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MATERNAL-FETAL MEDICINE

Maternal hepatitis B infection status and adverse pregnancy outcomes: a retrospective cohort analysis

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Abstract

Purpose To investigate the association between maternal HBsAg-positive status and pregnancy outcomes.

Methods The study enrolled women with singleton pregnancies who delivered during January–December 2018. Data of maternal demographics and main adverse pregnancy outcomes were collected from the institutional medical records and analyzed by univariate and multivariate logistic regression models to determine the association between maternal HBV markers (HBsAg/HBeAg/HBV-DNA loads status) and adverse pregnancy outcomes.

Results Total 1146 HBsAg-positive and 18,354 HBsAg-negative pregnant women were included. After adjusting for potential confounding variables, maternal HBsAg-positive status was associated with a high risk of gestational diabetes mellitus (GDM) [adjusted odds ratio (aOR) = 1.24; 95% confidence interval (CI) 1.07–1.43], intrahepatic cholestasis of pregnancy (ICP) (aOR = 3.83; 95% CI 3.14–4.68), preterm birth (aOR = 1.42; 95% CI 1.17–1.72), and neonatal asphyxia (aOR = 2.20; 95% CI 1.34–3.63). Further, higher risks of ICP and neonatal asphyxia remained with either HBeAg-positive status (aOR = 1.64; 95% CI 1.10–2.44; aOR = 3.08; 95% CI 1.17–8.00) or high HBV-DNA load during the second trimester (aOR = 1.52; 95% CI 1.06–2.35; aOR = 4.20; 95% CI 4.20–15.83) among HBsAg-positive pregnant women.

Conclusion Women with maternal HBsAg-positive status may have increased risks of GDM, ICP, preterm birth, and neonatal asphyxia; furthermore, the risks of ICP and neonatal asphyxia were higher in women with HBeAg-positive status and a high HBV-DNA load during the second trimester among the HBsAg-positive pregnant women, implying that careful surveillance for chronic HBV infection during pregnancy is warranted.

Keywords Hepatitis B virus infection · Pregnancy outcomes · Intrahepatic cholestasis of pregnancy · Neonatal asphyxia

Background

Hepatitis B virus (HBV) infection remains a major public health concern, with approximately 257 million people being chronically infected with this virus globally [1]. However, the global prevalence of HBV infection differs greatly, with it being concentrated in Asia and Africa [2]. In China, chronic HBV infection is highly endemic, with > 130 million patients diagnosed with chronic HBV infection [3, 4]. In addition, the prevalence rate of hepatitis B surface antigen (HBsAg) during pregnancy is 7.2% [5]. Hence, most pregnant women with HBV infection in China were identified as chronic HBV carriers, which needs pertinent clinical attention.

Pregnant women with chronic HBV infection or maternal HBsAg carriers experience a state of chronic inflammation, which may relate to adverse pregnancy outcomes, including miscarriage, preterm birth, antepartum hemorrhage, gestational diabetes mellitus (GDM), low infant birthweight, macrosomia, preeclampsia, hypertensive disorders of pregnancy (HDP), and intrahepatic cholestasis of pregnancy (ICP) [6–9]. Moreover, HBV carrier status was noted as an independent risk factor for long-term morbidity of the offspring, which could be infectious [10], endocrine [11], respiratory [12], or gastrointestinal [13] morbidities. However, current studies on maternal HBV infection mainly focused on mother-to-child vertical transmission [14, 15]. Although a few recent studies supported that maternal chronic HBV infection affected pregnancy outcomes, there is a lack of

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consensus in these findings. For instance, several studies found that the maternal HBsAg carrier status was highly associated with a risk of caesarean section [16], HDP [17], preterm birth [18, 19], GDM [20, 21], ICP [22] and macrosomia [16], whereas other studies demonstrated no significant association or even contrary results [9, 23, 24]. In addition to the limited and inconsistent results, most of these published studies had only evaluated the effects of maternal HBsAg carrier status on pregnancy outcomes and did not examine the association of maternal HBeAg with the HBV DNA status, which represents HBV replication among HBsAg carriers.

