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The Association of Hepatitis B Virus Replication During Pregnancy with Perinatal Outcomes: A Retrospective Cohort Study

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Abstract

Background

The effect of hepatitis B virus (HBV) replication during pregnancy on the outcomes of singleton pregnancies is not fully understood. In this study, we investigated the association between HBV replication and poor maternal and infant outcomes.

Methods

We retrospectively analyzed the clinical data of 836 pregnant inpatients with hepatitis B surface antigen positivity who delivered at two provincial tertiary grade A hospitals in Fujian Province from June 2016 to October 2020. The patients were divided into the HBV replication (n = 283) and non-HBV replication groups (n = 553). Chi-squared test of adverse maternal and infant outcomes was performed using SPSS 26.0 software, and univariate analysis of variance of basic clinical indexes of pregnant women and newborns was performed. $P<0.05$ was considered statistically significant.

Results

The incidences of perinatal outcomes of intrahepatic cholestasis of pregnancy, hypertensive syndrome complicating pregnancy, gestational diabetes mellitus, preterm birth, macrosomia, growth restriction, and vaginal infection in the HBV and non-HBV replication groups were not significantly different ($P>0.05$); however, there were significant differences between the two groups in the rate of cesarean section (53.8% vs. 45.0%; $P=0.017$) and neonatal jaundice (15.5% vs. 7.2%; $P=0.000$). After using propensity score analysis and multivariable modeling to adjust for glutamic pyruvic transaminase and glutamic oxaloacetic transaminase levels in the two groups, the replication group was found to have an increased risk for cesarean section (54.3% vs. 33.5%; $P=0.000$) and vaginal infection (3% vs. 0.4%; $P=0.038$), and their infants had a higher rate of newborn jaundice (16% vs.1.5%; $P=0.000$).

Conclusion

The findings provide further understanding of the association between maternal HBV replication status and perinatal outcomes. Pregnant women with viral replication have an increased risk of vaginal infection and cesarean section, and their infants appear to be at a higher risk for neonatal jaundice.

Background

Hepatitis B virus (HBV) infection is a global health problem. According to the World Health Organization, there are approximately 257 million cases of chronic HBV infections worldwide [1]. It is estimated that the prevalence rate of hepatitis B surface antigen (HBsAg) among the general population in China is

approximately 5–6% [1], and it is increasing. In addition, the carrier rate of the HBsAg during pregnancy is 7.2% [2]. Recent studies have shown that perinatal transmission is more likely to occur in women with HBsAg positivity and a high HBV DNA viral load during pregnancy. Viral hepatitis during pregnancy can increase adverse maternal and infant outcomes, such as pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy (ICP), preterm delivery, macrosomia, growth restriction, cesarean section (CS), neonatal jaundice, and racket placenta [2–5]. However, another study [6] found no significant correlation between these outcomes, while others[7] demonstrated a negative correlation. Although there are many studies on the relationship between HBV infection and poor maternal and infant outcomes, the data supporting the research conclusions are still considered insufficient. Currently, most studies have focused on the comparison of adverse maternal and fetal outcomes between HBsAg-positive and HBsAg-negative pregnant women; however, there is limited research on HPV replication during pregnancy and the associated maternal and infant adverse outcomes. Furthermore, there are few studies that have evaluated the differences in pregnancy outcomes between patients without HBV replication and those with replication levels below the treatment limit.

Therefore, this study compared the maternal and infant outcomes between pregnant women with and without HBV replication to explore the effect of HBV replication during pregnancy on maternal and infant outcomes.

Methods

This retrospective, open-label study was conducted with the use of an electronic medical record system and telephonic follow-up.

