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The impact of gestational diabetes mellitus on pregnancy outcomes in women with hepatitis B virus: a retrospective cohort study

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Abstract

Background To investigate the impact of hepatitis B virus carriers combined with gestational diabetes mellitus (HBVC & GDM) on pregnancy outcomes in a cohort of pregnant women from Hangzhou, China.

Methods We set-up a retrospective cohort study to analyze data from 12,815 pregnant women who delivered in three Hangzhou tertiary hospitals between 2015 and 2022. Four groups were created according to the presence of HBV and/or GDM as follows: a non-HBVC & GDM group ($n=5,323$), a HBVC group ($n=5,508$), a GDM group ($n=919$) and a HBVC & GDM group ($n=1,065$). Univariate analysis was carried out with the Mann-Whitney U test or the chi-squared test; $P<0.05$ was used as the screening criterion. Multivariate logistic regression analysis was then performed to investigate the effects of each of the relevant confounders on HBVC, GDM and HBVC & GDM. After adjusting for potential confounding variables, the results were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs), with $P<0.05$ considered as statistically significant.

Results The incidence of HBVC & GDM among pregnant women in Hangzhou, China was 0.96% (95% CI: 0.90–1.02%). The median maternal age of the pregnant women in the HBVC & GDM group was significantly higher than that in the HBVC, GDM and control groups (31.00 vs. 30.00, 30.00, 29.00, $P<0.001$). The proportions of low birth weight (4.0% vs. 3.8%, 3.4%, 3.4%) and macrosomia (6.8% vs. 5.4%, 3.7%, 4.3%) in the HBVC & GDM group were significantly higher than in the other three groups, with significant differences between groups ($P<0.05$). Multivariate logistic analysis revealed a progressive increase in risk values with increasing maternal age in the HBVC & GDM group ($OR_{\geq 25\&<30}=1.632$, $OR_{\geq 30\&<35}=3.257$, and $OR_{\geq 35}=5.611$). In addition, the carriage risk of pregnant women over 35 years was approximately two-fold higher than that in the HBVC and GDM groups (5.611/2.251 and 5.611/3.130), respectively. The risk value increased progressively with increasing gravidity ($OR_2=1.364$ and $OR_{\geq 3}=1.765$). The risk of a floating population was as follows: Zhejiang-registered but non-Hangzhou (OR = 2.246) > outside Zhejiang Province (OR = 1.953) > Hangzhou-local (OR = 1). HBVC & GDM also increased the risk of intrahepatic cholestasis of pregnancy (ICP) (OR = 3.143, 95%

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CI: 2.223–4.445), pre-eclampsia (PE) (OR = 2.017, 95%CI: 1.315–3.095), macrosomia (OR = 1.548, 95% CI: 1.161–2.064), assisted vaginal delivery (OR = 1.501, 95% CI: 1.185–1.901) and Caesarean section (OR = 1.258, 95% CI: 1.035–1.528). HBVC & GDM also reduced the chance of delayed labor (gestational age > 41 week, OR = 0.217, 95% CI: 0.126–0.374).

Conclusions The incidence rates of HBVC and GDM among pregnant women in Hangzhou City are relatively high. When HBVC & GDM co-existed, the risks of ICP, PE and macrosomia increased significantly. The risk of HBVC & GDM tended to increase progressively with increasing maternal age and increasing gravidity. For pregnant women of advanced age, those with increasing gravidity or those in a floating population, it is important to enhance educational awareness related to HBV, GDM, and especially HBVC & GDM in order to provide personalized antenatal medical care and reduce the risk of adverse pregnancy outcomes.

Keywords Hepatitis B virus, Pregnant women, Gestational diabetes mellitus, Hepatitis B virus carriers combined with gestational diabetes mellitus, Intrahepatic cholestasis of pregnancy, Pre-eclampsia, Odds ratios

Background

Hepatitis B virus (HBV) infection is a common public health problem worldwide. In 2019, the estimated global and all-age prevalence of chronic HBV infection was 4.1% [95% uncertainty interval (UI): 3.7–4.5], corresponding to 316 million (284–351) infected people [1]. Of these, the prevalence of all-age groups in China was reported to be 7.8% (95% UI: 7.0–8.7), thus representing moderately endemic area for HBV. The vertical transmission of HBV from infected mothers to their fetuses or newborns in the peripartum period remains a major source of perpetuating the reservoir of chronically infected individuals globally. During the period between 2016 and 2021, the prevalence of HBV in Chinese pregnant women was 6.64% [95% confidence interval (CI): 5.72–7.57%]. Among hepatitis B surface antigen (HBsAg) positive pregnant women, the rate of hepatitis B e-antigen (HBeAg) positivity is 25.80% (95% CI: 22.26–29.69%) and therefore highly infectious [2]. Physiological or pathological changes occurring in the mother during pregnancy may cause an increase in HBV replication, thus promoting the activity of hepatitis B. Research has found that pregnant women who are also carrier of HBV have an elevated risk of pregnancy complications and adverse pregnancy outcomes, including gestational diabetes mellitus (GDM) [3, 4].

GDM is a common complication of pregnancy defined as an abnormality of glucose metabolism detected for the first time in pregnancy. The 2021 Global and Regional GDM Prevalence Report indicated that the pooled global standardized prevalence of GDM was 14.0% while the regional prevalence ranged from 7.1 to 27.6% [5]. The 2019 survey of GDM in mainland China revealed that the total incidence of GDM in pregnant women was 14.8% (95% CI: 12.8–16.7%), which was higher than the global average [6]. The pathogenesis of GDM is similar to that of type 2 diabetes mellitus. The primary mechanisms include increased insulin resistance and pancreatic β-cell dysfunction, as well as a multitude of other factors, including adipokines, inflammatory mediators, and placental function [7–9]. GDM is associated with an increased rate of adverse pregnancy outcomes, including maternal complications such as preterm delivery, polyhydramnios, pre-eclampsia (PE) and elective Caesarean section (CS), along with neonatal complications, including admission to a neonatal intensive care unit, hypoglycemia, jaundice and respiratory distress syndrome [10]. A higher probability of developing obesity, glucose metabolism irregularities and high blood pressure has been reported for offspring born to mothers with GDM [11].

The liver is a target organ for HBV infection, as well as an important site for glucose metabolism and insulin resistance. Thus, there exists a strong association between HBV infection and GDM. Mechanistically, this may involve the occurrence of increased insulin resistance and the promotion of hepatic gluconeogenesis by HBV [12, 13]. Furthermore, the onset of HBV infection leads to increased levels of inflammatory factors in the body, including IL-2, tumor necrosis factor and ferritin, thereby fostering the progression towards GDM [14]. In consideration of the high rate of combined HBV infection and concomitant GDM within the population of pregnant women in China, we conducted a retrospective cohort study in order to investigate the impact of concomitant GDM status on pregnancy outcomes in a population of pregnant women with hepatitis B virus infection (HBVC & GDM) in Hangzhou, China.