Therefore, we performed a retrospective cohort study to comprehensively explore the influence of maternal HBsAg/HBeAg/HBV-DNA status on adverse pregnancy outcomes.

Methods

Study population and data collection

The retrospective cohort study was conducted at The Women's Hospital, School of Medicine of Zhejiang University, Hangzhou, China, which is the tertiary teaching hospital of obstetrics and gynecology in the Zhejiang Province. All clinical staff received the diagnostic criteria for various diseases in the obstetric department to ensure an adequate understanding of the medical data reporting format. All pregnant women attending their first antenatal clinical visit at our hospital were provided with a health record card having a unique medical record number. Physical examination, laboratory tests, and prescriptions of the pregnant women were recorded at all visits corresponding to their record card numbers. The WHO classification for the body mass index (BMI) was followed: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) or obesity (≥ 30 kg/m^2). Simultaneously, the women were closely monitored during regular follow-up visits until delivery and were routinely screened for HBsAg and the anti-hepatitis C virus (HCV) and anti-human immunodeficiency virus (HIV) antibodies by chemiluminescence (Sysmex, Tokyo, Japan), and those with HBsAg-positive status were also screened for HBeAg. Furthermore, blood samples of each HBsAg-positive pregnant woman in the second trimester were collected for quantifying the HBV-DNA load. The HBV-DNA load was quantified by the fluorescence quantitative polymerase chain reaction (FQ-PCR) assay (Daan, Guangzhou, China). HBV-DNA loads $> 10^3$ copies/mL were defined as high HBV-DNA loads when analyzing the associations between the maternal HBV-DNA status and pregnancy outcomes.

The women who delivered during January 1–December 31, 2018, were enrolled. Inclusion criteria comprised: (1) singleton pregnancy; (2) no evidence of Hepatitis A, C, or E virus, HIV, and *Treponema pallidum* infections; (3) absence of pre-gestational diabetes mellitus, chronic hypertension, or heart disease; (4) having complete medical records for the primary maternal outcomes. A total of 22,105 pregnant women delivered at our hospital. Of them, 2605 pregnant women were excluded after applying the inclusion criteria. Also, 501 women who experienced abortions or stillbirths and 350 women with incomplete medical records were excluded (Fig. 1). Finally, 19,500 pregnant women were included according to the inclusion criteria: 1146 (5.9%) had a positive HBsAg status (case group) and 18,354 (96.1%) had a negative HBsAg status (control group). Demographic characteristics, medical history, antenatal laboratory data, maternal complications, and outcome data were extracted from the institutional medical record database.

Adverse pregnancy outcomes

Our institutional obstetrician diagnosed the adverse pregnancy outcomes of the patients according to the current clinical practice guidelines, and these data were obtained from the clinical records. The adverse pregnancy outcomes we analyzed included GDM, ICP, HDP, placenta previa, abruptio placentae, cesarean sections, premature rupture of membrane (PROM), and fetal distress. Adverse neonatal outcomes consisted of preterm birth (delivery before 37 complete weeks of gestation) [25], low birth weight (LBW, birth weight of < 2500 g), macrosomia (birth weight of ≥ 4000 g), and neonatal asphyxia.

Statistical analysis

Relevant baseline and pregnancy characteristics were reported for descriptive analysis. Continuous data were expressed as mean ± standard deviation (SD) and categorical data as number or percentage. Differences in continuous variables were analyzed by Student's t test and categorical variables were analyzed by Pearson's χ^2 test (or Fisher's exact test where appropriate in the initial univariate analysis). The effect of maternal HBsAg/HBeAg/HBV-DNA status on pregnancy outcomes was examined by odds ratios (OR) or adjusted odds ratios (aOR) with 95% confidence interval (CI) before or after adjusting for potential confounding variables. The stepwise (Wald) method was used for multivariate logistic regression analysis. Statistical significance was set at $P < 0.05$ (two sided). All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA).