Study design and participants

A retrospective analysis was conducted in two provincial tertiary grade A hospitals in Fujian Province. Each medical record has a unique medical record number, which is linked to the antenatal examination outpatient number. To ensure the accuracy and consistency of the data, we performed replication entry and consistency check to collect data. This retrospective cohort study included pregnant women who delivered their infants between June 2016 and October 2020. Patients were included if they had a positive HBsAg test, no antiviral treatment during pregnancy, an HBV DNA load detected at least once during pregnancy, complete medical records, and any major maternal or infant adverse outcomes. Subjects were excluded if they had any significant comorbidities such as pre-pregnancy diabetes mellitus; liver diseases including liver cirrhosis or liver cancer; heart disease including chronic hypertension and heart failure; biliary diseases; co-morbid hepatitis A, C, D or E virus infection; and positive HIV status. The enrolled patients were divided into two groups according to their HBV replication status during pregnancy. These groups were labelled as the HBV (HBV DNA >500 IU/ml, N = 283) and non-HBV (HBV DNA ≤500 IU/ml, N = 553) replication groups. The HBV replication group was then further divided into the high (HBV DNA ≥2 $\times 10^5$ IU/ml, N = 145) and low (HBV DNA <2 $\times 10^5$ IU/ml, N = 124) HBV replication subgroups.

Outcome measures

The following data were collected: maternal hepatitis B virology indices, human papilloma virus serology, hepatic panel, creatinine levels, routine blood test results, and blood glucose levels (from the 12th week of pregnancy to the 1st month post-delivery). The pregnancy and delivery characteristics were also recorded, such as the patient's age; contact information; place of origin; date of their last menstruation; discharge diagnosis; other associated diseases; history of previous adverse pregnancy and delivery history; HBV vaccination status; and the pregnancy outcomes and maternal complications, such as the fetal age, neonatal weight, and other clinical indicators. Several predetermined pregnancy outcomes and maternal complications were reviewed, such as PIH, GDM, ICP, postpartum hemorrhage, intrauterine growth restriction (IUGR), neonatal jaundice, abnormal amniotic fluid (polyhydramnios or oligohydramnios [4]), preterm birth (delivery prior to 37 weeks of gestation [3]), macrosomia, ultrasonic diagnosis of umbilical cord around the fetal neck, fetal distress, and premature rupture of membranes. PIH was defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure of >90 mmHg after the 20th week of pregnancy [4], which included but was not limited to eclampsia and pre-eclampsia. GDM was diagnosed between the 24th and 28th week of gestation in pregnant women without a previous history of diabetes mellitus if their plasma glucose levels were 5.1 mmol/L at 0 h, 10.0 mmol/L at 1 h, and 8.5 mmol/L at 2 h on the 75-g oral glucose tolerance tests [4] or in those who exceeded the above plasma glucose levels at the noted time-points. Postpartum hemorrhage was defined as vaginal bleeding >500 ml within 24 h post vaginal delivery or bleeding >1000 ml after 24 h post CS.

Statistical analysis

The SPSS 26.0 (SPSS Inc., Chicago, IL, USA) statistical software was used to perform data analysis. The continuous data (e.g., age, liver function test results, creatinine level, and blood routine test results, among others) were analyzed using a univariate analysis of variance (ANOVA) and the data were expressed as mean ± standard deviation (SD). The Chi-squared (χ^2) test or a nonparametric test (Fisher's exact test) was used to analyze adverse maternal and infant outcomes, with dichotomous data expressed as a frequency and percentage. Regarding propensity score analysis, multivariable modeling was used to correct for confounding factors, such as glutamic pyruvic transaminase (ALT) and glutamic oxaloacetic transaminase (AST). $P<0.05$ was considered statistically significant.

A total of 1,169 records of pregnant women were reviewed; 333 cases were excluded, including 230 cases who received antiviral treatment during pregnancy and 103 cases who did not meet the inclusion criteria (Figure 1).

From the results of the statistical univariate ANOVA for the liver function and other continuous clinical data, we found that there were significant differences in ALT and AST between the HBV and non-HBV replication groups (Table 1).

