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The impact of maternal HBeAg carries status and elevated ALT values on adverse outcomes: a population-based cohort study in 198,049 pregnancies

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Abstract

Background Hepatitis B virus (HBV) infection is a common public health problem, and maternal HBV infection can cause adverse outcomes in both mothers and fetuses. However, the influence of hepatitis B e antigen (HBeAg) serostatus on obstetric outcomes is not well established. This study aims to investigate the prevalence trend of maternal HBV infection in China, and its impact on obstetric outcomes.

Methods This retrospective cohort study used data from an established population-based pregnancy registry (REPRESENT) in Xiamen, China. Maternal hepatitis B surface antigen (HBsAg) and HBeAg serostatus were regularly tested at the first antenatal visits. Multivariable regression was conducted to evaluate the impact of maternal HBV infection on maternal and neonatal outcomes.

Results From January 2015 to March 2019, 198,049 pregnancies were included. The overall prevalence of HBsAg + HBeAg + was 2.26% and has decreased during these years (relative risk 0.59, 95% CI 0.54–0.65). Compared to HBsAg-HBeAg- pregnancies, maternal HBsAg + HBeAg- was associated with a higher risk of intrahepatic cholestasis of pregnancy (ICP) (adjusted odds ratio 3.43, 95% CI 2.94-4.00) and cesarean section (1.04, 1.01–1.08). HBsAg + HBeAg + was further associated with a higher risk of ICP (3.44, 2.64–4.48), fetal distress (1.33, 1.05–1.67), and preterm birth (1.37, 1.04–1.81). In addition, subgroup analysis indicated that abnormal alanine aminotransferase status at the first antenatal visit may exacerbate the impact of maternal HBV infection on maternal and neonatal outcomes.

Conclusion The prevalence of maternal HBsAg + HBeAg + serostatus is still high, but has decreased over time. Given its significant adverse effects, prenatal screening for HBsAg and HBeAg should be performed.

Clinical trial number Not applicable.

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Keywords HBV, HBeAg, ALT, Pregnancy, Intrahepatic cholestasis of pregnancy

Introduction

Hepatitis B virus (HBV) infection has long been a global public health problem. Recent data demonstrated that there were approximately 290 million people living with HBV in 2019 and nearly 820 thousand deaths attributable to HBV infection per year [1]. Despite the implementation of the hepatitis B vaccination, which has slowed down the increase of newly infected persons since 1991 [2], The prevalence of HBV infection, which was define as hepatitis B surface antigen (HBsAg) seropositive, remains at high levels in many developing countries [3]. China is a well-recognized HBV epidemic area with 84 million HBsAg positive patients in 2018 [4]. Correspondingly, there is a huge group carrying HBV among pregnant women in China, with an estimated prevalence of 6.18% [5].

Several studies have evaluated the association between maternal HBV infection and adverse maternal and neonatal outcomes,[6–14] but the findings did not reach a consensus. For example, most studies reported a higher risk of gestational diabetes mellitus (GDM) [6, 7], intrahepatic cholestasis of pregnancy (ICP) [8, 9], pre-eclampsia (PE) [10], and preterm birth (PTB) [11] in the maternal HBsAg positive group. However, several other studies did not find similar associations or even reached opposite conclusions [12–14].

On the other hand, most previous studies have only evaluated the effect of HBsAg positive, while little is known about the impact of hepatitis B e antigen (HBeAg) seropositive on maternal and neonatal outcomes [14–16], which represents an active viral replication and a higher risk of liver progression [17]. In addition, whether the impact of maternal HBV infection on pregnancy outcomes differs according to alanine aminotransferase (ALT) status in early pregnancy is also poorly understood. A better understanding of the impact of different maternal HBV serostatus (i.e. HBsAg + HBeAg-, HBsAg + HBeAg+) is helpful for pregnancy management, such as recommending timing of conception for HBV-positive women, or providing appropriate drug interventions.

Considering that there have been few reports on a representative prevalence of HBV infection during pregnancy in China in recent years, and the impact of maternal HBsAg and HBeAg positivity on pregnancy outcome has not been fully elucidated, we conducted this retrospective cohort study to elucidate the prevalence trends of maternal HBsAg and HBeAg serostatus from 2015 to 2019 and the comprehensive impact on obstetric and neonatal outcomes based on a regional registry database in Xiamen, China.

Methods

Design overview

This population-based retrospective cohort study includes three analyses to comprehensively investigate the situation of maternal HBV infection and its impact on obstetric and neonatal outcomes. First, by using data from a pregnancy registry database (REPRESENT) [18], we described the prevalence of maternal HBsAg+, HBsAg + HBeAg-, and HBsAg + HBeAg+, and the temporal trend of these prevalences from 2015 to 2018. Second, multivariable regression was used to evaluate the association between maternal HBsAg + HBeAg-, HBsAg + HBeAg + and various obstetric and neonatal outcomes (e.g., GDM, cesarean section). Third, we additionally evaluated the impact of maternal HBV infection plus impaired liver function (i.e., abnormal ALT status) on obstetric and neonatal outcomes. This study was approved by the Ethics Committee of West China Hospital (2019 – 825) in Sichuan, China.

Data sources

This study was conducted using data from the Xiamen registry of pregnant women and offspring (REPRESENT), which has been described in detail elsewhere [18]. Briefly, REPRESENT is one of the longest accumulated pregnancy registry databases in China (11 years of data, 2008.01-2019.03), which collected healthcare data from 766,194 pregnant women and 765,746 newborns across all maternity departments in Xiamen City, Fujian Province, China. After confirmation of conception by ultrasonography, pregnant women were registered in REPRESENT at first antenatal visit (generally at 6–10 gestation weeks). A series of routine examinations was carried out at the first antenatal visit, including serous HBsAg and HBeAg test. In REPRESENT, a substantial number of variables were recorded by clinicians, including demographic characteristics, pregnancy co-morbidities, obstetric outcomes, and neonatal outcomes. In REPRESENT, pregnancy co-morbidities and gestational complications were grouped and coded according to the classification and codes of diseases published by the Chinese National Standards Institute (GB/T14396-2016) [19], and the National Health Standard Criteria [20], both of which were consistent with the International Classification of Diseases 10th Revision (ICD-10). During the construction of the REPRESENT database, 1000 cases were randomly selected for verification, and the results showed that these cases were 100% complete and in accordance with the raw data.