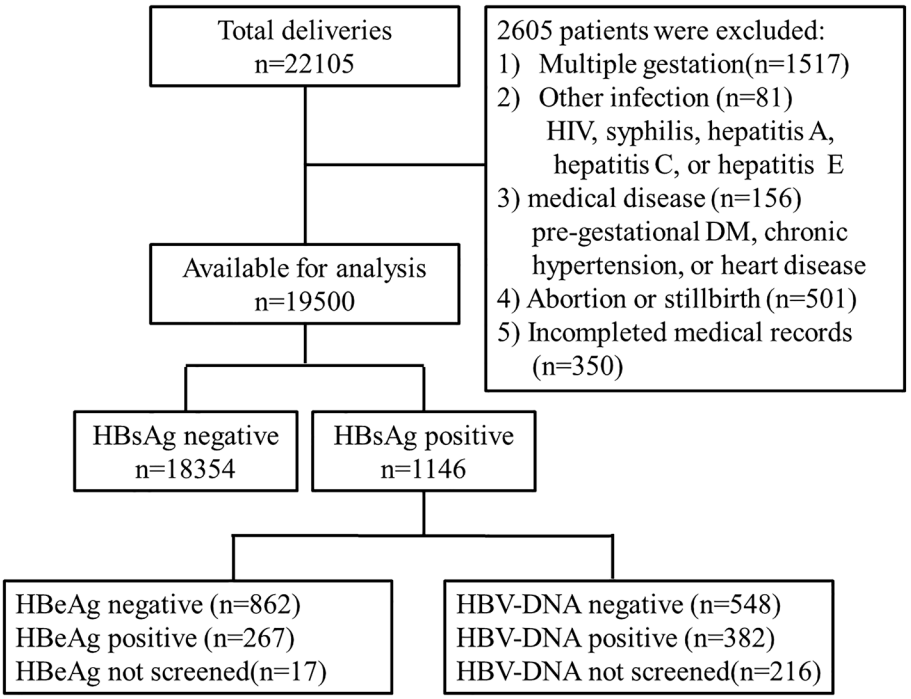

Fig. 1 Flowchart for study population. *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *DM* diabetes mellitus

Results

Demographic characteristics with respect to HBsAg status

Table 1 summarizes the demographic and clinical data of the HBsAg-positive ($n = 1146$) and HBsAg-negative ($n = 18,354$) groups. The HBsAg-positive pregnant women were significantly older than the HBsAg-negative pregnant women (mean age ± SD: 32.17 ± 4.46 vs 31.25 ± 4.44 years, $P < 0.01$). The HBsAg-positive pregnant women also had significantly higher proportions of in-vitro fertilization (IVF, 6.5% vs 3.8%, $P < 0.01$). Moreover, there were significant differences in the parity and abortion history between the two groups. In contrast, there were no statistically significant differences in the prenatal BMI, percentage of marital status, history of cesarean sections, anemia, serum ALT level, HbA1c, FBG, 1 h GLU, and 2 h GLU between the two groups (all $P > 0.05$) (Table 1).