Table 1
The comparison of basic information and clinical indices between the non-HBV and HBV replication groups

		Non-HBV replication group(N = 553)	HBV replication group (N = 283)	P
Age (years) [frequency (%)]	16–26	84 [15.2]	52 [18.4]	0.454
	26–36	413 [74.7]	206 [72.8]	
	36–46	56 [10.1]	25 [8.8]	
ALT (IU/L) [mean ± SD]		17.790 [41.073]	23.636 [38.586]	0.047
AST, (IU/L) [mean ± SD]		19.868 [21.789]	27.359 [33.812]	0.000
Total bilirubin (μmol/L) [mean ± SD]		7.117 [3.507]	7.730 [5.630]	0.054
Total bile acid (μmol/L) [mean ± SD]		5.234 [7.655]	5.822 [9.195]	0.328
Creatinine (μmol/L) [mean ± SD]		44.928 [10.657]	44.551 [10.979]	0.632
White blood count (· 10^9/L) [mean ± SD]		8.837 [2.324]	9.165 [2.536]	0.062
Hemoglobin (g/L) [mean ± SD]		120.582 [15.475]	119.198 [12.721]	0.195
ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; HBV, Hepatitis B Virus				

To reduce the influence of confounding factors on the results and ensure accurate conclusions, we conducted a propensity score analysis with multivariable modelling. Patients were divided into two groups according to HBV DNA viral load: HBV replication group propensity score matching (PSM) where the HBV DNA was >500 IU/ml (N=269), and non-HBV replication group PSM where the HBV DNA was

≤500 IU/ml (N=269; Figure 1). In addition, the χ^2 test or nonparametric test (Fisher's exact test) was used to analyze the data appropriately. A two-tailed p value <0.05 was considered statistically significant.

Results

Patient characteristics

The patient characteristics are presented in Table 1. There were no significant differences between the HBV and non-HBV replication groups in age, transaminase and other serological index. Table 2 describes the characteristics of the HBV and non-HBV replication group after PSM. The average age at delivery in the HBV replication group PSM was similar to that in the non-HBV replication group PSM (30.12 ± 4.429 and 29.81 ± 4.24 years, respectively; P = 0.404). There was no statistically significant difference in the demographic and clinical characteristics between the two groups after the propensity score analysis and multivariable modeling, as shown in Table 2.

Table 2
The comparison of the basic information and clinical indices between the two groups after PSM

	Non-HBV replication group PSM (N = 269)	HBV replication group PSM (N = 269)	P
Age (years) [mean ± SD]	29.81 [4.24]	30.12 [4.43]	0.404
ALT (IU/L) [mean ± SD]	20.198 [52.369]	20.484 [26.412]	0.936
AST (IU/L) [mean ± SD]	20.938 [27.936]	22.776 [18.686]	0.370
Total bile acid (μmol/L) [mean ± SD]	5.715 [8.345]	5.629 [8.699]	0.907
Creatinine (μmol/L) [mean ± SD]	43.779 [8.094]	45.108 [9.460]	0.081
White blood count ($\cdot 10^9$/L) [mean ± SD]	9.435 [7.544]	9.108 [2.546]	0.501
Hemoglobin (g/L) [mean ± SD]	119.911 [14.531]	119.309 [12.619]	0.608

ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; HBV, Hepatitis B Virus

Effect of the HBV DNA viral load on the outcomes of pregnant women

Table 3 describes the maternal and infant adverse outcomes of the HBV and non-HBV replication groups. Table 4 describes the adverse maternal and infant outcomes of the two groups after propensity score analysis and multivariable modeling. The analysis of the data before and after propensity score analysis and multivariable modeling showed that the prevalence rates of PIH, GDM, and ICP were similar between the two groups (P >0.05), but there was a statistically significant difference in the rate of CS (P <0.05). However, when we compared the incidence of vaginal infections, there were two contradictory conclusions. After PSM, the vaginal infection rate of the HBV replication group PSM was significantly higher than that of the non-HBV replication group PSM. In the original data (non-PSM), this difference was not statistically significant (P>0.05).