Methods

Study population

We analyzed data from the content shown on the front page of the electronic medical records of 110,827 pregnant women admitted to three tertiary hospitals in Hangzhou between January 2015 and December 2022: Hangzhou Women's Hospital (64,618 cases), Hangzhou Normal University Affiliated Hospital (14,484 cases) and Hangzhou Linping District Maternal and Child Health Hospital (45,502 cases). The dataset included maternal characteristics such as name, age, gravidity, parity and diagnosis at discharge, as well as neonatal demographic information, including sex, birth weight, length,

and Apgar score. Following the consideration of exclusion criteria, 12,815 pregnant women were included and divided into four groups: (1) no HBV infection and no GDM (the non-HBVC & GDM group, $n = 5323$), (2) HBV carriers only (the HBVC group, $n = 5{,}508$), (3) GDM only (the GDM group, $n = 919$), and (4) both HBV carriers and GDM (the HBVC & GDM group, $n = 1{,}065$) (Fig. 1). All pregnant women underwent a 75 g oral glucose tolerance

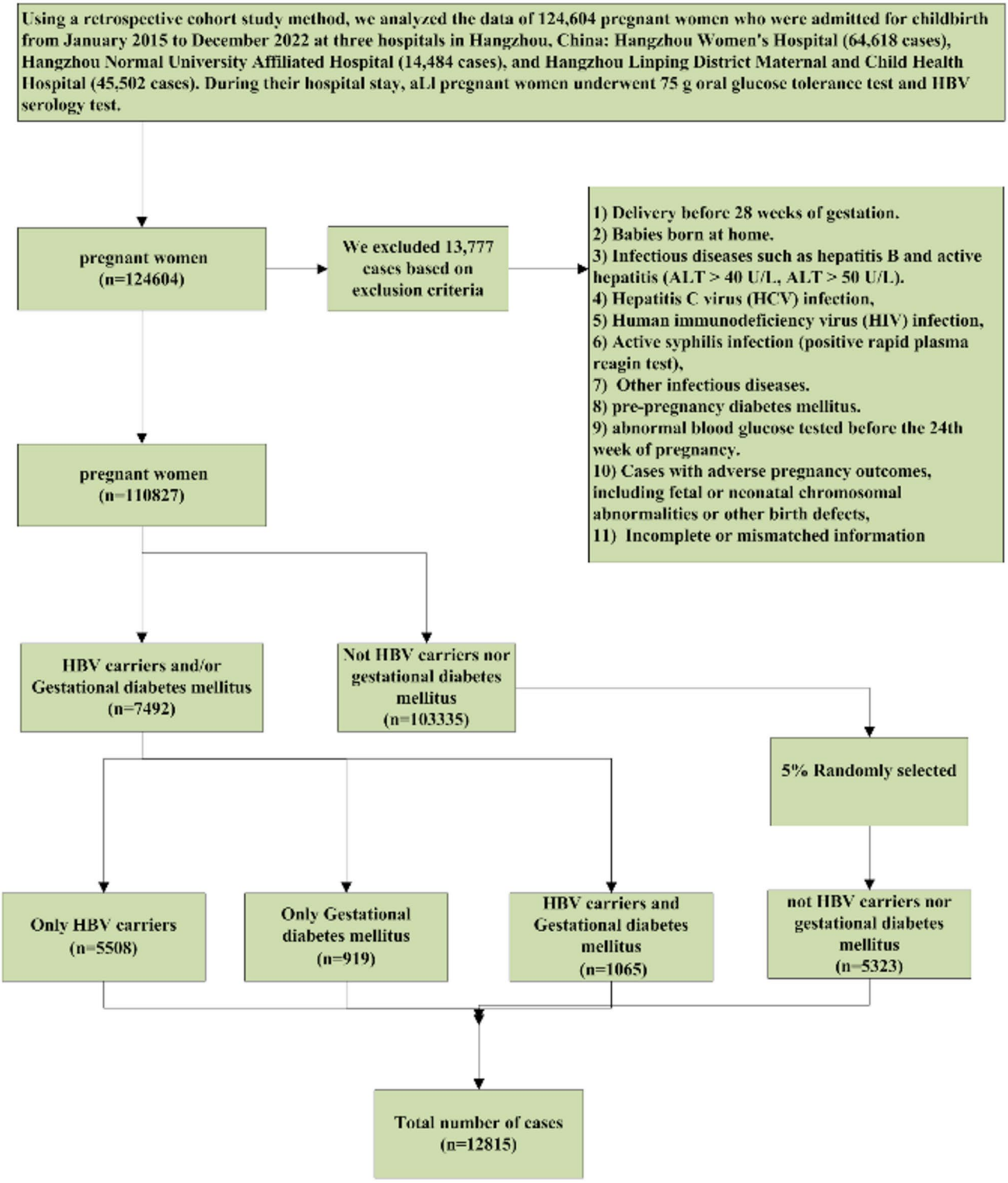

Fig. 1 Flow chart showing the selection of 12,815 pregnant women for this study. HBV: hepatitis B virus; ALT: serum alanine aminotransferase; AST: aspartate aminotransferase

test (OGTT), hepatitis B serology, medical and laboratory tests and received medical prescriptions during antenatal check-ups. These check-ups were recorded in the hospital's medical records and the subjects were followed up for 42 days postpartum. The Medical Ethics Committee at Hangzhou Women's Hospital granted approval for this study [(2024) Medical Review A No. (119)]. As this study was of a retrospective nature, the information regarding the subjects' privacy was omitted from data processing. Consequently, the hospital medical ethics committee waived the need for informed consent.

Diagnosis and exclusion criteria

GDM diagnostic criteria

Women who were not diagnosed with diabetes mellitus pre-pregnancy and at their first maternal screening test were diagnosed with GDM when they underwent a 75 g OGTT between 24 and 28 weeks of gestation and met or exceeded any of the following criteria: a fasting plasma glucose level > 5.1 mmol/L and/or a 1-h plasma glucose level > 10 mmol/L and/or a 2-h plasma glucose level > 8.5 mmol/L [15]. These diagnostic criteria were consistent with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria [16].

Diagnostic criteria for HBV carriers

Serum HBsAg positive for > 6 months, HBeAg-positive or HBeAg-negative with anti-HBe-positivity, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal limits (three consecutive follow-up visits within 1 year, each at least 3 months apart), and no abnormalities on liver histological examination or minimal lesions [17].

Exclusion criteria

Delivery before 28 weeks of gestation, babies born at home, infectious diseases such as hepatitis B and active hepatitis (ALT > 40 U/L, ALT > 50 U/L), hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, active syphilis infection (positive rapid plasma reagin test), other infectious diseases, pre-pregnancy diabetes mellitus, abnormal blood glucose tested before the 24th week of pregnancy, cases with adverse pregnancy outcomes, including fetal or neonatal chromosomal abnormalities or other congenital anomalies, and cases with incomplete or mismatched information (Fig. 1).

Pregnancy complications and pregnancy outcomes

Pregnancy complications

Hypertension disorders of pregnancy (HDP) were divided into gestational hypertension (GH) and preeclampsia (PE). GH was defined as HDP with a negative urine protein test. PE was defined as pregnancy-induced hypertension in conjunction with the occurrence of proteinuria, or dysfunction in at least one organ, such as the kidneys, liver, nervous system, blood system and placenta [18]. The diagnostic criteria for intrahepatic cholestasis of pregnancy (ICP) were as follows: the presence of otherwise unexplained pruritus and a total bile acid (TBA) level of ≥ 10 μmol/L or a normal TBA level with abnormal liver functionality [19]. Oligohydramnios referred to an amniotic fluid index (AFI) < 5 cm, whereas polyhydramnios was characterized by an AFI > 25 cm or a vertical pocket measuring at least 8 cm. Uterine scars were defined as postoperative uterine scars, including Caesarean section scars. Premature rupture of membranes (PROM) was defined as the sudden onset of vaginal fluid, an elevated vaginal fluid pH (pH ≥ 6.5) or amniotic crystals on vaginal fluid smears [20]. Placental abruption referred to the partial or complete separation of a normally positioned placenta from the uterine wall before the delivery of the fetus after 20 weeks of gestation. Its clinical features included abdominal pain, vaginal bleeding, uterine contractions, fetal distress, and abnormal maternal vital signs [21]. Placenta previa (lower edge of the placenta adjacent to or over the internal os cervix). Fetal distress was defined by comprehensive life-threatening symptoms such as an abnormal fetal heart rate due to fetal hypoxia in the third trimester of pregnancy. Postpartum hemorrhage was defined as an estimated blood loss ≥ 500 mL after vaginal delivery or ≥ 1,000 mL after Caesarean section. Prenatal hemorrhage was defined as vaginal bleeding after 28 weeks of gestation. Anemia was defined as a hemoglobin level < 110 g/L [22]. Hyperthyroidism (the increased synthesis and secretion of thyroxine hormone) and hypothyroidism (the reduced synthesis and secretion of thyroid hormone). Hyperlipidemia was defined as a serum total triglyceride level of 220 mg/dL (2.49 mmol/L) or a serum total cholesterol level of 240 mg/dL (6.24 mmol/L).