Association of maternal HBsAg status with adverse pregnancy outcomes

When pregnancy outcomes were analyzed according to HBsAg status, HBsAg-positive pregnant women had significantly higher incidences of maternal comorbidities, including GDM (22.7% vs 17.9%; P < 0.01; aOR = 1.24; 95% CI 1.07–1.43), ICP (11.3% vs 3.2%; $P < 0.01$; aOR = 3.83; 95% CI 3.14–4.68), preterm births (11.2% vs. 8.2%; $P < 0.01$, aOR = 1.42; 95% CI 1.17–1.72), and neonatal asphyxia (1.6% vs. 0.7%; $P < 0.01$, aOR = 2.20; 95% CI 1.34–3.63). The number of caesarean sections performed in HBsAg-positive pregnant women was higher than those performed in HBsAg-negative pregnant women ($P < 0.05$), while unconditional multivariate logistic regression analysis revealed that maternal HBsAg-positive status was not associated with an increased risk of caesarean section (aOR = 1.12; 95% CI 0.77–1.18). No statistically significant differences in the incidence of HDP (6.4% vs. 5.0%), placenta previa (3.7% vs. 2.9%), abruptio placentae (2.1% vs. 1.7%), PROM (20.4% vs. 18.5%), fetal distress (18.6% vs. 18.5%), LBW (2.2% vs. 1.5%), macrosomia (4.1% vs. 4.1%), and neonatal asphyxia (1.5% vs. 1.9%) were observed between the two groups ($P > 0.05$) (Table 2).

Associations of maternal HBeAg carrier status with adverse pregnancy outcomes among the HBsAg-positive pregnant women

To further evaluate the effect of the HBeAg carrier status on maternal outcomes, we compared the HBeAg-positive pregnant women with HBeAg-negative pregnant women. HBeAg-positive status was associated with a higher risk of ICP (15.9% vs 10.4%; aOR = 1.64; 95% CI 1.10–2.44) and neonatal asphyxia (15.9% vs 10.4%; aOR = 3.08; 95% CI 1.17–8.00) than HBeAg-negative status, but this was not observed with respect to the incidence of GDM (21.7% vs 23.1%; aOR = 0.87; 95% CI 0.61–1.25) and preterm birth (12.4% vs 10.8%; aOR = 1.11; 95% CI 0.70–1.76). Between the HBeAg-positive and

Table 1 Demographic and clinical characteristics with respect to HBsAg status

Variables	HBsAg positive ($n=1146$)	HBsAg negative ($n=18,354$)	P
Age (y)	32.17 ± 4.46	31.25 ± 4.44	< 0.01
Gestational age (w)	37.16 ± 3.92	38.69 ± 3.56	< 0.01
BMI	27.01 ± 6.97	26.79 ± 6.82	0.17
< 18.5	78 (6.8)	1568 (8.5)	0.29
18.5–24.9	911 (79.5)	14,454 (78.6)	
25–29.9	150 (13.1)	2271 (12.4)	
≥ 30	7 (0.6)	60 (0.3)	
Marital status			
Married	1143	18,315	0.87
Unmarried	3	39	
Caesarean history	310 (27.1)	4538 (24.7)	0.08
Parity			
0	571 (49.8)	10,363 (56.5)	< 0.01
1	547 (47.7)	7408 (40.4)	
≥ 2	28 (2.5)	583 (3.2)	
IVF	74 (6.5)	701 (3.8)	< 0.01
Abortion history			
0	514 (44.9)	9405 (51.2)	< 0.01
1	325 (28.3)	4964 (27.0)	
≥ 2	307 (26.8)	3985 (21.8)	
anemia	479 (41.8)	7562 (41.2)	0.62
ALT (U/L)	29.34 ± 7.97	31.02 ± 6.73	0.15
> 40	66 (5.8)	1155 (6.3)	0.24
≤ 40	1080 (94.2)	17,199 (93.7)	
HbA1c (%)	5.06 ± 0.27	5.14 ± 0.28	0.23
FBG (mmol/L)	4.35 ± 0.95	4.14 ± 0.48	0.19
1 h GLU(mmol/L)	8.18 ± 1.66	8.02 ± 1.56	0.38
2 h GLU(mmol/L)	7.38 ± 1.30	7.09 ± 1.18	0.19
TBA (μmol/L)			
≥ 10	130 (11.3)	593 (3.2)	< 0.01
< 10	1016 (88.7)	17,761 (96.8)	

