Pregnancy Complicated With Hepatitis B Virus Infection and Preterm Birth: A Retrospective Cohort Study

Shuisen Zheng
Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University
Huale Zhang
Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University
Rongxin Chen
Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University
Jianying Yan
Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University
Qing Han (fjcherry22@163.com)
Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University

Research Article

Keywords: hepatitis B virus, preterm birth, prospective cohort study, logistics regression

Posted Date: February 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-152431/v1

Version of Record: A version of this preprint was published at BMC Pregnancy and Childbirth on July 17th, 2021. See the published version at https://doi.org/10.1186/s12884-021-03978-0.

Abstract

Background: We aimed to investigate whether maternal chronic hepatitis B virus (HBV) infection affects preterm birth（PTB) in pregnant women.

Methods: We retrospectively analyzed HBV-infected and non-infected pregnant women attending antenatal care at Fujian Provincial Maternity and Child Health Hospital, Fuzhou, China between January 1, 2016 to December 31, 2018. Participants were divided into HBV infection (n = 1302) and control (n = 12813) groups. We compared baseline data, pregnancy and perinatal complications, and preterm delivery outcomes between groups and performed subgroup comparisons and multiple logistics regression analysis to adjust for confounding factors.

Results: The incidence of PTBs before 37 weeks was similar between the groups. PTBs before 34 weeks were significantly more among the HBV infection group than among the controls (1.6% VS. 0.8% ; P = 0.003) After adjusting for confounding factors through logistics regression, HBV infection was found to be an independent PTB risk factor before 34 weeks gestation (adjusted odds ratio 1.796; 95% confidence interval[1.071, 3.012]). According to the subgroup analysis based on whether hepatitis B e-antigen (HBeAg) was positive and whether alanine aminotransferase (ALT) levels were normal during the second trimester, PTB was more frequent in HBeAg negative HBV infection before 34 weeks than among controls(1.8% VS. 0.8%). The PTB rate for pregnant women with normal ALT and HBV infection before 34 weeks was higher than that of the controls (1.6% VS. 0.8%)

Conclusion HBV infection is an independent risk factor for PTB before 34 weeks. Comprehensive programs focusing on pregnant women with HBV infection would reduce the incidence of adverse outcomes.

1. Introduction

Hepatitis B virus (HBV) infection is a global health problem with 2 billion people being infected worldwide, and more than 360 million are carriers of HBV. However, the morbidity varies greatly in different countries and regions. China is one of the regions where HBV infection is highly endemic [1], the infection rate of HBV in women of childbearing age may be as high as 2–8%[2, 3]. Recent researches have shown that viral hepatitis during pregnancy can increase the incidence of preterm birth (PTB), increase fetal growth, and reduce pregnancy hypertensive disorders[4]. PTB is the leading cause of perinatal morbidity and mortality. The PTB rate in mainland China can reach 7.1%, and it is on the rise[5]. Although the current studies suggest that HBV can increase the incidence of PTB[6, 7], studies on the high-risk factors related to PTB in HBV patients lacks in-depth analysis, especially for pregnant women with normal alanine aminotransferase (ALT) and hepatitis B e-antigen (HBeAg) negative pregnant women[7], and the impact of the different degrees of HBV infection on PTB in pregnant women is not yet clear. Limited evidence limits the development of specific monitoring and intervention methods. Therefore, we aimed to conduct a retrospective cohort study to analyze the relationship between HBV infection in pregnant women and PTB

to provide clinical reference for pregnancy supervision and perinatal intervention, and improve the outcome of preterm infants

2. Methods

2.1 Study design and participants

We conducted a large population-based retrospective cohort study on pregnant women who had regular check-ups and deliveries in Fujian Provincial Maternity and Child Health Hospital from January 1, 2016 to December 31, 2018 were included in the cohort, and 14115 pregnant women were finally included in the study (Fig. 1). According to the two-half qualitative screening of HBsAg in the second trimester, they were divided into the HBV infection group (1302 cases) and the control group (12813 cases). In the subgroup analysis, we divided the HBV infection into HBeAg negative group (1034 cases) and HBeAg-positive group (247 cases) according to the presence of HBeAg; based on whether the ALT levels were normal in the second trimester (ALT > 40 IU/L is abnormal), the HBV infection group was divided into normal ALT group (1400 cases) and abnormal ALT group (48 cases). The study was legally approved by the institutional ethics committee of Fujian Provincial Maternity and Children's Hospital and conducted in accord with the guidelines of the Declaration of Helsinki, and the rights of all participants were protected. Consent waiver obtained from the institutional ethics committee of Fujian Provincial Maternity and Children's Hospital.

2.2 Diagnostic criteria.

The definition of PTB was spontaneous or medically induced labor occurring at 37 weeks of gestation respectively, according to the World Health Organization (WHO) guidelines [8].