Pregnancy outcomes

The mode of delivery was divided into vaginal delivery, forceps-assisted vaginal delivery, and Caesarean section. Gestational age was divided into four groups as follows: <34 weeks, 34–36 weeks, 37–41 weeks and > 41 weeks. Fetal growth restriction (FGR) was defined as a level of fetal growth that falls below its genetic potential due to maternal, fetal, placental and other pathological factors, with an ultrasound-estimated weight or abdominal circumference below the 10th percentile for the corresponding gestational age [23]. Low birth weight was defined as a birth weight < 2,500 g, macrosomia was defined as a birthweight > 4,000 g, and normal birth weight was defined as 2,500–4,000 g. Household registration was categorized as: (1) Hangzhou-local, (2) Zhejiang-registered but non-Hangzhou (intra-provincial migrants), and (3) outside Zhejiang Province (extra-provincial migrants).

Categories 2 and 3 were collectively classified as a floating population.

All of the above pregnancy complications and pregnancy outcomes were obtained from clinical data and diagnosed by obstetricians according to Chinese guidelines.

Statistics and analysis

Statistical analyses were performed using IBM-SPSS, version 24.0 Statistics (IBM-SPSS, Chicago, USA). The one-sample Kolmogorov-Smirnov test was used to assess the normality of quantitative data. The raw data exhibited a skewed distribution. Therefore, the Mann-Whitney U test or the Kruskal-Wallis H test was applied between groups and data were expressed as medians and interquartile ranges (IQRs). Univariate analysis was performed on qualitative data by Pearson's x^2test or the continuity correction x^2 test. Following univariate analysis, we applied significant variables ($P<0.05$) as the standard to include in binary multivariate analysis. Multivariate logistic regression analysis was performed with the following covariates: household register, maternal age, days of hospitalization, gravidity, parity, infant weight, mode of delivery, gestational age at delivery, HDP, ICP, hyperlipidemia, uterine scar, prenatal anemia, prenatal hemorrhage and PROM. After adjusting for potential confounding variables, the results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs), with $P<0.05$ considered as statistically significant.

Results

Basic demographic data of the maternal groups

The dataset comprised 12,815 pregnant women, with 5,323 cases in the non-HBVC & GDM group, 5,508 cases in the HBVC group, 919 cases in the GDM group and 1,065 cases in the HBVC & GDM group, in the following proportions (41.54%, 42.98%, 7.17% and 8.31%, respectively). The incidences of HBVC, GDM and HBVC & GDM were 4.97% (95% CI: 4.84–5.10%, 5,508/110,827), 0.83% (95% CI: 0.78–0.88%, 919/110,827), and 0.96% (95% CI: 0.90–1.02%, 1,065/110,827). The median maternal age of pregnant women in the HBVC & GDM group was significantly higher than in the HBVC, GDM and control groups (31.00 (29.00–35.00) years vs. 30.00 (27.00–33.00) years, 30.00 (27.00–33.00) years, 29.00 (26.00–31.00) years, $P<0.001$). There were significant differences between the four groups ($P<0.001$) in terms of maternal domicile, days of hospitalization, gravidity, parity and gestational age at delivery, as shown in Table 1.

Basic demographics of the neonatal population

As demonstrated in Table 2, the proportions of low birth weight (4.0% vs. 3.8%, 3.4%, 3.4%) and macrosomia (6.8% vs. 5.4%, 3.7%, 4.3%) in the HBVC & GDM group were significantly higher than in the GDM, HBVC, and control groups, with statistically significant differences between groups ($P<0.05$). Compared with the control group, the absolute risk increase (ARI) for macrosomia in the HBVC & GDM, GDM, and HBVC groups were +2.5%, +1.1%, and −0.8%, respectively, while the ARIs for low birth weight were +0.6%, +0.4%, and 0%, respectively. There was no significant difference between the four groups in terms of neonatal sex and height ($P>0.05$).

Univariate analysis of influencing factors

Analysis revealed statistically significant differences between the groups in terms of maternal domicile, maternal age, days of hospitalization, gravidity, parity, gestational age at delivery, infant weight, mode of delivery, HDP, ICP, hyperlipidemia, thyroid function, uterine scarring, PROM, antenatal anemia, and antepartum hemorrhage (all, $P<0.05$), as shown in Tables 1, 2 and 3.

Multivariate logistic analysis of each variable

Multivariate logistic analyses demonstrated that the risk values increased progressively with increasing maternal age in the HBVC group ($OR_{\geq 25\&<30}$=1.363, $OR_{\geq 30\&<35}$=1.684, and $OR_{\geq 35}$=2.251), the GDM group ($OR_{\geq 25\&<30}$=1.396, $OR_{\geq 30\&<35}$=1.945, and $OR_{\geq 35}$=3.130), and the HBVC & GDM group ($OR_{\geq 25\&<30}$=1.632, $OR_{\geq 30\&<35}$=3.257, and $OR_{\geq 35}$=5.611), as illustrated in Fig. 2A. Furthermore, the risk of carriage in the HBVC & GDM group at ≥35 years-of-age was two-fold higher than that in the HBVC and GDM groups, respectively. The HBVC group (OR_2 = 1.156 and $OR_{\geq 3}$=1.356) and the HBVC & GDM group (OR_2 = 1.364 and $OR_{\geq 3}$=1.765) had progressively higher risk values with increasing gravidity, as shown in Fig. 2B; Table 4. The risk changes for the mobile population in the GDM group and the HBVC & GDM group were as follows: Zhejiang-registered but non-Hangzhou (OR_{GDM}=1.818 and $OR_{HBVC\ \&GDM}$=2.246) > outside Zhejiang Province (OR_{GDM}=1.228 and $OR_{HBVC\ \&\ GDM}$=1.953) > Hangzhou-local (OR = 1). The risk changes in the HBVC group were as follows: outside Zhejiang Province (OR = 1.524) > Zhejiang-registered but non-Hangzhou (OR = 1.346) > Hangzhou-local (OR = 1).

The HBVC & GDM group exhibited an elevated risk of ICP (OR = 3.143, 95% CI: 2.223–4.445), PE (OR = 2.017, 95% CI: 1.315–3.095), macrosomia (OR = 1.548, 95% CI: 1.161–2.064), assisted vaginal delivery (OR = 1.501, 95% CI:1.185–1.901) and Caesarean section (OR = 1.258, 95%CI:1.035–1.528) (P for all <0.05). However, the HBVC & GDM group exhibited a reduced risk of gestational age > 41 weeks (OR = 0.217, 95% CI: 0.126–0.374, $P<0.05$).