Table 3
Pregnancy outcomes and complications of the study population

	PIH (%)	GDM (%)	ICP (%)	CS (%)	Vaginal infection (%)
Non-HBV replication group (N = 553)	24 (4.3)	82 (14.8)	24 (4.3)	247 (45.0)	13 (2.4)
HBV replication group (N = 283)	13 (4.6)	42 (14.8)	7 (2.5)	149 (53.8)	8 (2.8)
P	0.866	0.996	0.177	0.017	0.677

CS, cesarean section; HBV, hepatitis B virus; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PIH, pregnancy-induced hypertension

Table 4
Pregnancy outcomes and complications of the study population after propensity score analysis

	PIH (%)	GDM (%)	ICP (%)	CS (%)	Vaginal infection (%)
Non-HBV replication group PSM (N = 269)	9 (3.3)	48 (17.8)	12 (4.5)	90 (33.5)	1 (0.4)
HBV replication group PSM (N = 269)	6 (2.2)	38 (14.1)	7 (2.6)	144 (54.3)	8 (3.0)
P	0.432	0.239	0.243	0.000	0.038

CS, cesarean section; HBV, hepatitis B virus; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PIH, pregnancy-induced hypertension

Neonatal outcomes

Mother to child transmission of HBV infection can occur in the uterus, during delivery, and during the perinatal period. Table 5 shows the frequency of outcomes of newborns born to both groups of pregnant women before the propensity score analysis and multivariable modeling. There was a higher risk of neonatal jaundice in the HBV replication group than in the other group ($P<0.05$). However, the incidence of preterm delivery, macrosomia, and IUGR in the two groups was similar. The results of the two groups after propensity score analysis and multivariable modeling are shown in Table 6.

Table 5
Neonatal outcomes of the study population

	Non-HBV replication group (N = 553)	HBV replication group (N = 283)	P
Neonatal jaundice (%)	40 (7.2)	44 (15.5)	0.000
IUGR (%)	19 (3.4)	17 (6.0)	0.083
Macrosomia (%)	30 (5.4)	9 (3.2)	0.145
Preterm birth (%)	36 (6.5)	22 (7.8)	0.496
CAN (%)	129 (23.3)	68 (24.0)	0.821
Fetal distress (%)	15 (2.7)	9 (3.2)	0.702
Premature rupture of membranes (%)	118 (21.3)	50 (17.7)	0.210
Abnormal amniotic fluid volume (%)	12 (2.2)	5 (1.8)	0.696
CAN, umbilical cord around neck; HBV, hepatitis B virus; IUGR, intrauterine growth restriction			

Table 6
Neonatal outcomes of the study population after propensity score analysis

	Non-HBV replication group PSM(N = 269)	HBV replication group PSM(N = 269)	P
Neonatal jaundice (%)	4 (1.5)	43 (16.0)	0.000
IUGR (%)	13 (4.8)	14 (5.2)	0.084
Macrosomia (%)	12 (4.5)	8 (3.0)	0.362
Preterm birth (%)	23 (8.6)	21 (7.8)	0.753
CAN (%)	55 (20.4)	67 (24.9)	0.217
Fetal distress (%)	8 (3.0)	9 (3.3)	0.805
Premature rupture of membranes (%)	64 (23.8)	47 (17.5)	0.070
Abnormal amniotic fluid volume (%)	3 (1.1)	4 (1.5)	1.000
CAN, umbilical cord around neck; HBV, hepatitis B virus; IUGR, intrauterine growth restriction			

There was a statistically significant difference in the incidence of neonatal jaundice between the HBV and the non-HBV replication group after PSM (16% vs. 1.5%, P = 0.00). However, there was no statistically significant difference between groups in the incidences of preterm births (7.8% and 8.6%, respectively;

P=0.753), macrosomia (3.0% and 4.5%, respectively; P = 0.362), neonatal growth restriction (5.2% and 4.8%, respectively; P = 0.843), and umbilical cord around the neck (24.9% and 20.4%, respectively; P = 0.217).

Other comparisons of the study population

When we further compared the outcomes of the low and high HBV replication subgroups and the non-HBV replication group, no significant difference was observed in the CS rate, neonatal jaundice incidence, and vaginal infection rate between the high and low HBV replication subgroups. Interestingly, these outcomes in the non-HBV replication group were lower than those in the low HBV replication group (Table 7).