Participant selection

As serologic testing for HBV infection was fully implemented in Xiamen in 2015, this study included singleton pregnancies who were registered in REPRESENT between January 1, 2015 and March 31, 2019. Pregnant women were excluded if they (a) did not deliver in Xiamen or continued their pregnancy until March 31, 2019; (b) were > 20 gestation weeks at the first antenatal visit; (c) did not have a serological test for HBsAg or HBeAg at the first antenatal visit; (d) had chronic hypertension, pregestational diabetes mellitus (type I or type II), epilepsy, psychosis, hyperthyroidism, hypothyroidism; (e) had been infected with hepatitis A virus, hepatitis C virus, or have non-HBV liver diseases; (f) had been infected with treponema pallidum subspecies pallidum (i.e., syphilis) or human immunodeficiency virus; (g) used antiviral medication (e.g., tenofovir) during pregnancy.

Exposure

HBV infection refers to pregnant women who were HBsAg seropositive, regardless of HBeAg serostatus. According to the Chinese guidelines for preconception and prenatal care [21, 22], the serostatus of HBsAg or HBeAg was routinely tested by an enzyme-linked immunosorbent assay at the first antenatal visit. To comprehensively assess the prevalence of maternal HBV infection, we divided all pregnant women into two groups, the HBsAg seropositive (HBsAg+) group and the HBsAg seronegative (HBsAg-) group. Then, according to the serostatus of HBsAg and HBeAg, we divided all pregnant women into three groups, including HBsAg + HBeAg + group (HBsAg and HBeAg coseropositivity), HBsAg + HBeAg- group (HBsAg seropositivity in the absence of HBeAg seropositivity), and HBsAgHBeAg- group (HBsAg and HBeAg coseronegativity) for further study.

Outcomes

The primary outcome in this study was ICP (ICD-10 code: O26.606), and secondary outcomes included PE (O14), GDM (O24.4), fetal distress (O36.301, O36.302, O36.304, O36.305, O68.003, O68.101, O68.201, O68.901), premature rupture of membranes (PROM) (O42), placenta previa (O44), cesarean section (O82), postpartum hemorrhage, PTB (< 37 gestational weeks), low birthweight (LBW) (< 2500 g), Apgar score < 7 at 1, 5, and 10 min. According to the guidelines for prevention and management of postpartum hemorrhage in China [22], postpartum hemorrhage was defined as blood loss within 24 h after delivery of ≥ 500 ml for vaginal delivery or ≥ 1000 ml for cesarean delivery.

Potential confounders

Based on the literature and discussions with clinicians, we identified the following potential confounders: maternal age, paternal age, maternal prepregnancy body mass index (BMI), year of education (≤ 6 years, 7–12 years, and > 13 years), location (urban or rural area), parity (nulliparity or multiparity), smoking before pregnancy (yes or no), drinking before pregnancy (yes or no), floating population status (yes or no), assisted reproductive therapy (ART) treatment (yes or no), and year of delivery.

Data analysis

The prevalence of HBsAg and HBeAg seropositivity and the temporal trend of these prevalences from 2015 to 2018 were calculated. To evaluate the impact of maternal HBV infection (HBsAg + HBeAg- or HBsAg + HBeAg+) on obstetric and neonatal outcomes, we first calculated the crude relative risk (cRR) and 95% confidence interval (CI) by using univariable analyses. Then, multivariable logistic regression including confounders described above was used to evaluate the adjusted odds ratio (aOR) and 95%CI of exposure. We conducted subgroup analyses to explore whether the effect of maternal HBV infection differed by ALT status (normal vs. abnormal [greater than or equal to 25 U/L]) at the first antenatal visit. Sensitivity analyses were performed by using an alternative approach - after removing pregnancies with missing data, inverse probability weighting of propensity score (PS) was performed by adjusting for the above confounders. The balance of characteristics between exposure and control groups was considered adequate if the absolute standardized differences (ASD) were less than 0.2.

Categorical data were presented as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. The mean ± SD was used to describe these variables with a normal distribution. Medians and interquartile ranges were used to describe these variables with skewed distributions. Pearson's chi-squared test or Fisher's exact test was used for categorical variables. Two- sided p values < 0.05 were considered to indicate statistically significant results. PS weighting was performed by using the R package twang [23, 24]. All statistical analyses were performed with R software (version 3.6.1, R Project for Statistical Computing, Austria, Vienna).

Results

Population characteristics

From January 2015 to March 2019, 198,049 pregnancies were finally included in this study (Fig. 1). The median maternal age was 28 years old (interquartile range 26–32), and 11.36% of pregnant women were older than 35 years (Table 1). No significant differences were observed between the HBsAg-HBeAg-,