The HBVC group exhibited an increased risk of ICP (OR = 2.666, 95% CI: 2.068–3.435), uterine scar

Table 1 Basic demographic data of the maternal groups, N (%)

Variables	Number of pregnant women (%)	Groups				Z/x^2	*P* value
		non-HBVC & GDM (*n* = 5323)	HBVC (*n* = 5508)	GDM (*n* = 919)	HBVC & GDM (*n* = 1065)		
Household registration						202.181	< 0.001
outside Zhejiang Province	4199 (32.8)	1471 (27.6)	2029 (36.8)	266 (28.9)	433 (40.7)		
Zhejiang-registered but non-Hangzhou	816 (6.4)	282 (5.3)	350 (6.4)	81 (8.8)	103 (9.7)		
Hangzhou-local	7800 (60.9)	3570 (67.1)	3129 (56.8)	572 (62.2)	529 (49.7)		
Maternal age (years), M (IQR)	29.00 (27.00–32.00)	29.00 (26.00–31.00)	30.00 (27.00–33.00)	30.00 (27.00–33.00)	31.00 (29.00–35.00)	434.919	< 0.001
Maternal age (years)						426.443	< 0.001
≥ 25&<30	5235 (40.9)	2444 (45.9)	2154 (39.1)	349 (38.0)	288 (27.0)		
≥ 30&<35	4403 (34.4)	1663 (31.2)	1968 (35.7)	330 (35.9)	442 (41.5)		
≥ 35	1813 (14.1)	495 (9.3)	874 (15.9)	166 (18.1)	278 (26.1)		
< 25	1364 (10.6)	721 (13.5)	512 (9.3)	74 (8.1)	57 (5.4)		
Hospital day (days), M (IQR)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	5.00 (4.00–6.00)	72.185	< 0.001
Hospital day (days)						17.395	0.001
> 7	1020 (8.0)	400 (7.5)	423 (7.7)	78 (8.5)	119 (11.2)		
≤ 7	11,795 (92.0)	4923 (92.5)	5085 (92.3)	841 (91.5)	946 (88.8)		
Gravidity, M (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (2.00–3.00)	362.310	< 0.001
Gravidity						349.928	< 0.001
2	3835 (29.9)	1600 (30.1)	1664 (30.2)	266 (28.9)	305 (28.6)		
≥ 3	4583 (37.6)	1514 (28.4)	2228 (40.5)	309 (33.6)	532 (50.0)		
≤ 1	4397 (34.3)	2209 (41.5)	1616 (29.3)	344 (37.4)	228 (21.4)		
Parity, M (IQR)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	2.00 (1.00–2.00)	1.00 (1.00–2.00)	2.00 (1.00–2.00)	312.193	< 0.001
Parity						312.965	< 0.001
2	5718 (44.6)	1995 (37.5)	2729 (49.5)	389 (42.3)	605 (56.8)		
≥ 3	511 (4.0)	148 (2.8)	267 (4.8)	36 (3.9)	60 (5.6)		
≤ 1	6586 (51.4)	3180 (59.7)	2512 (45.6)	494 (53.8)	400 (37.6)		
Gestational age (weeks), M (IQR)	39.00 (38.00–40.00)	39.00 (38.00–40.00)	39.00 (38.00–40.00)	39.00 (38.00–39.00)	39.00 (38.00–39.00)	108.973	< 0.001
Gestational age (weeks)						114.869	< 0.001
< 34	131 (1.0)	47 (0.9)	54 (1.0)	14 (1.5)	16 (1.5)		
34–36	648 (5.1)	235 (4.4)	282 (5.1)	58 (6.3)	73 (6.9)		
> 41	794 (6.2)	404 (7.6)	363 (6.6)	13 (1.4)	14 (1.3)		
37–41	11,242 (87.7)	4637 (87.1)	4809 (87.3)	834 (90.8)	962 (90.3)		

HBVC: hepatitis B carriers; GDM: gestational diabetes mellitus; HBVC & GDM: both hepatitis B virus carriers and gestational diabetes mellitus; non-HBVC & GDM: no hepatitis B carriers and no gestational diabetes; M: Median; IQR: Interquartile Range

(OR = 1.202, 95% CI: 1.042–1.387) and prenatal anemia (OR = 1.173, 95% CI: 1.071–1.286) (*P* for all < 0.05). However, the HBVC group had a reduced risk of hyperlipidemia (OR = 0.619, 95% CI: 0.484–0.793), PROM at term (OR = 0.643, 95% CI: 0.473–0.875) and Caesarean section (OR = 0.880, 95% CI: 0.789–0.981) (*P* for all < 0.05).

The following risk factors were also observed in the GDM group: gestational age at delivery < 34 week (OR = 2.211, 95% CI: 1.038–4.712), hyperlipidemia (OR = 2.119, 95%CI: 1.570–2.858), antepartum hemorrhage (OR = 2.113, 95% CI: 1.222–3.654), PE (OR = 1.762, 95% CI: 1.101–2.822), GH (OR = 1.515, 95% CI: 1.025–2.239), gestational age at delivery 34 – 36 weeks (OR = 1.397, 95% CI: 1.004–1.944) (*P* for all < 0.05). In contrast, the GDM group exhibited risk-reducing factors, including a gestational age > 41 weeks (OR = 0.202, 95% CI: 0.115–0.355) and antepartum anemia (OR = 0.771, 95% CI: 0.642–0.927) (all *P* < 0.05), as shown in Table 4.

Discussion

GDM is a common metabolic disorder during pregnancy. HBV infection is not uncommon in pregnant women, and mother-to-child vertical transmission is a major route of HBV infection. The two conditions interact through mechanisms such as insulin resistance and inflammatory responses. Our study found that the incidences of HBVC, GDM and HBVC & GDM in Hangzhou, China were 4.97% (95% CI: 4.84–5.10%), 0.83% (95% CI: 0.7–0.88%) and 0.96% (95% CI: 0.90–1.02%), respectively. In addition, there was an elevated risk of ICP, PE and macrosomia in pregnant women within the HBVC & GDM group. The risk of HBVC & GDM in pregnant women was associated

Table 2 Basic demographics of the neonatal population, N (%)

Variables	Number of pregnant women (%)	Groups				Z/x^2	*P* value
		non-HBVC & GDM (*n* = 5323)	HBVC (*n* = 5508)	GDM (*n* = 919)	HBVC & GDM (*n* = 1065)		
Infant gender						3.95	0.267
Female	6753 (52.7)	2823 (53.0)	2866 (52.0)	477 (51.9)	587 (55.1)		
Male	6062 (47.3)	2500 (47.0)	2642 (48.0)	442 (48.1)	478 (44.9)		
Infant length (cm), M (IQR)	50.00 (50.00–50.00)	50.00 (50.00–50.00)	50.00 (50.00–50.00)	50.00 (50.00–50.00)	50.00 (50.00–50.00)	4.198	0.241
Infant length (cm)						26.764	0.187
< 47	263 (2.1)	98 (1.8)	107 (1.9)	28 (3.0)	30 (2.8)		
≥ 50	1522 (11.9)	566 (10.6)	718 (13.0)	99 (10.8)	139 (13.1)		
47–50	11,030 (86.1)	4659 (87.5)	4683 (85.0)	792 (86.2)	896 (84.1)		
Infant weight (g), M (IQR)	3300 (3000–3550)	3300 (3000–3550)	3270 (3000–3550)	3300 (3020–3600)	3300 (3015–3600)	14.213	0.003
Infant weight (g)						25.759	< 0.001
< 2500	447 (3.5)	179 (3.4)	190 (3.4)	35 (3.8)	43 (4.0)		
> 4000	554 (4.3)	230 (4.3)	202 (3.7)	50 (5.4)	72 (6.8)		
2500–4000	11,814 (92.2)	4914 (92.3)	5116 (92.9)	834 (90.8)	950 (89.2)		

HBVC: hepatitis B carriers; GDM: gestational diabetes mellitus; HBVC & GDM: both hepatitis B virus carriers and gestational diabetes mellitus; non-HBVC & GDM: no hepatitis B carriers and no gestational diabetes; M: Median; IQR: Interquartile Range

with maternal age, increasing gravidity and household register.