Table 7
The comparison of other outcomes among the study population

	Low HBV replication subgroup (N = 124)	High HBV replication subgroup (N = 145)	P	Non-HBV replication group (N = 269)	Low HBV replication subgroup (N = 124)	P
CS (%)	69 (56.6)	75 (52.4)	0.537	90 (33.5)	69 (56.6)	0.000
Neonatal jaundice (%)	17 (13.7)	26 (17.9)	0.495	4 (1.5)	17 (13.7)	0.000
Vaginal infection (%)	5 (4.0)	3 (2.1)	0.477	1 (0.4)	5 (4.0)	0.013
CS, cesarean section; HBV, hepatitis B virus						

Discussion

Our study demonstrated the relationship between HBV replication during pregnancy and maternal and fetal adverse outcomes. One of the main findings was that HBV replication during pregnancy had a statistically significant effect on the rate of CS, including after propensity score matching. Several well-established risk factors for CS have been reported including fetal factors, uterine scarring, abnormal fetal position, and pregnancy complications [8, 9]. However, in our analysis, there were no statistically significant differences observed between the two groups in the aforementioned factors. Therefore, other factors may affect the mode of delivery, such as family education and economic status [8]. Another study reported that nearly 30% of women believe that a CS is the safest option for the fetus [8]. We previously reported that most mothers believe that CS is safer than natural delivery, shortens the time of delivery, and reduces the risk of neonatal HBV infection during vaginal birth [10]. These beliefs and opinions are considered to directly influence the mode of delivery. In addition, we believe that the CS rate of the HBV replication group was also affected by their willingness and compliance with the HBV treatment during pregnancy. Therefore, our results do not rule out that the increased CS rate may be a result of an overlap

between poor willingness and compliance with antiviral therapy during pregnancy and also may be due to pregnant women choosing CS. Alternatively, an increasing number of pregnant women choose to be admitted to the hospital before their due date, which, to a certain extent, increases the psychological pressure and results in an increase in the rate of dystocia and CS [9]. In addition, the development of aseptic surgery and the decline of CS complications have also changed patients' attitudes toward CS [11]. Furthermore, our study compared the CS rate between the high and low HBV replication subgroups, and found no statistically significant difference between groups (P>0.05; Table 7). In other words, the increase in the rate of CS did not seem to be influenced by HBV DNA viral load. In addition, some scholars believe that the likelihood of newborn exposure to maternal blood comparable during CS and natural delivery [12]. Therefore, improving patient education and guidance on the mode of delivery is important and may potentially reduce the rate of selective CS.

Neonatal jaundice is divided into physiological and pathological jaundice [13]. Severe pathological jaundice can progress to bilirubin encephalopathy and neurological damage. Our study found that the incidence of neonatal jaundice in infants born to mothers in the low HBV replication subgroup was significantly higher than that in the non-HBV replication group (P<0.05); however, the comparison between the low and high HBV replication subgroups showed no statistically significant difference (Table 7). The mechanism underlying the relationship between HBV replication and neonatal jaundice has not been clearly elucidated. A possible mechanism involves the destruction of a large number of red blood cells in newborns that leads to hemolysis and neonatal bilirubin excretion [14–16]. Other studies have revealed that maternal HBV carrier status is not an independent risk factor for neonatal jaundice, although other factors can be aggravated in carriers, such as pathological jaundice caused by breast milk [6]. Another possible mechanism of jaundice in infants born to HBV carriers is disturbed fat metabolism in HBV patients which significantly increases maternal blood cholesterol levels and subsequently increases the neonatal blood cholesterol level through umbilical cord circulation. Thus, jaundice develops secondary to the significant increase in the erythrocyte membrane triglyceride content that changes the shape of the erythrocytes and leads to their destruction in the spleen [6]. Other studies have suggested that CS increases the risk of neonatal jaundice [17], which may be related to the delayed feeding associated with CS that may cause neonatal dehydration and jaundice. By contrast, CS has also been reported as a protective factor against the development of neonatal jaundice [7, 18, 19]. Most newborns born by CS are not breastfed in time and do not pass through the birth canal, and as a result, the risk of delivery trauma or bruising is minimal [19]. However, in our study, the incidence of CS and neonatal jaundice in the HBV replication group was high. Since CS is considered by some scholars to be protective against the development of neonatal jaundice, it suggests a clear correlation and clinical significance between the HBV replication and neonatal jaundice. Taken together, these results highlight the importance of increased awareness of the onset of neonatal jaundice in newborns born to mothers with HBV replication.