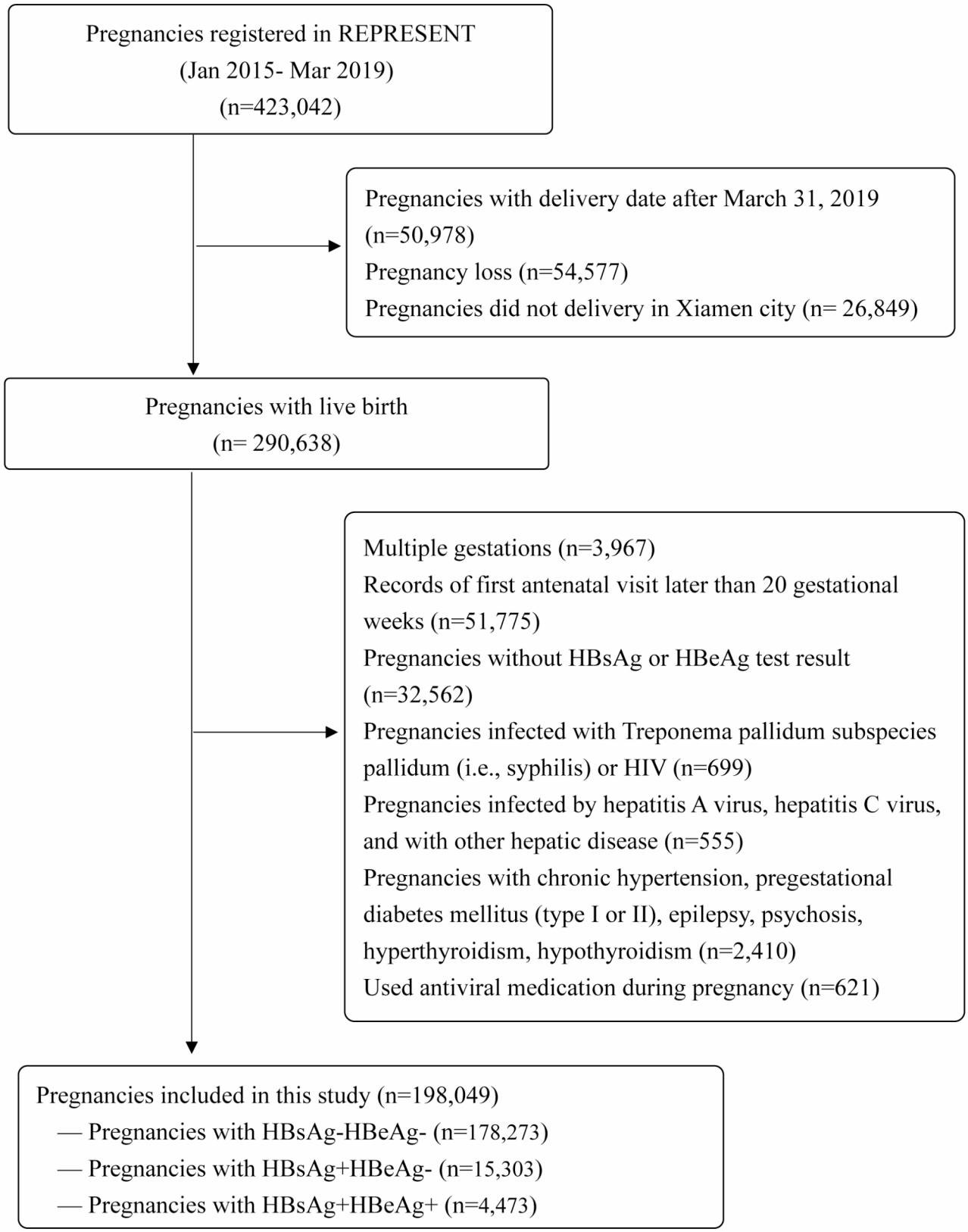

Fig. 1 Flow chart of pregnancies included in this study. REPRESENT, Xiamen Registry of Pregnant Women and Offspring; HBsAg, hepatitis B surface antigen, HBeAg, hepatitis B e antigen, HIV, human immunodeficiency virus

Table 1 Characteristics of the included pregnancies

Characteristics	Categories	Overall (198,049), *n* (%)	HBsAg-HBeAg- (178,273), *n* (%)	HBsAg + HBeAg- (15,303), *n* (%)	HBsAg + HBeAg+ (4,473), *n* (%)	*P* value
Maternal Age (mean ± SD)		28.69 ± 4.58	28.63 ± 4.60	29.76 ± 4.41	27.65 ± 4.03	< 0.001
Maternal age (years)	< 20	2730 (1.38)	2603 (1.46)	66 (0.43)	61 (1.36)	< 0.001
	20–24	30,211 (15.25)	27,962 (15.69)	1400 (9.15)	849 (18.98)	
	25–29	87,541 (44.20)	78,810 (44.21)	6445 (42.12)	2286 (51.11)	
	30–34	55,052 (27.80)	48,904 (27.43)	5125 (33.49)	1023 (22.87)	
	≥ 35	22,506 (11.36)	19,987 (11.21)	2265 (14.80)	254 (5.68)	
Education level	≤ 6 years	4441 (2.24)	3983 (2.25)	373 (2.45)	85 (1.91)	< 0.001
	7–12 years	93,296 (47.11)	83,845 (47.30)	7140 (46.97)	2311 (52.03)	
	> 13 years	99,169 (50.07)	89,434 (50.45)	7689 (50.58)	2046 (46.06)	
Pre-pregnancy BMI (kg/m^2)	< 18.50	38,591 (19.49)	34,663 (19.46)	2828 (18.50)	1100 (24.60)	< 0.001
	18.50-23.99	135,242 (68.29)	121,743 (68.35)	10,584 (69.24)	2915 (65.20)	
	24.00-27.99	19,746 (9.97)	17,848 (10.02)	1516 (9.92)	382 (8.54)	
	≥ 28.00	4307 (2.17)	3876 (2.18)	357 (2.34)	74 (1.66)	
Smoking	yes	55 (0.03)	53 (0.03)	1 (0.01)	1 (0.02)	0.25
	no	197,993 (99.97)	178,219 (99.97)	15,302 (99.99)	4472 (99.98)	
Drinking	yes	126 (0.06)	113 (0.06)	10 (0.07)	3 (0.07)	0.99
	no	197,922 (99.94)	178,159 (99.94)	15,293 (99.93)	4470 (99.93)	
Floating population	yes	53,871 (27.20)	48,157 (27.03)	4220 (27.59)	1494 (33.41)	< 0.001
	no	144,069 (72.74)	130,015 (72.97)	11,076 (72.41)	2978 (66.59)	
Location	urban	170,570 (86.13)	153,602 (86.17)	13,165 (86.03)	3803 (85.02)	0.08
	rural	27,464 (13.87)	24,656 (13.83)	2138 (13.97)	670 (14.98)	
Paternal age (years)	< 20	388 (0.20)	369 (0.21)	11 (0.07)	8 (0.18)	< 0.001
	20–25	17,468 (8.82)	16,176 (9.20)	850 (5.62)	442 (10.06)	
	25–30	77,223 (38.99)	69,967 (39.81)	5227 (34.58)	2029 (46.17)	
	30–35	59,855 (30.22)	53,351 (30.36)	5191 (34.34)	1313 (29.87)	
	≥ 35	40,314 (20.36)	35,875 (20.41)	3836 (25.38)	603 (13.72)	
Parity	nulliparity	83,542 (42.18)	75,890 (42.57)	5604 (36.62)	2048 (45.79)	< 0.001
	multiparity	114,507 (57.82)	102,383 (57.43)	9699 (63.38)	2425 (54.21)	
ART	yes	3457 (1.75)	3066 (1.72)	319 (2.08)	72 (1.61)	0.003
	no	194,592 (98.25)	175,207 (98.28)	14,984 (97.92)	4401 (98.39)	
ALT	normal	186,477 (94.16)	168,504 (95.57)	14,284 (94.36)	3689 (83.56)	< 0.001
	abnormal	9390 (4.74)	7811 (4.43)	853 (5.64)	726 (16.44)	