Two independent sample t tests were used for continuous variables; Pearson's Chi-square test or Fisher's exact test were used for categorical variables

HBsAg hepatitis B surface antigen, *BMI* body mass index, *IVF* In vitro fertilization, *ALT* alanine transaminase, *FBG* fasting blood glucose, *GLU* glucose, *TBA* total bile acid

HBeAg-negative groups, no significant differences were found in the incidence of HDP (5.6% vs. 4.8%), caesarean section (43.1% vs. 47.6%), placenta previa (3.0% vs. 3.6%), abruptio placentae (3.0% vs. 1.5%), PROM (15.4% vs. 19.6%), fetal distress (14.2% vs. 17.4%), LBW (3.4% vs. 1.9%), and macrosomia (2.0% vs. 4.9%, Table 3).

Associations between maternal HBV-DNA status in the second trimester and adverse maternal outcomes among HBsAg-positive pregnant women

We analyzed the associations between the maternal HBV DNA status in second trimester and the pregnancy outcomes in a cohort of 930 HBsAg-positive women with high HBV-DNA loads in second trimester. Maternal HBV-DNA load status in the second trimester of HBsAg-positive pregnant women was associated with significantly increased risk of ICP (15.4% vs 10.2%; $P=0.02$; aOR = 1.52; 95% CI 1.06–2.35) and neonatal asphyxia (2.4% vs 0.5%; aOR = 4.20; $P=0.02$; 95% CI 4.20–15.83). No significant differences in the incidence of GDM (22.3% vs. 21.7), HDP (6.5% vs. 3.8%), caesarean Section (43.2% vs. 48.9%), placenta previa (3.7% vs. 2.9%), abruptio placentae (1.8% vs 2.2%), PROM (17.0% vs 17.5%), preterm births (11.0% vs. 9.7%), fetal distress (18.1% vs. 18.2%), LBW (1.8% vs 2.0%), and macrosomia (3.9% vs. 4.2%) were found between both the groups (Table 4).

Discussion

This retrospective cohort study demonstrated that maternal HBsAg-positive status was associated with a significantly higher incidence of GDM, ICP, preterm birth, and neonatal asphyxia than that observed with the maternal HBsAg-negative status. Further, HBsAg-positive pregnant women with HBeAg-positive and HBV-DNA load status in the second trimester had a higher risk of ICP and neonatal asphyxia. However, there was no association between maternal HBsAg status and HDP, caesarean section, placenta previa, abruptio placentae, PROM, fetal distress, LBW, or macrosomia.

Meanwhile, we found a potential association of maternal HBsAg-positive status with a significantly higher risk of ICP (aOR = 3.83; 95% CI 3.14–4.68) after adjustments for potential confounders, which is consistent with the results of recent studies [22, 24]. While Cui et al. reported a similar incidence of ICP between HBV-positive carriers and non-HBV pregnant women [26]. Given that ICP is the most common pregnancy-specific liver disorder manifested with pruritus and elevated bile, occurring in the second to the third trimester, it may cause premature delivery, fetal distress, meconium-stained amniotic fluid formation, and even stillbirth [27, 28]. The underlying mechanism for the higher risk of ICP among HBV-positive carrier mothers is unclear. However, it is anticipated that the HBV-positive carrier status, acceleration of viral replication, and their further interactions induce a hepatocellular systemic inflammatory effect, which leads to a deterioration of the hepatic function of an expectant mother [29]. In this analysis, we further explored the potential effects of maternal