Chronic HBV infection was defined as either presence of HBsAg in the serum for at least 6 months or presence of HBsAg in a person who tested negative for immunoglobulin M antibodies to hepatitis B core antigen [1].

2.3 Procedures

We collected the clinical data of the two groups of pregnant women using electronic medical records of the hospital, including: (1) General conditions: age of delivery, gestational age,pre-pregnancy body mass index (BMI), prenatal BMI, the number of prenatal check-up, education level, previous PTB history, uterine malformation, etc.; (2) Laboratory investigations: ALT, aspartate aminotransaminase (AST), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), triglyceride (TG), cholesterol (CHOL) (4) maternal complications: gestational hypertension, preeclampsia, chronic hypertension, abortion, placental abruption, hyperthyroidism gestational diabetes mellitus, hypertension during pregnancy, intrahepatic cholestasis of pregnancy (ICP) etc. (5) perinatal outcome and complications: premature infants, neonatal asphyxia, small-for-gestational age infants etc. We retrospectively analyzed the differences in the

baseline data, test parameters and maternal and child outcomes, and explored the correlation between HBV infection and PTB.

2.4 Statistical analysis

The data collection and storage tools of this study were conducted using Excel (Microsoft ® Excel ® 2010), and the SPSS 25.0 statistical software was used to analyze the data in the experimental design stage to perform the normality test on the measurement data. Data that showed normal distribution are presented as mean ± standard deviation, denoted as X ± SD. The differences between the two groups were compared using the independent sample *t* test to clarify the differences between the groups. Qualitative data are expressed as frequencies and percentages, and the Pearson's chi-square test, corrected chi-square test, or Fisher exact probability method were used as appropriate. A logistic regression model was used to correct confounding factors, such as age of childbirth and BMI. The odds ratio (OR) and 95% confidence interval (CI) were calculated. $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1 Participant characteristics

An analysis of the baseline situation between the HBV infection group and the control group found that the two groups of pregnant women had no statistically significant differences in pre-pregnancy BMI, prenatal BMI, previous PTB history, uterine malformation, and the number of prenatal check-up. The age of delivery was slightly older than that of the controls (30.22 ± 4.35 VS. 29.46 ± 4.16, $P < 0.001$), and the gestational week of delivery was slightly lesser than that in the control group (39.17 ± 2.06 VS. 39.29 ± 1.74, $P = 0.045$). There were statistically significant differences in ALT, AST, TG, ALB and CHOL levels between the two groups of pregnant women (P□0.05); there was no statistically significant difference in GGT and LDH levels ($P > 0.05$) (Table 1).

Table 1
Maternal baseline characteristics with respect to pre-pregnancy status of hepatitis B virus infection

Characteristics	Control group	HBV group	P
Age (y)	29.46 ± 4.16	30.22 ± 4.35	< 0.001
gastational age (weeks)	39.29 ± 1.74	39.17 ± 2.06	0.045
the number of prenatal check-up	13.20 ± 2.93	13.08 ± 3.06	0.175
Pre-pregnancy BMI(kg/m^2)	20.84 ± 2.76	20.80 ± 2.75	0.621
Prenatal BMI(kg/m^2)	26.21 ± 3.21	26.06 ± 3.80	0.103
Education			
Primary school or below (n(%))	84(0.7%)	7(0.5%)	0.005
Junior and Senior high school (n(%))	2738(21.5%)	328(25.4%)	
College or higher (n(%))	9941(77.6%)	958(74.1%)	
previous PTB history(n(%))	224(1.7%)	28(2.2%)	0.296
Uterine malformation (n(%))	118(0.9%)	16(1.2%)	0.275
ALT (U/L)	12.94 ± 16.81	17.20 ± 17.16	< 0.001
AST (U/L)	17.18 ± 8.51	20.68 ± 13.12	< 0.001
GGT (U/L)	14.86 ± 10.67	14.46 ± 9.41	0.196
ALB(g/L)	34.86 ± 2.77	34.47 ± 2.91	< 0.001
CHOL(mmol/L)	6.32 ± 1.18	6.03 ± 1.18	< 0.001
TG(mmol/L)	3.35 ± 1.40	3.15 ± 1.31	< 0.001
LDH(U/L)	194.06 ± 83.81	190.79 ± 72.68	0.129

2.2 Pregnancy outcomes complications of the study population

There was no significant difference in the incidence of premature rupture of membranes, gestational diabetes mellitus, preeclampsia, gestational hypertension, HELLP, hypertensive disorders of pregnancy, chronic hypertension, miscarriage, or placental abruption. ICP and hyperthyroidism showed statistically significant incidence between the groups (Table 2).