Note: BMI, body mass index; ART, assisted reproductive therapy; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase

HBsAg + HBeAg-, and HBsAg + HBeAg + groups with respect to smoking, alcohol consumption, and location. Compared with the HBsAg-HBsAg- group, both maternal and paternal age were younger in the HBsAg + HBeAg + group (Table 1). A higher proportion of women in the HBsAg + HBeAg + group were underweight, nulliparous, and floating. In addition, a lower proportion of women in the HBsAg + HBeAg + group had achieved higher education and received ART treatment. In the HBsAg + HBeAg- group, when compared with the HBsAg-HBsAg- group, a higher proportion of women were older than 35 years (Table 1).

Prevalence of maternal HBsAg and hbeag seropositivity

The overall prevalence of maternal HBsAg + was 9.99% (19,776/198,049, 95%CI 9.85-10.12%) and has decreased in these years (Fig. 2). For example, the prevalence of maternal HBsAg + decreased from 10.80% in 2015 to 9.37% in 2018 (RR = 0.86, 95% CI 0.82–0.90) (Fig. 3). Similarly, the overall prevalence of HBsAg + HBeAg + was 2.26% (4473/198,049, 95%CI 2.20-2.32%) and decreased from 2.99% in 2015 to 1.86% in 2018 (RR = 0.59, 95% CI 0.54–0.65) (Figs. 2 and 3). However, the prevalence of HBsAg + HBeAg- did not decrease between these years with an overall prevalence of 7.73% (15,303/198,049, 95%CI 7.61-7.84%) (Fig. 2).

The impact of maternal HBV infection on obstetric and neonatal outcomes

The results indicated that compared with the HBsAg-HBeAg- group, maternal HBsAg + HBeAg + was associated with a higher risk of ICP (1.39% vs. 0.42%, aOR = 3.44, 95%CI 2.64–4.48), fetal distress (aOR = 1.33, 95%CI 1.05–1.67), preterm birth (< 37 gestational

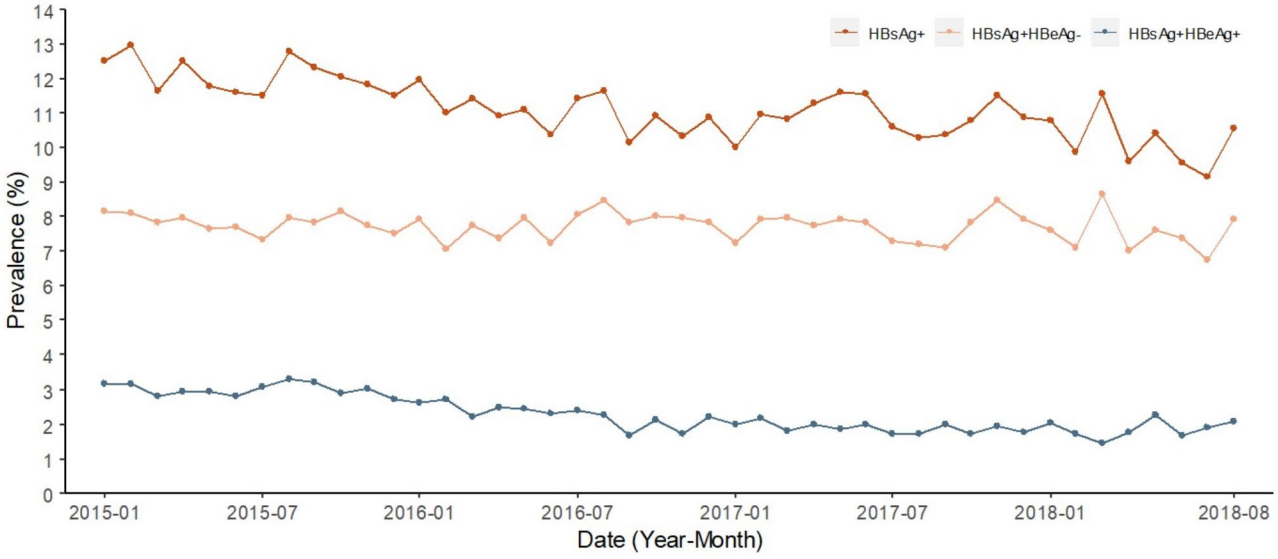

Fig. 2 The prevalence of different maternal HBV seropositivity statuses. Note: Pregnancies registered after August 2018 are not shown in this figure, as most of these pregnancies did not give birth before March 2019