The prevalence of HBVC & GDM in pregnant women in Hangzhou, China was 0.96% (95% CI: 0.90–1.02%); this was similar to the prevalence of 0.93% (366/39,539) reported in Guangzhou, China [4] and much higher than the prevalence of 0.26% (409/154,000) reported in Zhejiang, China [24]. The cause of these differences in the incidence of HBVC & GDM in different geographical areas may be closely related to variations in dietary habits and lifestyle factors. Furthermore, the non-uniformity of the inclusion and exclusion criteria employed across various study cohorts may have contributed to the observed variations.

ICP is the most prevalent pregnancy-specific liver disease, with symptoms including generalized pruritus and elevated bile acids. In the present study, we found that pregnant women in the HBVC & GDM group had an increased risk of ICP, which was 1.19-fold higher than that in the HBVC group (3.188/2.668). This finding was consistent with a previous publication [25] which reported that pregnant women with HBVC & GDM were more likely to develop ICP than those in a GDM alone group (6.4% vs. 3.0%, $P < 0.001$). The association between HBV and ICP is well established. First, HBV infection promotes intrahepatic oxidative stress and impairs bile canaliculi function [26]. Furthermore, HBV infection affects bile acid metabolism by altering the expression of genes related to lipid and bile acid metabolism, as well as inhibiting bile acid transporters such as the Na^+-taurocholate co-transporting polypeptide (NTCP) [27]. These factors may exacerbate the impact of HBV infection on ICP. Chen et al. suggested that GDM is one of the risk factors for ICP [28]. Pregnant women with GDM often exhibit insulin resistance, leading to free fatty acid deposition in the liver and impaired intrahepatic bile excretion [8, 9]. The farnesoid X receptor (FXR) plays a critical role in regulating bile acid synthesis and metabolism, promoting bile acid excretion and absorption, and maintaining bile acid homeostasis. However, reduced FXR expression in GDM contributes to abnormal bile acid metabolism, thus exacerbating cholestasis [29]. Thus, both HBV infection and GDM can influence the process of bile acid metabolism. Consequently, it is important to strengthen the clinical monitoring of bile acid levels in pregnant women with HBVC & GDM.

Previous research has yielded inconsistent results with regards to the correlation between HBV infection and HDP. The findings of this study demonstrated an elevated risk of PE in pregnant women within the HBVC & GDM group, which exhibited a 1.26-fold increase when compared to the GDM group (2.511/1.990). Similarly, a meta-analysis by Afraie et al. found that HBV infection during pregnancy was associated with an increased risk of PE, with a correlation coefficient of 1.10 between the two events [30]. However, a previous Chinese study found no association between HBVC and PE, although the relative risk of PE was 0.79 with a 95% CI of 0.32–1.95, thus indicating that the sample size of this study was insufficient [31]. However, Lok et al. [32] reported an inverse correlation between HBV and PE. These discrepancies between studies may be attributed to differences in the diagnostic criteria for PE, HBV activity status, and population characteristics (e.g., ethnicity and geographic region). HBeAg-positivity typically indicates a high viral load. Our study population included some HBeAg-positive

Table 3 Perinatal characteristics and pregnancy outcomes of the maternal groups, N (%)

Variables	Number of pregnant women (%)	Groups				x^2	*P* value
		non-HBVC & GDM (*n* = 5323)	HBVC (*n* = 5508)	GDM (*n* = 919)	HBVC & GDM (*n* = 1065)		
Mode of delivery						99.054	< 0.001
Assisted vaginal delivery	1693 (13.2)	738 (13.9)	699 (12.7)	130 (14.1)	126 (11.8)		
Caesarean section	5423 (42.3)	2084 (39.2)	2329 (42.3)	433 (47.1)	577 (54.2)		
Vaginal delivery	5699 (44.5)	2501 (47.0)	2480 (45.0)	356 (38.7)	362 (34.0)		
HDP						57.790	< 0.001
Gestational hypertension	290 (2.3)	122 (2.3)	100 (1.8)	35 (3.8)	33 (3.1)		
Preeclampsia	211 (1.6)	78 (1.5)	69 (1.3)	26 (2.8)	38 (3.6)		
Blood pressure normal	12,314 (96.1)	5123 (96.2)	5339 (96.9)	858 (93.4)	994 (93.3)		
ICP						96.934	< 0.001
NO	12,412 (96.9)	5234 (98.3)	5271 (95.7)	905 (98.5)	1002 (94.1)		
YES	403 (3.1)	89 (1.7)	237 (4.3)	14 (1.5)	63 (5.9)		
HLP						76.532	< 0.001
NO	12,422 (96.9)	5141 (96.6)	5401 (98.1)	854 (92.9)	1026 (96.3)		
YES	393 (3.1)	182 (3.4)	107 (1.9)	65 (7.1)	39 (3.7)		
Thyroid functions						4.366	0.037
Hypothyroidism	1264 (9.9)	561 (10.5)	522 (9.5)	84 (9.1)	97 (9.1)		
Hyperthyroidism	29 (0.2)	16 (0.3)	7 (0.1)	1 (0.1)	1 (0.1)		
Thyroiditis	34 (0.3)	17 (0.3)	11 (0.2)	2 (0.2)	2 (0.2)		
Normal thyroid function	11,488 (89.6)	4729 (88.8)	4968 (90.2)	826 (89.9)	965 (90.6)		
Amniotic fluid volume						3.298	0.069
Oligohydramnios	630 (4.9)	270 (5.1)	279 (5.1)	38 (4.1)	43 (4.0)		
Polyhydramnios	57 (0.4)	23 (0.4)	22 (0.4)	7 (0.8)	5 (0.5)		
Meconium-stained amniotic fluid	145 (1.1)	73 (1.4)	55 (1.0)	7 (0.8)	10 (0.9)		
Normal	11,983 (93.5)	4957 (93.1)	5152 (93.5)	867 (94.3)	1007 (94.6)		
Scar uterus						151.395	< 0.001
NO	10,194 (79.5)	4485 (84.3)	4248 (77.1)	713 (77.6)	748 (70.2)		
YES	2621 (20.5)	838 (15.7)	1260 (22.9)	206 (22.4)	317 (29.8)		
Fetal growth restriction						0.439	0.508
NO	12,783 (99.8)	5307 (99.7)	5497 (99.8)	916 (99.7)	1063 (99.8)		
YES	32 (0.2)	16 (0.3)	11 (0.2)	3 (0.3)	2 (0.2)		
PROM						18.387	0.005
Preterm PROM	2409 (18.8)	1025 (19.3)	1021 (18.5)	170 (18.5)	193 (18.1)		
Term PROM	220 (1.7)	118 (2.2)	67 (1.2)	18 (2.0)	17 (1.6)		
NO PROM	10,186 (79.5)	4180 (78.5)	4420 (80.2)	731 (79.5)	855 (80.3)		
Placental abruption						2.908	0.406
NO	12,744 (99.4)	5291 (99.4)	5481 (99.5)	911 (99.1)	1061 (99.6)		
YES	71 (0.6)	32 (0.6)	27 (0.5)	8 (0.9)	4 (0.4)		
Placenta previa						5.154	0.161
NO	12,672 (98.9)	5266 (98.9)	5444 (98.8)	914 (99.5)	1048 (98.4)		
YES	143 (1.1)	57 (1.1)	64 (1.2)	5 (0.5)	17 (1.6)		
Fetal distress						6.348	0.096
NO	11,806 (92.1)	4890 (91.9)	5073 (92.1)	866 (94.2)	977 (91.7)		
YES	1009 (7.9)	433 (8.1)	435 (7.9)	53 (5.8)	88 (8.3)		
Prenatal anemia						24.253	< 0.001
NO	9900 (77.3)	4134 (77.7)	4166 (75.6)	756 (82.3)	844 (79.2)		
YES	2915 (22.7)	1189 (22.3)	1342 (24.4)	163 (17.7)	221 (20.8)		
Postpartum anemia						0.512	0.916
NO	11,370 (88.7)	4717 (88.6)	4884 (88.7)	821 (89.3)	948 (89.0)		
YES	1445 (11.3)	606 (11.4)	624 (11.3)	98 (10.7)	117 (11.0)		
Prenatal hemorrhage						21.062	< 0.001
NO	12,659 (98.8)	5280 (99.2)	5437 (98.7)	899 (97.8)	1043 (97.9)		