Table 2 Pregnancy outcomes with respect to HBsAg status

Variables	HBsAg positive ($n=1146$) (%)	HBsAg negative ($n=18,354$)(%)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
GDM	260 (22.7)	3289 (17.9)	< 0.01	1.34 (1.17–1.55)	1.24 (1.07–1.43)
ICP	130 (11.3)	593 (3.2)	< 0.01	4.00 (3.27–4.90)[a]	3.83 (3.14–4.68)[a]
HDP	57 (5.0)	1031 (5.6)	0.36	0.88 (0.67–1.16)	0.86 (0.66–1.14)
Caesarean delivery	531 (46.3)	7385 (40.2)	< 0.01	1.28 (1.14–1.45)[b]	0.95 (0.77–1.18)
Placenta previa	39 (3.4)	500 (2.7)	0.17	1.26 (0.90–1.75)	1.07 (0.68–1.67)
abruptio placentae	21 (1.8)	361 (2.0)	0.75	0.93 (0.60–1.45)	1.30 (0.73–2.31)
PROM	184 (20.4)	352 (18.5)	0.80	0.98 (0.84–1.14)	1.09 (0.87–1.46)
Fetal distress	190 (16.6)	2720 (14.8)	0.11	1.14 (0.97–1.34)	1.11 (0.90–1.38)
Preterm birth	128 (11.2)	1502 (8.2)	< 0.01	1.41 (1.17–1.71)[a]	1.42 (1.17–1.72)[a]
LBW	20 (1.7)	257 (1.4)	0.34	1.25 (0.79–1.98)	1.27 (0.70–2.32)
Macrosomia	48 (4.1)	854 (4.1)	0.47	0.90 (0.66–1.20)	0.96 (0.64–1.44)
Neonatal asphyxia	18 (1.6)	136 (0.7)	< 0.01	2.14 (1.30–3.51)[a]	2.20 (1.34–3.63)[a]

Multivariate analyses were adjusted for age, parity, caesarean history, IVF, abortion history. The results were presented with an adjusted odds ratio, aOR (95% CI)

GDM gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *ICP* intrahepatic cholestasis pregnancy, *PROM* premature rupture of the membranes, *LBW* low birth weight, *OR* odds ratio

[a] $P < 0.01$

[b] $P < 0.05$,compared with the HBsAg-negative subjects

Table 3 The association between HBeAg status in pregnancy outcomes Among HBsAg postive status

Variables	HBeAg positive ($n=267$) (%)	HBeAg negative ($n=862$) (%)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
GDM	58 (21.7)	199 (23.1)	0.64	0.93 (0.66–1.29)	0.87 (0.61–1.25)
ICP	42 (15.9)	88 (10.4)	0.01	1.70 (1.14–2.56)[a]	1.64 (1.10–2.44)[a]
HDP	15 (5.6)	41 (4.8)	0.57	1.19 (0.65–2.19)	1.27 (0.68–2.37)
Caesarean delivery	115 (43.1)	410 (47.6)	0.20	0.83 (0.63–1.10)	1.22 (0.87–1.71)
Placenta previa	8 (3.0)	31 (3.6)	0.64	0.89 (0.38–1.83)	0.73 (0.30–1.73)
Abruptio placentae	8 (3.0)	13 (1.5)	0.12	2.02 (0.83–4.92)	1.60 (0.62–4.17)
PROM	41 (15.4)	169 (19.6)	0.12	0.74 (0.51–1.08)	0.70 (0.47–1.03)
Fetal distress	38 (14.2)	150 (17.4)	0.23	0.79 (0.54–1.16)	0.75 (0.51–1.09)
Preterm birth	33 (12.4)	93 (10.8)	0.48	1.12 (0.76–1.78)	1.11 (0.70–1.76)
LBW	9 (3.4)	12 (1.9)	0.40	1.52 (0.58–3.86)	1.48 (0.53–3.69)
Macrosomia	8 (3.0)	40 (4.6)	0.25	0.64 (0.29–1.37)	0.63 (0.24–1.26)
Neonatal asphyxia	8 (3.4)	9 (1.0)	< 0.01	3.31 (1.30–8.42)[a]	3.08 (1.17–8.00)[a]

Multivariate analyses were adjusted for age, BMI, parity, caesarean history, abortion history, ALT. The results were presented with an adjusted odds ratio, aOR (95% CI)