weeks) (aOR = 1.16, 95%CI 1.01–1.33), and preterm birth (< 37 gestational weeks) (aOR = 1.37, 95%CI 1.04–1.81) (Table 2). However, maternal HBsAg + HBeAg + was associated with a lower risk of PROM (aOR = 0.88, 95%CI 0.79–0.97) (Table 2). In addition, the results indicated that maternal HBsAg + HBeAg- status was also associated with a higher risk of ICP (1.42% vs. 0.42%, aOR = 3.43, 95%CI 2.94-4.00), and cesarean section (aOR = 1.04, 95%CI 1.01–1.08) (Table 2). No significant differences were observed in the incidence of other maternal and neonatal outcomes. Sensitivity analyses result also showed that maternal HBsAg + HBeAg+ (aOR = 2.98, 95%CI 2.09–4.26) and HBsAg + HBeAg- (aOR = 3.38, 95%CI 2.76–4.14) associated with higher risk of ICP (Table S1).

Subgroup analyses showed that the impact of maternal HBsAg + HBeAg- and HBsAg + HBeAg + on ICP was more severe in pregnancies with abnormal ALT than in those with normal ALT (Table 3). For example, the aOR of maternal HBsAg + HBeAg + for ICP was 5.04 (95% CI 3.00–8.47) in the abnormal ALT group and 2.65 (95% CI 1.90–3.68) in the normal ALT group (Table 3). In addition, the maternal HBsAg + HBeAg + in the abnormal ALT group may associated with a higher risk of low birthweight (< 2500 g) (aOR = 1.47, 95%CI 1.03–2.08) and PE (aOR = 2.47, 95%CI 1.01–6.01).

Discussion

Summary of main findings

By including 198,049 pregnancies covering about 5-year period, this population-based cohort study comprehensively investigated the prevalence of maternal HBsAg and HBeAg seropositivity and the impact of maternal HBV infection (i.e., HBsAg + HBeAg + and HBsAg + HBeAg-) on obstetric and neonatal outcomes. The overall prevalence of maternal HBsAg+, and HBsAg + HBeAg + was 9.99% and 2.26%, which decreased by 14% and 41% from 2015 to 2018, respectively. Our results indicated that maternal HBsAg + HBeAg + was associated with a higher risk of ICP, fetal distress, and PTB after adjusting for confounders. In the HBsAg + HBeAg- group, the risk of ICP and cesarean section was also higher. In addition, our results suggested that the impact of maternal HBV infection on ICP was more severe in pregnancies with abnormal ALT than in those with normal ALT.

Comparison with previous studies

Despite widespread vaccination, HBV infection remains a major global health problem, affecting an estimated 257–291 million people worldwide [25]. Among pregnant women, the global prevalence rate has been estimated at 3% [26]. Previous studies showed that the prevalence rate was higher in developing countries than that in developed countries [25, 26]. Based on a large-scale population, our study showed that the prevalence of maternal HBV infection (HBsAg seropositivity) was 9.99%, which was higher than a previously reported national average prevalence [5, 27]. By including 42 studies conducted in 20 provinces in China, a meta-analysis reported the pooled prevalence of HBV infection in Chinese pregnant women between 2016 and 2021 was 6.64% (95%CI: 5.72–7.57%) [27]. Similarly, a national observational study reported that the prevalence of maternal HBV infection in China was 6.17% (95%CI 6.16–6.18%) between 2015 and 2020 [5]. Although it has indeed decreased in recent years, the prevalence of maternal HBV infection in China