Table 3 (continued)

Variables	Number of pregnant women (%)	Groups				x^2	*P* value
		non-HBVC & GDM (*n* = 5323)	HBVC (*n* = 5508)	GDM (*n* = 919)	HBVC & GDM (*n* = 1065)		
YES	156 (1.2)	43 (0.8)	71 (1.3)	20 (2.2)	22 (2.1)		
Postpartum hemorrhage						7.28	0.063
NO	11,908 (92.9)	4949 (93.0)	5120 (93.0)	867 (94.3)	972 (91.3)		
YES	907 (7.1)	374 (7.0)	388 (7.0)	52 (5.7)	93 (8.7)		

HBVC: hepatitis B carriers; GDM: gestational diabetes mellitus; HBVC & GDM: both hepatitis B virus carriers and gestational diabetes mellitus; non-HBVC & GDM: no hepatitis B carriers and no gestational diabetes; HDP: Hypertensive disorders in pregnancy; ICP: Intrahepatic cholestasis of pregnancy; HLP: Hyperlipidaemia; PROM: Premature rupture of membranes

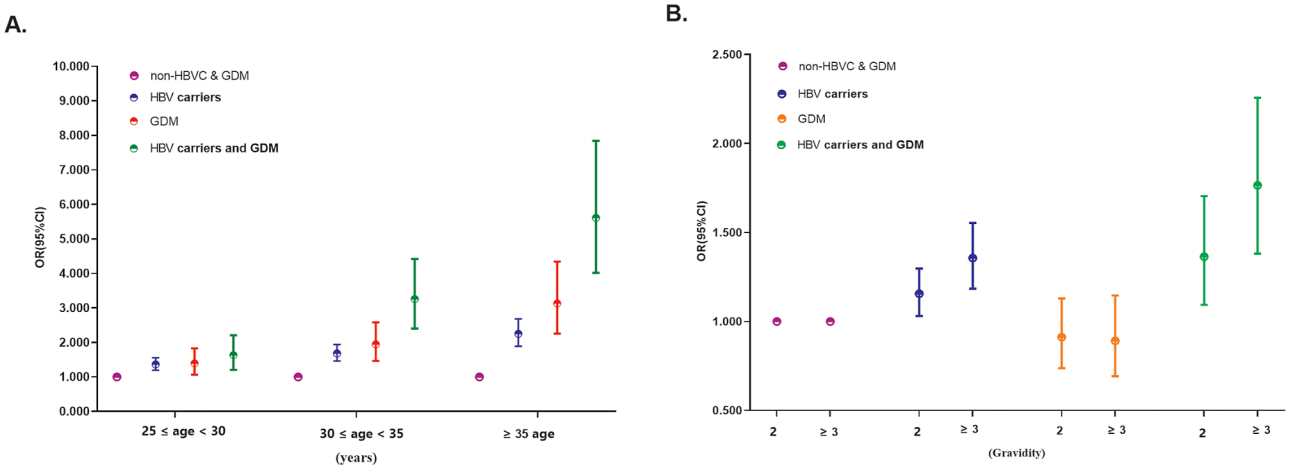

Fig. 2 Odds ratios of maternal age and gravidity in the HBVC group, GDM group, and HBVC & GDM group by multivariate logistic regression analysis. (**A**) Odds ratios of maternal age in the HBVC group, GDM group, and HBVC & GDM group; (**B**) Odds ratios of gravidity in the HBVC group, GDM group, and HBVC & GDM group; HBVC: hepatitis B carriers; GDM: gestational diabetes mellitus; HBVC & GDM: both hepatitis B virus carriers and gestational diabetes mellitus; OR: odds ratio; CI: confidence interval

pregnant women; previous work has shown that HBeAg may promote placental inflammation via the TLR2 pathway, thus increasing fetal rejection and predisposing to PE [33]. GDM and HDP share similar risk factors, including pre-pregnancy obesity and gestational weight gain. Insulin resistance has been shown to affect the synthesis of prostaglandin E2, resulting in increased peripheral vascular resistance and increased blood pressure. A recent study found that GDM was independently associated with the development of PE in singleton pregnancy [34]. Moreover, Xue Zhanhua et al. [35] demonstrated that the occurrence of HDP in pregnant women with HBVC & GDM was considerably higher than that observed in pregnant women with GDM alone, and that the incidence of HDP in the group with abnormal liver function was found to be higher than that in pregnant women with normal liver function. HBV infection can increase the incidence of PE in pregnant women with GDM, and optimizing the treatment and management of GDM during pregnancy can reduce the incidence of PE.

This study found that maternal age represented a key factor contributing to an increased risk of HBVC & GDM in pregnant women. As maternal age increased, so did the risk of developing HBVC & GDM. The risk of carrying HBVC & GDM in the advanced maternal age (AMA) group was not only 5.611-fold higher than that in the group of pregnant women under 25 years of age, but also two-fold higher than that in the HBVC and GDM groups. A Chinese nationwide study [2] found that the rate of HBsAg-positivity in pregnant women increased with age. In the Yunnan region, AMA was found to be more susceptible to HBV infection [36]. This may be related to weakening of the protective effect of the hepatitis B vaccine. Several studies have reported an independent correlation between AMA and the occurrence of GDM. Li et al. [37] reported a positive linear association between maternal age and GDM, which decreases in younger mothers and increases in AMA. The risk of GDM in the 35–39 maternal age group and the ≥40 maternal age group was 4.96-fold and 6.45-fold higher than that of the 20–24 maternal age group, respectively, with ORs consistent with the findings of our present study. Cao et al. [38] suggested that the risk of GDM is higher in pregnant women maternal aged 30 years and above. Zhou et al. suggested that the risk of GDM is increased in HBsAg-positive pregnant women with AMA [39]. Collectively,

Table 4 Multivariate logistic regression analysis of perinatal characteristics and pregnancy outcomes