GDM gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *ICP* intrahepatic cholestasis pregnancy, *PROM* premature rupture of the membranes, *LBW* low birth weight, *OR* odds ratio

[a] $P < 0.05$, compared with the HBsAg postive with HBeAg-negative subjects

HBeAg status on adverse maternal outcomes in HBsAg-positive pregnant women. Remarkably, our results showed that the maternal HBeAg-positive status was associated with a higher risk of ICP both in the univariate (OR = 1.70; 95% CI 1.14–2.56) and multivariate analyses (aOR = 1.64; 95% CI 1.10–2.44). Moreover, we found similar results while investigating the associations between the maternal HBV-DNA status in the second trimester and adverse pregnancy outcomes among HBsAg-positive pregnant women, which previously were not examined. Since HBeAg serves as a qualitative marker of HBV replication or a qualitative surrogate marker of the viral copy number among HBsAg carriers, we hypothesized that maternal HBeAg-positive and high HBV-DNA load status in the second trimester

Table 4 The association between HBV-DNA status in second trimester and pregnancy outcomes among HBsAg postive status

Variables	High HBV-DNA loads ($n=382$) (%)	Low HBV-DNA loads ($n=548$) (%)	*P*	Crude OR (95% CI)	Adjusted OR (95% CI)
GDM	69 (22.3)	90 (21.7)	0.85	1.03 (0.75–1.41)	1.12 (0.81–1.54)
ICP	59 (15.4)	56 (10.2)	0.02	1.61 (1.07–2.37)[a]	1.52 (1.06–2.35)[a]
HDP	25 (6.5)	21 (3.8)	0.06	1.76 (0.99–3.19)	1.26 (0.88–2.86)
Caesarean delivery	165 (43.2)	268 (48.9)	0.09	0.79 (0.61–1.03)	0.81 (0.58–1.13)
Placenta previa	14 (3.7)	16 (2.9)	0.53	1.27 (0.61–2.62)	1.27 (0.61–2.65)
Abruptio placentae	7 (1.8)	12 (2.2)	0.71	0.83 (0.33–2.14)	0.84 (0.33–2.17)
PROM	65 (17.0)	96 (17.5)	0.84	0.97 (0.68–1.37)	0.93 (0.65–1.32)
Preterm birth	42 (11.0)	53 (9.7)	0.51	1.15 (0.75–1.77)	1.12 (0.73–1.75)
Fetal distress	69 (18.1)	100 (18.2)	0.94	0.99 (0.70–1.37	0.89 (0.59–1.35)
LBW	7 (1.8)	11 (2.0)	0.97	0.98 (0.38–2.66)	0.82 (0.43–2.49)
Macrosomia	15 (3.9)	23 (4.2)	0.84	0.93 (0.48–1.81)	0.96 (0.64–1.44)
Neonatal asphyxia	9 (2.4)	3 (0.5)	0.02	4.38 (1.18–16.30)[a]	4.20 (1.11–15.83)[a]

Multivariate analyses were adjusted for maternal age, BMI, parity, abortion history, IVF, ALT. The results were presented with an adjusted odds ratio, aOR (95% CI)

GDM gestational diabetes mellitus, *HDP* hypertensive disorders of pregnancy, *ICP* intrahepatic cholestasis pregnancy, *PROM* premature rupture of the membranes, *OR* odds ratio

[a] $P<0.05$, compared with the low HBV-DNA loads subjects

might exacerbate the inflammatory response, which is a mediator of ICP [30].