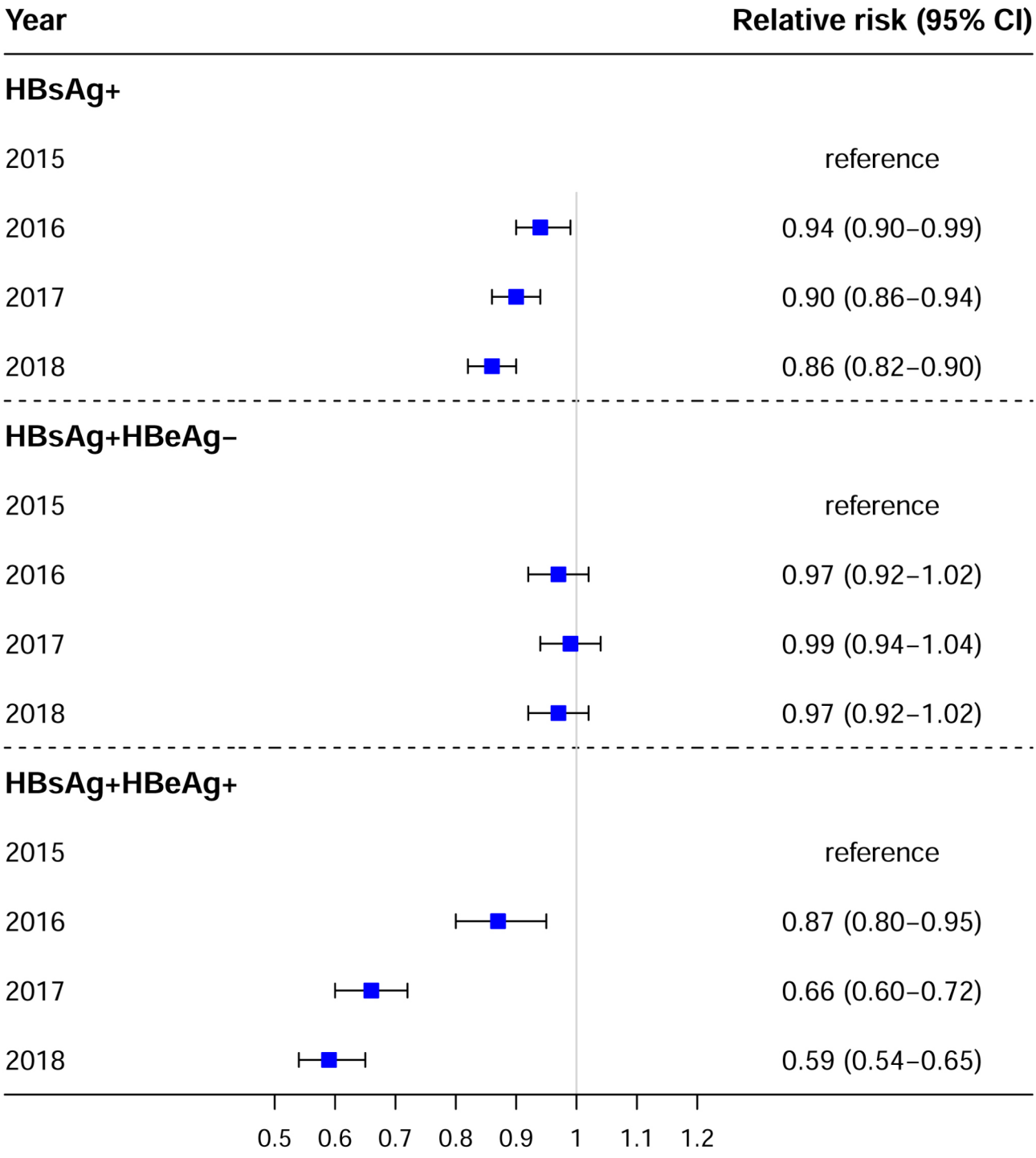

Fig. 3 The forest map of the temporal trend of different maternal HBV seropositivity status. Notes: RR, relative risk

remains high [5]. Our study showed that the prevalence of maternal HBsAg + decreased significantly from 2015 to 2018 (from 10.80 to 9.37%), which was consistent with the report in a national study, which reported a significant decrease from 7.30% in 2015 to 5.44% in 2020 [5]. Besides HBsAg+, our study also showed that the overall prevalence of HBsAg + HBeAg + was 2.57% and decreased in from 2015 to 2018 (from 2.99 to 1.86%). This type of HBV infection status has been under-reported.

As a common liver disease of pregnancy, the prevalence of ICP ranges from 0.2 to 2.5% worldwide [28, 29], and has been estimated at 1.2% in China [30]. Although ICP is a risk factor for several adverse perinatal outcomes, such as PTB, meconium-stained amniotic fluid, and stillbirth

Table 2 Obstetric and neonatal outcomes with respect to HBsAg and hbeag status

Outcomes[a]	(1) HBsAg- HBeAg- *n* (%)	(2) HBsAg+ HBeAg- *n* (%)	(3) HBsAg+ HBeAg+ *n* (%)	cRR		aOR[b]	
				(2) vs. (1)	(3) vs. (1)	(2) vs. (1)	(3) vs. (1)
Obstetric outcomes							
PE	573 (0.32)	50 (0.33)	19 (0.42)	1.02 (0.76–1.36)	1.32 (0.84–2.09)	0.98 (0.73–1.32)	1.48 (0.93–2.34)
GDM	22,756 (12.76)	2177 (14.23)	513 (11.47)	1.11 (1.07–1.16)	0.90 (0.82–0.98)	1.05 (1.00-1.10)	1.04 (0.94–1.14)
ICP	747 (0.42)	217 (1.42)	62 (1.39)	3.38 (2.91–3.94)	3.31 (2.55–4.29)	3.43 (2.94-4.00)	3.44 (2.64–4.48)
Fetal distress	2416 (1.36)	204 (1.33)	78 (1.74)	0.98 (0.85–1.13)	1.29 (1.03–1.61)	1.01 (0.87–1.16)	1.33 (1.05–1.67)
PROM	19,034 (10.68)	1678 (10.97)	411 (9.19)	1.03 (0.98–1.08)	0.86 (0.78–0.95)	1.03 (0.98–1.09)	0.88 (0.79–0.97)
Placenta previa	1068 (0.60)	87 (0.57)	27 (0.60)	0.95 (0.76–1.18)	1.01 (0.69–1.48)	0.83 (0.66–1.04)	1.12 (0.76–1.66)
Caesarean section	55,479 (31.13)	5189 (33.92)	1353 (30.25)	1.09 (1.06–1.12)	0.97 (0.92–1.03)	1.04 (1.01–1.08)	1.05 (0.98–1.12)
PPH within 24 h	1813 (1.38)	153 (1.39)	47 (1.40)	1.01 (0.85–1.19)	1.02 (0.76–1.36)	0.98 (0.82–1.16)	1.06 (0.79–1.43)
Neonatal outcomes							
PTB (< 37 gestational weeks)	8050 (4.52)	716 (4.68)	221 (4.94)	1.04 (0.96–1.12)	1.09 (0.96–1.25)	0.99 (0.92–1.07)	1.16 (1.01–1.33)
LBW (< 2500 g)	6434 (3.61)	506 (3.31)	186 (4.16)	0.92 (0.84-1.00)	1.15 (1.00-1.33)	0.91 (0.83-1.00)	1.16 (1.00-1.35)
Apgar score (< 7) at 1 min	1890 (1.06)	174 (1.14)	59 (1.32)	1.07 (0.92–1.25)	1.24 (0.96–1.61)	1.06 (0.90–1.24)	1.29 (0.99–1.68)
Apgar score (< 7) at 5 min	583 (0.33)	59 (0.39)	19 (0.42)	1.18 (0.90–1.54)	1.30 (0.82–2.05)	1.16 (0.89–1.53)	1.28 (0.80–2.05)
Apgar score (< 7) at 10 min	403 (0.23)	44 (0.29)	16 (0.36)	1.27 (0.93–1.74)	1.58 (0.96–2.61)	1.25 (0.91–1.71)	1.55 (0.93–2.61)