Table 2
Pregnancy outcomes, complications and neonatal outcomes of the study population.

	Control group	HBV group	P
PPROM(n(%))	3859 (30.1)	367 (28.2)	0.147
Gestation hypertension(n(%))	198(1.5)	18(1.4)	0.637
Preeclampsia(n(%))	255(2.0)	35(2.7)	0.091
Chronic hypertension(n(%))	64(0.5)	4(0.3)	0.256
HELLP(n(%))	7(0.1)	2(0.1)	0.191
HDP(n(%))	453(3.5)	53(4.1)	0.322
GDM (n(%))	1857(14.5)	210(16.1)	0.113
ICP(n(%))	94(0.7)	32 (2.5)	< 0.001
abortion(n(%))	56 (0.4)	10 (0.8)	0.097
Placental abruption(n(%))	189(1.5)	24(1.8)	0.299
hyperthyroidism(n(%))	196(1.5)	7(0.5)	0.004
Preterm birth before 37 weeks	598(4.7)	75(5.9)	0.077
Preterm birth before 34 weeks	103(0.8)	21(1.6)	0.003
neotal jaundice(n(%))	3136 (24.5)	302 (23.2)	0.305
SGA(n(%))	246 (2.1)	36 (2.8)	0.039
admission to NICU (n(%))	1055 (8.2)	119 (9.1)	0.259
asphyxia (n(%))	64 (0.5)	10 (0.8)	0.201
LBW (n(%))	449(3.5)	73(5.6)	< 0.001
Weight of neonates (g)			0.002
< 1500 g (n(%))	94(0.7)	15(1.2)	
1500–2499 g (n(%))	355(2.8)	58(4.5)	
2500–3999 g (n(%))	11806(92.7)	1173(90.7)	
≥ 4000 g (n(%))	480(3.8)	47(3.6)	

Abbreviations: GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; LBW, low birth weight; ICP, intrahepatic cholestasis of pregnancy; PPROM, preterm premature rupture of the membrane

2.3 Neonatal outcomes in singleton pregnancy

There were no significant differences in the incidence of neonatal asphyxia, admission to neonatal intensive care unit (NICU), and neonatal jaundice between the two groups; there were statistically significant differences in small for weight of neonates, gestational age, and low birth weight between the two groups (Table 2).

2.4 Preterm birth outcomes

We finally included 13,916 pregnant women in our study. A total of 637 premature babies with a gestational age of less than 37 weeks were noted, with a PTB rate of 4.8%, and 124 premature babies with a gestational age of less than 34 weeks, with an incidence rate of 0.9%. The incidence rate of delivery gestational week less than 37 weeks was 5.9% and 4.7% in the in HBV infection group and control group, respectively. The incidence of premature delivery less than 34 weeks gestational week in the HBV infection group was higher than that in the control group (1.6% vs 0.8%) (Table 2).

There were some differences in the baseline data between the two groups of study subjects. Therefore, a logistic regression model was constructed to adjust the confounding factors to estimate the OR value of PTB before 37 weeks of gestation and 34 weeks of pregnancy in women with HBV infection. After screening the confounding factors according to the results of univariate analysis and clinical significance, age, pre-pregnancy BMI, prenatal BMI, gravida, number of inspections, previous PTB history, uterine malformation ALT, AST, TG, and LDH were included in the model (Table 3). Univariate logistic regression suggested that HBV infection status was significantly related to the risk of PTB before 34 weeks of gestation. After adjusting for related confounding factors (models A-C), HBV infection was an independent risk factor for PTB < 34 weeks (AOR = 1.796, 95% CI [1.071, 3.012]). However, regardless of single factor or multivariate logistics regression, and there was no correlation between HBV infection and premature delivery (before 37 weeks) (Table 3)

Table 3
Adjusted ORs for preterm birth according to baseline data

	Unadjusted	Model A	Model B	Model C
	OR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Preterm birth before 37 weeks				
Control group	1	1	1	1
HBV group	1.250(0.976-1.600)	1.135(0.867–1.486)	1.136(0.867–1.486)	1.062(0.789–1.412)
Preterm birth before 34 weeks				
Control group	1	1	1	1
HBV group	2.024(1.262–3.248)	1.846(1.116–3.054)	1.845(1.108–3.072)	1.796(1.071–3.012)

Model A: adjustment was made for age,pre-pregnancy BMI□prenatal BMI, gravida, and number of inspections

Model B: adjustment was made for age, pre-pregnancy BMI, prenatal BMI, gravida, number of inspections, previous preterm birth history, and uterine malformation

Model C: adjustment was made for the variables used in Model B and for ALT, AST, TG, and LDH

2.5 Subgroup analysis

Based on whether HBeAg was positive and whether ALT was normal in the second trimester, the subgroups of the premature birth before 34 weeks of gestation were analyzed, and the chi-square test was performed, and the correction $\alpha' = 0.025$. The difference between the control group and the HBV infection group with normal ALT was statistically significant ($P < 0.025$) (Table 4), and the difference with the HBeAg negative HBV infection group was statistically significant ($P < 0.025$) (Table 5). In the subgroup analysis, pregnant women with HBV infection with HBeAg negative and normal ALT showed increased risk of PTB.