We also found that maternal HBsAg-positive pregnant women have an increased risk for neonatal asphyxia (aOR = 2.20; 95% CI 1.34–3.63), which confirms the results of previous studies. For example, Luo et al. showed in their meta-analysis that HBV-carrier status in pregnant women was significantly associated with neonatal asphyxia [31]. Xiao et al. demonstrated that pregnancy with HBV infection increased the incidence rate of neonatal asphyxia [4]. Thus, our results further showed that HBsAg-positive pregnant women with both HBeAg-positive status and high HBV DNA-load status in the second trimester have an increased risk of neonatal asphyxia. Additionally, we observed a positive association between the maternal HBsAg-positive status and preterm birth rates (aOR = 1.56; 95% CI 1.18–2.05), which was congruent with the results of a population-based cohort study and a meta-analysis [18, 19]. However, other studies found no significant association between maternal HBsAg-positive status and preterm birth rates [24, 32]. This inconsistency could be attributed to the differences in HBV infections, ethnicities, sample sizes, and the confounding variables of those studies. HBV infects all layers of the placenta, alters the intrauterine environment and inflammatory changes in the placenta, which caused respiratory, metabolic and nutrition insufficiency of the placenta, they might contribute to preterm births and neonatal asphyxia [33, 34]. Moreover, the higher incidence of ICP in the HBsAg-positive pregnant women in our results might affect the association between neonatal asphyxia/preterm births and maternal HBsAg-positive status, since ICP with HBV infection was reported to affect perinatal/neonatal outcomes including the risk of neonatal asphyxia [35] and preterm births [36].

The association between the maternal HBsAg-positive status and GDM remains controversial. Previous studies showed a positive association between maternal HBsAg-positive status and GDM, among which retrospective studies suggested that HBsAg-positive carrier women had a higher risk of GDM [8, 21, 22]. Other studies on the mechanisms for the influence of HBV infection on GDM suggested that pregnancy with HBV infection might exacerbate the insulin resistance related to a chronic inflammatory state [37–40]. Our present study showed maternal HBsAg-positive status to be associated with a higher incidence of GDM (aOR = 1.24; 95% CI 1.07–1.43), which is consistent with the results of previous studies. However, studies by Cui et al. and Lao et al. showed a negative association between the maternal HBsAg-positive status and GDM [19, 41]. This inconsistency could be attributed to ethnic differences since the HBV infection rate and genetic factors affect people differently [42, 43]. Additionally, the varied diagnostic criteria of GDM might contribute to the inconsistency [21].

There were few limitations in our study; first, being the retrospective study design and the avoidance of comprehensive factors, which is the primary limitation. Second, we did not consider the pre-gravid maternal weights, which might affect pregnancy outcomes. Third, as the data on antiviral treatments for these pregnant women with HBsAg-positive status were not completely recorded, our investigation was limited to examining the effect of HBV-DNA load status in the second trimester among maternal HBsAg-positive status women on the possibilities of adverse pregnancy outcomes.

Therefore, a large-scale prospective multicenter study on the association between the maternal HBsAg-positive status and adverse pregnancy outcomes is warranted in the future.

This study also has several strengths. First, a relatively large sample size was used and we adjusted the data according to anticipated confounding factors of adverse pregnancy outcomes by multivariable logistic regression analysis to ensure reliable assessments. Second, our study comprehensively assessed the associations between maternal HBsAg/HBeAg/HBV DNA status and adverse pregnancy outcomes and revealed remarkably significant associations with ICP and neonatal asphyxia, which previously lacked sufficient clinical investigation.

In conclusion, our study suggested that maternal HBsAg-positive pregnant women had a significantly higher risk of GDM, ICP, preterm births, and neonatal asphyxia than HBsAg-negative pregnant women. Furthermore, the risks of ICP and neonatal asphyxia were still higher in HBsAg-positive women with HBeAg-positive status and high HBV-DNA loads in the second trimester. Careful surveillance of maternal HBsAg/ HBeAg /HBV-DNA load status is crucial. Meanwhile, further investigation is required to explain the potential role of chronic HBV infection in the occurrence of adverse pregnancy outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by the Medical Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China (Approval number: IRB-20200063-R).

Informed consent Not applicable for this study.

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