[a] PE: preeclampsia; GDM: gestational diabetes mellitus; ICP: intrahepatic cholestasis pregnancy; PROM: premature rupture of the membranes; PPH: postpartum hemorrhage; PTB: preterm birth; LBW: low birthweight; cRR: crude relative risk; aOR: adjusted odds ratio

[b] Multivariate analyses were adjusted for age, pre-pregnancy BMI, parity, gestations, smoking, drinking, location, paternal age, floating population, ART, and year of delivery

[31], it is a poorly understood complication of pregnancy. Except for genetic mutation, advanced maternal age, and hepatitis C virus infection [32, 33], the impact of HBV infection on ICP has not been adequately studied. Our study showed that the prevalence of ICP was 0.52%, and maternal HBsAg + HBeAg-, HBsAg + HBeAg + can increase the risk of ICP with aORs of 3.44 and 3.41, respectively. In addition, subgroup analyses indicated that the association was stronger in pregnancies with abnormal ALT status (≥ 40 U/L) at the first antenatal visit. These results were consistent with previous studies [9, 34, 35]. For example, Cai et al. reported that maternal HBsAg + HBeAg- and HBsAg + HBeAg + was associated with an increased risk of ICP with aORs of 1.70 (95% CI 1.16-2.49) and 2.96 (95%CI 1.33-6.62), respectively [35]. Similar association was found in a meta-analysis study published in 2020 that included four studies and reported a pooled OR for maternal HBsAg + of 1.68 (95%CI 1.43–1.97) [8].

Specifically, our study indicated that the risk of developing fetal distress was higher in pregnant women with HBsAg + HBeAg + status, reflecting hypoxia. Under the influence of HBV (i.e., causing placental vascular lesions, endothelial cell swelling, luminal narrowing), the placenta may suffer from the problem of respiratory, metabolic and nutritional insufficiency, which may lead to inadequate oxygen supply [36, 37]. However, this result was controversial in previous studies. For example, Cai et al. [35] and Wu et al. [36] did not find a significant association between the HBeAg-carrier status in pregnant women and fetal distress, but Wan et al. [38] observed an increased risk of fetal distress (aOR = 1.40, 95%CI 1.09–1.78) in the maternal HBsAg carrier group. This inconsistency may be attributed to the sample size. In particular, the number of pregnant women with HBsAg + HBeAg + in these studies was less than 500.

Several studies have investigated the impact of maternal HBV infection on PE, GDM, PTB, LBW and so on [9, 35, 39–41]. After controlling for potential confounders, our results showed that maternal HBsAg + HBeAg + slightly increased the risk of PE, GDM, PTB and LBW, but some of them were not statistically significant and were partially inconsistent with previous studies. For example, our results showed that the incidence of GDM was comparable among HBsAg-HBeAg-, HBsAg + HBeAg-, and HBsAg + HBeAg + groups. However, by including 23 cohort studies involving more than 3 million pregnant women, a systematic review concluded that maternal HBsAg positivity has a moderate effect on an increased risk of GDM with pooled aOR of 1.47 (95%CI 1.22–1.76) [7]. The association between maternal HBV infection and PTB has long been debated [11, 39–42]. Our study showed that maternal HBsAg + HBeAg + slightly increased the risk of PTB (< 37 gestational weeks) with an aOR of 1.16 (95%CI 1.01–1.33), which was consistent with several previous studies [39, 40, 42]. However, an updated meta-analysis published at 2017 reported that the risk of PTB was significantly increased by 16% and 21% in HBsAg + HBeAg- and HBsAg + HBeAg + pregnant women compared with uninfected pregnant women [41]. Furthermore, our results suggested that maternal HBV infection, including HBsAg + HBeAg-, and

Table 3 Subgroup analyses by ALT group with respect to HBsAg and hbeag status

Outcomes	HBsAg + HBeAg-		HBsAg + HBeAg+	
	Normal liver enzyme	Abnormal liver enzyme	Normal liver enzyme	Abnormal liver enzyme
Obstetric outcomes				
PE	0.95 (0.70–1.30)	1.24 (0.71–2.15)	1.16 (0.41–3.31)	2.47 (1.01–6.01)
GDM	1.04 (0.99–1.10)	1.02 (0.91–1.13)	1.14 (0.94–1.37)	1.07 (0.85–1.34)
ICP	3.34 (2.84–3.93)	2.65 (1.90–3.68)	4.26 (2.52–7.20)	5.04 (3.00-8.47)
Fetal distress	1.01 (0.87–1.18)	1.38 (1.07–1.76)	0.80 (0.40–1.60)	1.20 (0.64–2.27)
PROM	1.04 (0.98–1.10)	0.89 (0.79-1.00)	0.93 (0.74–1.19)	0.84 (0.64–1.10)
Placenta previa	0.79 (0.62-1.00)	0.94 (0.59–1.51)	1.16 (0.55–2.47)	1.20 (0.47–3.06)
Caesarean section	1.04 (1.00-1.08)	1.06 (0.99–1.14)	0.99 (0.85–1.15)	0.85 (0.71–1.01)
PPH within 24 h	0.99 (0.83–1.18)	1.07 (0.78–1.48)	0.82 (0.41–1.65)	0.83 (0.38–1.83)
Neonatal outcomes				
PTB (< 37 gestational weeks)	0.96 (0.88–1.04)	1.14 (0.98–1.33)	1.20 (0.90–1.60)	1.14 (0.81–1.60)
LBW (< 2500 g)	0.88 (0.80–0.97)	1.10 (0.92–1.30)	1.03 (0.72–1.48)	1.47 (1.03–2.08)
Apgar score (< 7) at 1 min	1.01 (0.85–1.19)	1.29 (0.97–1.72)	1.65 (0.96–2.84)	1.31 (0.65–2.65)
Apgar score (< 7) at 5 min	1.11 (0.83–1.48)	1.29 (0.77–2.16)	1.41 (0.54–3.68)	0.92 (0.22–3.94)
Apgar score (< 7) at 10 min	1.18 (0.84–1.66)	1.52 (0.85–2.71)	1.29 (0.45–3.73)	1.01 (0.24–4.33)