In our study, the incidence of vaginal infection in the HBV replication group was higher than that in the non-HBV replication group (P<0.05) after matching confounding factors, with no significant difference observed between the high and low HBV replication subgroups (P>0.05; Table 7); this has not been

reported in any previous studies. A vaginal infection refers to a series of diseases that are caused by an imbalance in the normal vaginal microbiome. The reproductive tract microbiome has its own characteristics that vary at different ages, and its structural composition is closely related to the levels of estrogen and progesterone in the body [20]; the peak level of estrogen is 1000 times higher in pregnancy than in non-pregnancy. This microbiome is also affected by other interfering factors, such as the changes in maternal immune status, adaptability of major systems, and drug use [20]. Previous studies suggested that the numbers of *Lactobacillus* in the vagina of pregnant women was negatively correlated with the concentration of pro-inflammatory factors interleukin (IL)-6 and IL-8 [21]. Concurrently, some studies have shown a higher detection rate of HBV DNA in the vagina of patients with active HBV replication than that of the general population [10], and the concentration of IL-6 and IL-8 was also found to be higher than that of the non-HBV infected population [22, 23]. Therefore, we hypothesize that active HBV replication may interfere with the normal vaginal environment of pregnant women through pro-inflammatory factors. Furthermore, it could reduce the numbers of *Lactobacillus* and promote the development of a vaginal infection. Moreover, previous studies have shown that hyperglycemia is a risk factor for vaginal infections. Our analysis showed that, although there was no significant difference in the prevalence of GDM between the two groups, the difference in fasting blood glucose level was significant ($P<0.05$). Therefore, we speculate that hyperglycemia is another possible reason for the higher vaginal infection rate. Although HBV replication during pregnancy is linked to an increase in the vaginal infection rate, it does not increase the probability of other adverse outcomes, such as premature rupture of membranes and premature birth.

This study has some limitations worth noting. First, HBV DNA levels were not monitored dynamically, hindering a detailed comparison of our data. In addition, due to the retrospective study design, it was not possible to evaluate differences in bacterial communities before and during pregnancy between the two groups; thus, in our follow-up prospective study, we will obtain additional data to more accurately evaluate the vaginal flora of pregnant women.

Conclusions

Earlier studies have demonstrated an association of poor maternal and fetal outcomes, such as higher preterm birth rate and ICP, with chronic inflammation caused by HBV infection [24, 25]. Nevertheless, other studies and ours have yielded inconsistent results [26]. This study indicates that pregnant women with HBV replication during pregnancy have an increased risk for CS and a higher incidence of vaginal infection; furthermore, their newborns are at a higher risk of developing neonatal jaundice. However, there was no significant difference observed regarding the poor maternal and fetal outcomes of PIH, GDM, ICP, preterm delivery, macrosomia, and IUGR. Notably, we found significantly higher rates of vaginal infection in mothers and hyperbilirubinemia in infants in both the high and low HBV replication subgroups than in the non-HBV replication group. It is unclear whether these perinatal outcomes are reduced after antiviral therapy. If so, should we focus on pregnant women with low HBV replication who are excluded from antiviral treatment? This question is expected to be addressed in our prospective study in the future.

Abbreviations

ALT, glutamic pyruvic transaminase; ANOVA, analysis of variance; AST, glutamic oxaloacetic transaminase; CS, cesarean section; DNA, deoxyribonucleic acid; GDM, gestational diabetes mellitus; HBV, hepatitis B virus; ICP, intrahepatic cholestasis of pregnancy; IUGR, intrauterine growth restriction; PIH, pregnancy-induced hypertension; PSM, propensity score matching; SD, standard deviation

Declarations

Ethical approval and consent to participate

The study was approved by the Ethics Committee of the affiliated Union Hospital of Fujian Medical University, China (No.2021KY173). The informed consent is waived by the Ethical committee of the Ethics Committee of the affiliated Union Hospital of Fujian Medical University for our study due to it was a retrospective study and no interventions was given to the participants. All methods were performed in accordance with the relevant guidelines and regulations. This manuscript reported adherence to Declaration of Helsinki.

