271	7	2025	10	0.68 (0.60–0.78)	1.01 (0.82–1.24)

Abbreviations: CI, confidence interval; GDM, gestational diabetes; HBV, hepatitis B virus; LBW, low birth weight; LGA, large for gestational age; PTD, preterm delivery; RR, relative risk; SGA, small for gestational age.

[a]Total numbers of exposed and unexposed pregnant women vary by outcome due to different patterns of missing data.

[b]Adjusted for maternal age, race, country of birth, and body mass index (BMI).

[c]Adjusted for maternal age, race, and country of birth.

[d]Adjusted for maternal age, race, country of birth, and tobacco consumption.

[e]Adjusted for maternal age, race, country of birth, BMI, and hepatitis C.

[f]SGA is defined as the lowest 10% and LGA the highest 10% of the Washington State birth weight range for a given gestational age and infant gender.

subgroup of women with excess weight gain during pregnancy, HBV was not significantly associated with GDM (aRR, 1.12; 95% CI, 0.80–1.57), and there was no interaction between HBV and country of origin with respect to GDM.

Women with HBV had a lower risk of delivering SGA infants (13% among HBV-positive vs 10% among HBV-negative; aRR, 0.79; 95% CI, 0.67–0.93). No statistically significant differences were observed in pre-eclampsia (5% among HBV-positive vs 4% among HBV-negative; aRR, 1.06; 95% CI, 0.82–1.35), eclampsia (0.5% among HBV-positive vs 0.3% among HBV-negative; aRR, 2.31; 95% CI, 0.90–5.91), placenta previa (0.4% among HBV-positive vs 0.2% among HBV-negative; aRR, 1.16; 95% CI, 0.35–3.84), PTD (7% among HBV-positive vs 7% among HBV-negative: aRR, 1.15; 95% CI, 0.98–1.34), LBW (5% among HBV-positive vs 5% among HBV-negative; aRR, 1.08; 95% CI, 0.90–1.29), and LGA (7% among HBV-positive vs 10% among HBV-negative; aRR, 1.01; 95% CI, 0.82–1.24) between HBV-infected and -uninfected women.

DISCUSSION

Routine prenatal screening for hepatitis B infection has been recommended by the US Centers for Disease Control and Prevention (CDC) since 1988 and is important for the prevention of MTCT through targeted HBV immunoglobulin and vaccination postdelivery [24]. Our retrospective cohort study, the largest to date conducted in a low-HBV-endemic setting, provides important insights into maternal HBV and risk of adverse maternal and newborn outcomes. We found that infants born to HBV-infected pregnant women did not experience a higher risk of adverse outcomes.

Though the issue remains controversial, several studies in high-burden settings in Asia have suggested an association between maternal HBV infection and other non-transmission-related adverse pregnancy outcomes [5, 6, 8]. Findings across the literature remain inconsistent, with small sample sizes limiting statistical power. A recent large cohort study in China by Liu et al. found maternal HBV carrier status (positive HBsAg) to be modestly associated with increased risk of preterm delivery (odds ratio [OR], 1.18; 95% CI, 1.04–1.34) [11]. However, though statistical significance was achieved in the setting of large sample sizes, the overall effect size was small. As pregnant HBV-infected women may differ with respect to chronicity of infection, degree of liver damage, comorbid conditions, and access to health care, findings from a highly endemic setting may not be relevant for women in the United States where chronic HBV infection is less common [19].

Our large cohort study conducted in a low endemic US setting does not demonstrate statistically significant associations between HBV and adverse pregnancy outcomes. The magnitude of the risk estimate for PTD was, however, similar to findings presented by Liu et al. [11]. Moreover, we found that HBV was associated with a 21% reduction in the risk of SGA. Though the clinical significance of this finding is uncertain, a smaller retrospective cohort study of 1458 HBV-infected women in Florida also found that women with hepatitis B infection were less likely to have SGA infants, with a similar magnitude of association (OR, 0.79; 95% CI, 0.66–0.95) [14]. Another US-based retrospective cohort study encompassing 37 states and 814 HBV-infected women did not find an association between maternal HBV and GDM, intrauterine growth

restriction, or pre-eclampsia, though the risk of PTD was significantly higher in HBV-infected women (adjusted OR, 1.65; 95% CI, 1.34–2.02) [10]. A direct comparison of adverse pregnancy outcomes is limited by notable differences in these study populations as compared with ours. For one, fewer HBV-infected women were Asian (14% [10] and 16% [14] vs 61% in our cohort). Furthermore, substance use, which was not routinely ascertained in our study, was more common in infected women than controls in both studies. Finally, the association between HBV infection and pre-eclampsia remains unclear, with some studies hypothesizing that impaired maternal immune response leads to immunotolerance of the fetus and reduced incidence of pre-eclampsia [25]. We did not identify such an association in our cohort. Given the lack of consensus regarding HBV-associated maternal and neonatal outcomes and geographic heterogeneity of demographic patterns throughout the United States, our study contributes important information about HBV-related pregnancy outcomes among infected women of Asian descent.

Our study has several limitations. Most importantly, we were not able to confirm maternal HBV status by serologic testing. In the United States, routine screening of all women for HBsAg during each pregnancy is recommended to prevent neonatal transmission. Specifically, HBV envelope antigen positivity and high HBV DNA levels are important risk factors for vertical transmission [26–28]. Furthermore, liver dysfunction has been independently associated with adverse neonatal outcomes [18]. We were not able to ascertain HBV envelope antigen status, quantify HBV viremia, assess the administration of preventive antiviral therapy, or measure abnormalities in liver function tests, factors that influence the likelihood of viral transmission as well as pregnancy and neonatal outcomes.

Additional limitations include lack of complete information on adequate prenatal care in our data sources. Notably, prenatal care data were missing more frequently among foreign-born and Asian populations, for whom the prevalence of chronic HBV is expected to be the highest. Thus, HBV exposure is likely underascertained in our cohort. Precision of risk estimates for eclampsia and placenta previa was limited as data for these outcomes were only available from 1992–2002. Finally, missing data limited complete evaluation of additional potential confounders, including BMI, HIV status, alcohol consumption, socioeconomic status, and hepatitis C.

CONCLUSIONS

In our Washington State study population, HBV was not associated with clinically significant adverse pregnancy outcomes. Women with HBV were more likely to be Asian, foreign born, and older in age. Given the overall heterogeneity of findings in the literature, it remains important to identify and counsel women with HBV during routine prenatal screening.

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