[a] PE: preeclampsia; GDM: gestational diabetes mellitus; ICP: intrahepatic cholestasis pregnancy; PROM: premature rupture of the membranes; PPH: postpartum hemorrhage; PTB: preterm birth; LBW: low birthweight

[b] Multivariate analyses were adjusted for age, Pre-pregnancy BMI, parity, gestation, smoking, drinking, location, paternal age, floating population, ART, and year of delivery

HBsAg + HBeAg+, may not increase the risk of LBW, which was consistent with previous studies [16, 36].

In this study, we explored whether the impact of maternal HBV infection was differed according to ALT status at the first antenatal visit, which has rarely been investigated [43, 44]. Our results indicate that the impact of maternal HBV infection on obstetric and neonatal outcomes was potentially more severe in pregnancies with abnormal ALT than in these with normal ALT. For example, maternal HBsAg + HBeAg + increased the risk of ICP with an aOR of 5.04 in in the abnormal ALT group, but with an aOR of 2.65 in the normal ALT group. In addition, compared with pregnancies with normal ALT, maternal HBsAg + HBeAg + in the abnormal ALT group also increased the risk of pre-eclampsia, LBW.

Previous studies have suggested that the underlying mechanisms between maternal HBV infection and adverse pregnancy outcomes involved direct viral effects, immune dysregulation, chronic inflammation, metabolic disturbances, and placental dysfunction [45–48]. For example, for maternal HBsAg/HBeAg co-seropositivity, HBV replication can impair hepatocyte function, resulting in bile acid accumulation. Additionally, immune activation and systemic inflammation, marked by elevated tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6), exacerbate liver injury and disrupt bile acid metabolism, thereby increasing the risk of ICP. Similarly, the systemic inflammation may stimulate myometrial contractility, leading to premature uterine contractions and cervical ripening, thereby increasing the risk of PTB. Furthermore, HBV infection induced oxidative stress and inflammatory cytokines may weaken fetal membranes, making them more susceptible to premature rupture and preterm delivery. HBV infection can also cause chorionic vascular lesions and placental dysfunction, contributing to fetal distress and other complications. Overall, the impact of maternal HBV infection on adverse pregnancy outcomes is the result of a combination of the underlying mechanisms mentioned above.

Implication for obstetric practice

Given the impact of maternal HBV infection on adverse pregnancy outcomes, routine HBV screening during pre-pregnancy or in early pregnancy should be considered in obstetric clinical practice, which is critical for identifying women at risk. For HBV-positive pregnant women, enhanced obstetric care, such as monitoring of liver function and viral load throughout pregnancy or antiviral therapy for women with high HBV viral loads, is urgently needed to reduce the risk of adverse pregnancy outcomes. These results suggest that, in order to provide better pregnancy care, in addition to HBV infection, clinicians also need to pay attention to the status of liver function in clinical practice [49, 50].

Strengths and limitations

The current study had two main major strengths. First, based on a population-based pregnancy registry, this study included a large number of pregnancies over a long period of time, which enhanced the representativeness of this study. Second, in addition to HBsAg serostatus, we further investigated the impact of HBsAg/HBeAg co-seropositivity (representing HBV activity) on pregnancy outcomes. A sufficient number of HBsAg/HBeAg co-seropositive pregnant women were enrolled in this study, which is relatively large among similar studies. Further sensitivity and subgroup analyses were conducted to test the robustness of our findings. On the other hand, the viral load of the HBV in HBV-seropositive pregnant

women was not available, which was the main limitation of this study. The data included in this study was only up to March 2019, which could not reflect the situation and impact of maternal HBV infection in recent years of China, was another limitation of this study.

Conclusions

The prevalence of HBsAg seropositivity and HBsAg/HBeAg coseropositivity were high in Chinese pregnant women, and both decreased significantly over time. On the other hand, this study indicated that maternal HBsAg/HBeAg co-seropositivity increased the risk of ICP, fetal distress and preterm birth, and the association was may be more pronounced in pregnancies with abnormal ALT.

Abbreviations

HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
GDM	Gestational diabetes mellitus
ICP	Intrahepatic cholestasis of pregnancy
PE	Pre-eclampsia
PTB	Preterm birth
HBeAg	Hepatitis B e antigen
ALT	Alanine aminotransferase
ICD-10	International Classification of Diseases 10th Revision
HBsAg+	HBsAg seropositive
HBsAg−	HBsAg seronegative
PROM	Premature rupture of membranes
LBW	Low birthweight
BMI	Body mass index
ART	Assisted reproductive therapy
cRR	Crude relative risk
CI	Confidence interval
aOR	Adjusted odds ratio
PS	Propensity score
ASD	Absolute standardized difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07410-9.

Supplementary Material 1

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Not applicable.

Author contributions

KZ and YQX: data analysis and manuscript preparation; SYH, CRL and PZ: data analysis; JG, WQW, GHY, YYQ, QYZ, MLC and JWC: data collection, cleaning and standardization; SX, JT and YQX, conceptualization and revised the manuscript.

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Data availability

The datasets analyzed in the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of West China Hospital (2019−825) in Sichuan, China. The requirement for informed consent for data collection was waived because of the retrospective nature of the study.

Consent for publication

The requirement for informed consent for data collection was waived because of the retrospective nature of the study.

Competing interests

The authors declare no competing interests.

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