Consent for publication

All data were anonymized. Therefore, individual consent for publication was not required.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available and cannot be uploaded at any website due to the risk of compromising the individual privacy of participants. On the other hand, the data used to reach the aforementioned conclusions are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PY J, YZ H, and KY M performed the data recording and telephonic follow-ups. PY J and YX L performed the statistical analyses. PY J and LD drafted the manuscript. NL and FL C participated in the study design and coordination and helped to refine the manuscript. All authors have read and approved the final manuscript.

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Figures

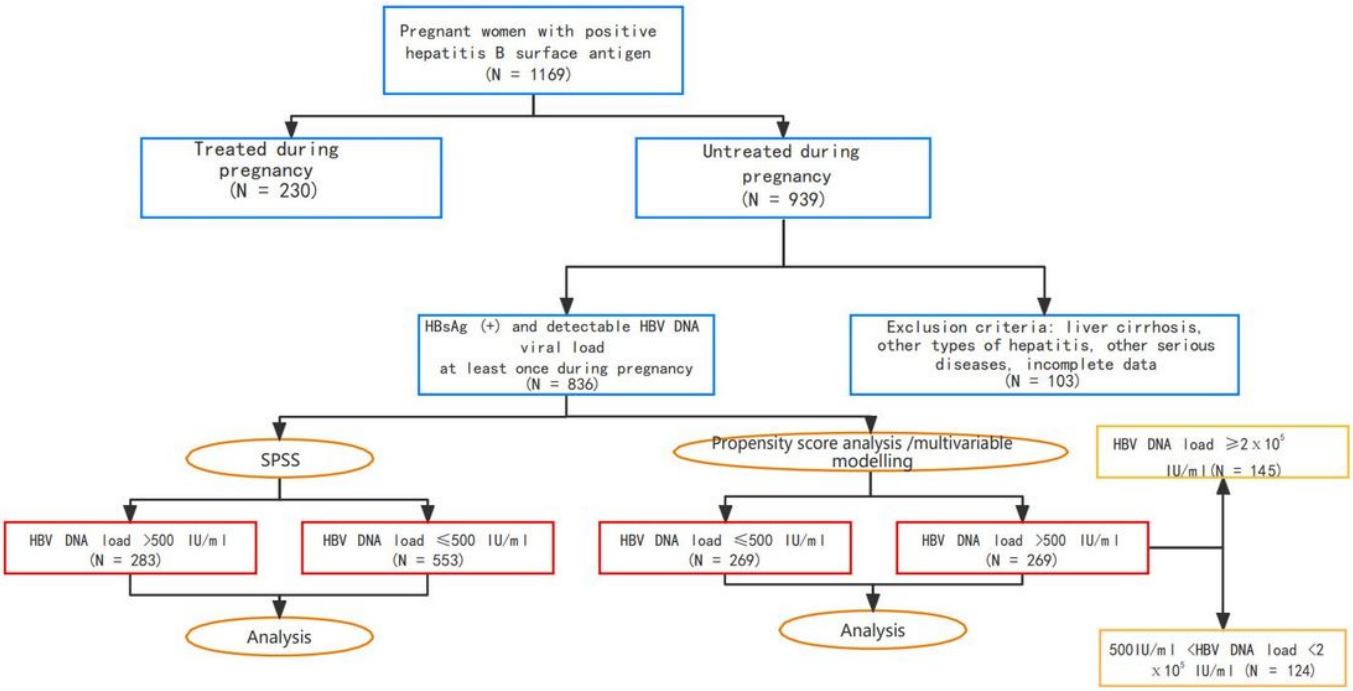

Figure 1

A flowchart of the selection of the participants for the study cohort

DNA, deoxyribonucleic acid; HBV, Hepatitis B Virus;