Indicators	non-HBVC & GDM[#] (*n* = 5323)	HBVC (*n* = 5508)				GDM (*n* = 919)				HBVC & GDM (*n* = 1065)			
	n (%)	*n* (%)	OR	95% CI	*P* value	*n* (%)	OR	95% CI	*P* value	*n* (%)	OR	95% CI	*P* value
Household registration													
outside Zhejiang Province	1471 (27.6)	2029 (36.8)	1.524	1.393–1.668	< 0.001	266 (28.9)	1.228	1.035–1.457	0.018	433 (40.7)	1.953	1.673–2.280	< 0.001
Zhejiang-registered but non-Hangzhou	282 (5.3)	350 (6.4)	1.346	1.138–1.593	0.001	81 (8.8)	1.818	1.391–2.378	< 0.001	103 (9.7)	2.246	1.744–2.893	< 0.001
Hangzhou-local[#]	3570 (67.1)	3129 (56.8)	1			572 (62.2)	1			529 (49.7)	1		
Maternal age (years)													
≥ 25&<30	2444 (45.9)	2154 (39.1)	1.363	1.194–1.555	< 0.001	349 (38.0)	1.396	1.066–1.829	0.015	288 (27.0)	1.632	1.207–2.208	0.001
≥ 30&<35	1663 (31.2)	1968 (35.7)	1.684	1.461–1.940	< 0.001	330 (35.9)	1.945	1.465–2.581	< 0.001	442 (41.5)	3.257	2.400–4.420	< 0.001
≥ 35	495 (9.3)	874 (15.9)	2.251	1.888–2.683	< 0.001	166 (18.1)	3.130	2.256–4.341	< 0.001	278 (26.1)	5.611	4.016–7.840	< 0.001
< 25[#]	721 (13.5)	512 (9.3)	1			74 (8.1)	1			57 (5.4)	1		
Hospital day (days)													
> 7	400 (7.5)	423 (7.7)	0.977	0.840–1.138	0.767	78 (8.5)	1.047	0.801–1.369	0.737	119 (11.2)	1.266	0.999–1.604	0.051
≤ 7[#]	4923 (92.5)	5085 (92.3)	1			841 (91.5)	1			946 (88.8)	1		
Gravidity													
2	1600 (30.1)	1664 (30.2)	1.156	1.030–1.297	0.014	266 (28.9)	0.912	0.737–1.129	0.399	305 (28.6)	1.364	1.093–1.704	0.006
≥ 3	1514 (28.4)	2228 (40.5)	1.356	1.184–1.553	< 0.001	309 (33.6)	0.891	0.692–1.146	0.368	532 (50.0)	1.765	1.381–2.257	< 0.001
≤ 1[#]	2209 (41.5)	1616 (29.3)	1			344 (37.4)	1			228 (21.4)	1		
Parity													
2	1995 (37.5)	2729 (49.5)	1.116	0.982–1.269	0.092	389 (42.3)	0.925	0.727–1.178	0.528	605 (56.8)	1.030	0.823–1.289	0.799
≥ 3	148 (2.8)	267 (4.8)	1.153	0.902–1.475	0.255	36 (3.9)	0.971	0.619–1.523	0.898	60 (5.6)	0.875	0.594–1.290	0.502
≤ 1[#]	3180 (59.7)	2512 (45.6)	1			494 (53.8)	1			400 (37.6)	1		
Infant weight (g)													
< 2500	179 (3.4)	190 (3.4)	0.966	0.740–1.261	0.801	35 (3.8)	0.670	0.411–1.093	0.109	43 (4.0)	0.713	0.452–1.125	0.146
> 4000	230 (4.3)	202 (3.7)	0.825	0.677–1.007	0.058	50 (5.4)	1.321	0.957–1.823	0.091	72 (6.8)	1.548	1.161–2.064	0.003
2500–4000[#]	4914 (92.3)	5116 (92.9)	1			834 (90.8)	1			950 (89.2)	1		
Mode of delivery													
Assisted vaginal delivery	738 (13.9)	699 (12.7)	1.093	0.965–1.239	0.162	130 (14.1)	1.248	0.992–1.569	0.059	126 (11.8)	1.501	1.185–1.901	0.001
Caesarean section	2084 (39.2)	2329 (42.3)	0.880	0.789–0.981	0.021	433 (47.1)	1.098	0.903–1.337	0.349	577 (54.2)	1.258	1.035–1.528	0.021
Vaginal delivery[#]	2501 (47.0)	2480 (45.0)	1			356 (38.7)	1			362 (34.0)	1		
Gestational week (weeks)													
< 34	47 (0.9)	54 (1.0)	1.037	0.647–1.664	0.879	14 (1.5)	2.211	1.038–4.712	0.040	16 (1.5)	1.521	0.737–3.142	0.257
34–36	235 (4.4)	282 (5.1)	1.025	0.839–1.254	0.806	58 (6.3)	1.397	1.004–1.944	0.047	73 (6.9)	1.169	0.856–1.597	0.326
> 41	404 (7.6)	363 (6.6)	1.002	0.860–1.169	0.975	13 (1.4)	0.202	0.115–0.355	< 0.001	14 (1.3)	0.217	0.126–0.374	< 0.001
37–41[#]	4637 (87.1)	4809 (87.3)	1			834 (90.8)	1			962 (90.3)	1		
HDP													
Gestational hypertension	122 (2.3)	100 (1.8)	0.789	0.599–1.039	0.091	35 (3.8)	1.515	1.025–2.239	0.037	33 (3.1)	1.185	0.788–1.783	0.415
Preeclampsia	78 (1.5)	69 (1.3)	0.858	0.610–1.208	0.381	26 (2.8)	1.762	1.101–2.822	0.018	38 (3.6)	2.017	1.315–3.095	0.001
Blood pressure normal[#]	5123 (96.2)	5339 (96.9)	1			858 (93.4)	1			994 (93.3)	1		
ICP													

Table 4 (continued)

Indicators	non-HBVC & GDM[#] (*n* = 5323)	HBVC (*n* = 5508)				GDM (*n* = 919)				HBVC & GDM (*n* = 1065)			
	n (%)	*n* (%)	OR	95% CI	*P* value	*n* (%)	OR	95% CI	*P* value	*n* (%)	OR	95% CI	*P* value
YES	89 (1.7)	237 (4.3)	2.666	2.068–3.435	< 0.001	14 (1.5)	0.796	0.448–1.416	0.438	63 (5.9)	3.143	2.223–4.445	< 0.001
NO[#]	5234 (98.3)	5271 (95.7)	1			905 (98.5)	1			1002 (94.1)	1		
HLP													
YES	182 (3.4)	107 (1.9)	0.619	0.484–0.793	< 0.001	65 (7.1)	2.119	1.570–2.858	< 0.001	39 (3.7)	1.167	0.809–1.684	0.409
NO[#]	5141 (96.6)	5401 (98.1)	1			854 (92.9)	1			1026 (96.3)	1		
Scar uterus													
YES	838 (15.7)	1260 (22.9)	1.202	1.042–1.387	0.012	206 (22.4)	1.183	0.917–1.526	0.195	317 (29.8)	1.073	0.856–1.344	0.543
NO[#]	4485 (84.3)	4248 (77.1)	1			713 (77.6)	1			748 (70.2)	1		
Prenatal anemia													
YES	1189 (22.3)	1342 (24.4)	1.173	1.071–1.286	0.001	163 (17.7)	0.771	0.642–0.927	0.006	221 (20.8)	1.005	0.851–1.188	0.951
NO[#]	4134 (77.7)	4166 (75.6)	1			756 (82.3)	1			844 (79.2)	1		
Prenatal hemorrhage													
YES	43 (0.8)	71 (1.3)	1.211	0.820–1.789	0.336	20 (2.2)	2.113	1.222–3.654	0.007	22 (2.1)	1.423	0.832–2.434	0.197
NO[#]	5280 (99.2)	5437 (98.7)	1			899 (97.8)	1			1043 (97.9)	1		
PROM													
Preterm PROM	1025 (19.3)	1021 (18.5)	1.010	0.913–1.118	0.843	170 (18.5)	0.973	0.806–1.174	0.773	193 (18.1)	1.078	0.899–1.293	0.416
Term PROM	118 (2.2)	67 (1.2)	0.643	0.473–0.875	0.005	18 (2.0)	0.872	0.524–1.452	0.600	17 (1.6)	0.955	0.564–1.620	0.866
NO PROM[#]	4180 (78.5)	4420 (80.2)	1			731 (79.5)	1			855 (80.3)	1		

HBVC: hepatitis B carriers; GDM: gestational diabetes mellitus; HBVC & GDM: both hepatitis B virus carriers and gestational diabetes mellitus; non-HBVC & GDM: no hepatitis B carriers and no gestational diabetes; HDP: Hypertensive disorders in pregnancy; ICP: Intrahepatic cholestasis of pregnancy; HLP: Hyperlipidaemia; PROM: Premature rupture of membranes; OR: odds ratio; CI: confidence interval; [#]References.

these previous findings were consistent with those of the present study. Consequently, women of childbearing age should be tested for hepatitis B antibody levels as early as possible and given booster doses in a timely manner. Clinicians should pay more attention to monitoring blood glucose and glucose tolerance in the AMA population to prevent GDM.

The risk of developing HBVC & GDM was significantly higher among pregnant women with mobile populations compared to Hangzhou-local. Compared to extra-provincial migrants, intra-provincial migrants exhibited significantly higher risks of developing HBVC & GDM and GDM, albeit with a reduced risk of HBVC. Studies have shown that the rate of HBV infection among pregnant women varies by region, with rates ranging from 1.88 to 11.99% in different provinces. The infection rate in Zhejiang Province was previously reported to be 5.15%, making this a moderately endemic area [40]. The rate of HBV infection also varied in different areas of the same province, with higher rates of HBsAg-positivity in rural areas and regions with lower levels of education [2]. Similar regional disparities exist in the prevalence of GDM. For example, the reported prevalence rates were 17.42% in Qingdao, 7.30% in Zhejiang (6.24% in rural areas and 9.13% in urban areas) and 17.6% in Xiamen [41–43]. These regional differences may be related to variations in local living standards, healthcare conditions, and education levels.

Furthermore, we found that the risk of developing HBVC & GDM and HBVC increased with gravidity. In 2021, China implemented the three-child policy, which led to an increase in the proportion of women with increasing gravidity. Studies showed that multigravid and multiparous statuses were associated with an increased rate of HBV infection, as multigravidity and multiparity increase the likelihood of HBV transmission [2, 36]. Liu et al. reported that women with ≥ 3 pregnancies had a 1.27-fold higher risk of GDM in a fully adjusted model [44]. However, in our study, gravidity did not result in a significant effect on the risk of GDM in pregnant women. Interestingly, we observed that the ORs for the HBVC & GDM group with a gravidity ≥ 3 and those with two gravidity were higher than those in the HBVC group ($OR_{\geq 3}$ = 1.765 vs. 1.356; OR_2 = 1.364 vs. 1.156), thus suggesting that increasing gravidity may have a certain influence on the risk of GDM in HBV-infected pregnant women.

In this study, we also found that the HBVC & GDM group exhibited the highest incidence of macrosomia (6.8%), with an ARI of + 2.5% and a significant 54.8% higher risk ($P < 0.05$). The GDM group exhibited an ARI of + 1.1%, lower than the HBVC & GDM group, with a trend towards an increased risk (32.1%), although the intergroup difference was not statistically significant. In contrast, HBV infection alone did not increase the risk of macrosomia. Furthermore, the ARI for low birth weight was < 1% across all three groups, indicating that HBVC and GDM had minimal absolute effects on low birth weight. GDM was identified as an independent risk factor for macrosomia [45]. Elevated maternal blood glucose levels can lead to fetal hyperinsulinemia. Insulin cannot cross the placental barrier and therefore promotes hepatic glycogen storage, protein synthesis, and fat deposition, thereby influencing fetal growth. Tu et al. [24] used the same grouping method as ours and found that combined HBV infection and GDM significantly increased the risks of excessive fetal femur length growth (OR = 2.88, 95% CI: 1.13–7.35) and macrosomia (OR = 4.19, 95% CI: 1.66–10.56). These findings suggest a synergistic effect between HBVC and GDM, substantially elevating the risk of macrosomia.

The data presented in Table 4 of this study revealed that the risk of delivery at a gestational age of < 37 weeks was increased in the GDM group, whereas the risk of delivery at a gestational age of > 41 weeks was decreased. Similarly, in the HBVC & GDM group, the risk of delivery at a gestational age of > 41 weeks was reduced, whereas no significant difference was observed in the HBVC group. We observed that in the group with a gestational age > 41 weeks, the ORs for the HBVC & GDM group and the GDM group were 0.217 and 0.202, respectively, indicating little difference. This meant that gestational age at delivery was primarily influenced by GDM. GDM was found to be an independent risk factor in terms of premature birth, cesarean delivery, uterine inertia and placental abruption [45], which may contribute to preterm delivery or early caesarean section in pregnant women with HBVC & GDM. Furthermore, we observed that HBV and GDM exerted opposing effects on hyperlipidemia and prenatal anemia. When HBVC & GDM coexisted, the risk of developing these conditions was not increased. Whether this balance could be disturbed by different HBV infection status or varying blood glucose levels remains to determined.

In this retrospective study, we analyzed the relationship between HBVC & GDM and pregnancy outcomes among pregnant women in Hangzhou. Although we included a relatively large multi-center sample size, this study still had several limitations that need to be considered. First, our findings were only representative of the Hangzhou region in China. Second, our study did not include data relating to pre-pregnancy BMI, smoking, alcohol consumption, or educational level, making it impossible to assess the potential influence of these variables. For instance, a high BMI is a known independent risk factor for GDM [41, 43]. If HBV infection rates are higher among obese pregnant women, then failure to adjust for BMI could overestimate the effect of HBV. Populations

with lower education levels tend to have higher rates of HBV infection but often demonstrate poorer health literacy, thus resulting in reduced compliance with prenatal care and sub-optimal GDM management [2, 45]. Finally, the absence of HBV DNA and liver function data prevented us from evaluating how viral replication levels or hepatic inflammatory activity might influence pregnancy outcomes. This limitation may obscure the true risks for pregnant women with high viral loads or active hepatitis. Both high HBV DNA levels ($>10^6$ IU/mL) and proinflammatory mechanisms associated with elevated ALT have been linked to increased GDM risk [14]. Nevertheless, this represented a key focus for our future research.

Conclusions

In summary, the incidence rates of HBVC, GDM, and HBVC & GDM among pregnant women in Hangzhou, China, were 4.97% (95% CI: 4.84–5.10%), 0.83% (95% CI: 0.78–0.88%) and 0.96% (95% CI: 0.90–1.02%), respectively. When HBVC & GDM co-existed, the risks of ICP, PE and macrosomia were increased significantly. The risks of HBVC, GDM, and HBVC & GDM increased with advancing maternal age. The risk of HBVC and HBVC & GDM increased with increasing gravidity. When treating pregnant women of advanced age, multiple gravidity and from a floating population, clinical efforts should focus on strengthening education and the dynamic monitoring of HBVC, GDM, and HBVC & GDM, as well as providing personalized and high-quality prenatal care to reduce the risk of adverse pregnancy outcomes.

Abbreviations

HBV	Hepatitis B virus
GDM	Gestational diabetes mellitus
HBVC	Hepatitis B virus carriers
ICP	Intrahepatic cholestasis of pregnancy
HDP	Hypertensive disorders of pregnancy
OGTT	Oral glucose tolerance test
GH	Gestational hypertension
PE	Pre-eclampsia
FGR	Foetal growth restriction
PROM	Premature rupture of membranes
OR	Odds ratio
CI	Confidence interval
BMI	Body Mass Index

Supplementary Information

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Supplementary Material 1

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Author contributions

L. W and Y.M.C design and statistical analysis; L.W and C.J wrote the first draft of the manuscript. H.S.S, provision of study material or patients; Y.M.C writing-review & editing. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Data availability

All data generated or analyzed during this study are included in the supplementary file and this published article.

Declarations

Ethics approval and consent to participate

The study has been conducted under the approval of the Human Research Ethics Committee of the Hangzhou Women's Hospital [Medical Ethics Review 2024 – 119], and the procedures have been performed in accordance with the Declaration of Helsinki. Since this study is a retrospective study, the need to obtain informed consent was waived by the Human Research Ethics Committee of the Hangzhou Women's Hospital.

Consent for publication

Not applicable, this was a retrospective study and no individual person's personal information is included.

Competing interests

The authors declare no competing interests.

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