Table 4
.subgroup analysis based on whether alanine aminotransferase (ALT) levels were normal

	PTB before 34 weeks (n)	PTB before 34 weeks (%)	χ^2	P
Control group	103	0.8	8.546[a]	0.003
HBV group with ALT normal	20	1.6		

Table 5
subgroup analysis based on whether hepatitis B e-antigen (HBeAg) was positive

	PTB before 34 weeks (n)	PTB before 34 weeks (%)	χ^2	P
Control group	103	0.8	11.244[a]	0.001
HBsAg positive and HBeAg negative	19	1.8		

4. Discussion

The results of the study indicate that pregnancy and HBV infection is not an independent risk factor for PTB (< 37 weeks), but it significantly increases the risk of PTB before 34 weeks of gestation. For pregnant women with HBV infection with HBeAg negative and normal ALT, it may increase the risk of PTB before 34 weeks of gestation.

There is still some controversy about the relationship between HBV infection and PTB in China and worldwide[9–11]. Jue Liu et al. studied 489,965 pregnant women through a national cohort study and found that HBsAg positive patients increase the risk of premature delivery. The risk of premature delivery in HBeAg negative and HBeAg-positive pregnant women with HBV infection increased by 26% and 20%, respectively. In addition, the risk of PTB before 34 weeks increased by 18% and 34%[12]. This is partly contradictory to our findings that HBV infection is not an independent risk factor for PT[13]B before 37 weeks. Chen et al. reached similar conclusions to our findings; they investigated perinatal data and neonatal outcomes in 380 HBsAg positive and 428 HBsAg-negative women in Jiangsu province and found that the prevalence of PTB was relatively higher in HBsAg positive group (2.9% vs. 1.4%), but it failed to reach statistical significance (p = 0.140)[13]. Similarly, Jing Tan and colleagues conducted a retrospective cohort study of 21,947 singleton newborns and their mothers and found no statistically significant association between maternal HBsAg positivity and PTB (aOR 1.20, 95% CI 0.95–1.51)[14]. This may be related to the different characteristics of the study population. Jiangsu province and Fujian province are southeast coastal areas, where the prevalence of HBV infection is higher, while the PTB rate is lower than that in the southwest regions of China[5, 15], which may lead to insignificant results. In addition, the prospective study of Xu Zhuang et al. [16] suggested that AST, GGT, and elevated bilirubin are independent risk factors for PTB, rather than HBsAg positivity. In our study, after correcting ALT, AST, GGT and other indicators, we found that HBsAg positivity is an independent risk factor for PTB less than 34 weeks, suggesting that the correlation between HBV infection and PTB is not a single abnormal liver function (ALT, AST, GGT). This indicates that the mechanism by which HBV infection causes PTB may be much more complicated.

The related mechanism of HBV infection and PTB is not clear. Some studies believe that the occurrence of PTB is closely related to the maternal-fetal interface. The rich blood supply of the maternal-fetal interface and the immune tolerance microenvironment created by the interaction of immune cells are the

key to embryo implantation. When delivery is approaching, the *in situ* or recruited immune cells form an inflammatory reaction environment locally at the maternal-fetal interface, prompting the fetus to be delivered by the mother. Therefore, the maternal-fetal interface immune microenvironment regulates all aspects of pregnancy and childbirth, and disorder or abnormality in its balance can lead to miscarriage or PTB[17]. The accumulation of HBV-DNA in the placenta and trophoblast cells may trigger the placental inflammatory response at the maternal-fetal interface, prompting the fetus to be discharged from the mother. Zhihua Wan et al. believe that HBV-DNA levels vary in different periods of pregnancy, and that placental inflammation may be caused by HBV-DNA in the second trimester, rather than HBV-DNA in the third trimester. In addition, HBV infects placental trophoblasts in the second trimester, leading to an increase in the level of interleukin-6 (IL-6) in the amniotic fluid secreted by placental trophoblasts[18]. This might be because HBV infection increases the risk of PTB before 34 weeks of gestation, but does not increase the risk of PTB before 37 weeks of gestation. In addition, Ciloannis S. Elefsiniotis et al. found that the presence of HBV-DNA in the cord blood was significantly related to spontaneous preterm delivery in pregnant women with chronic HBV infection [19], but the dose-response relationship needs to be further explored in future studies.

In addition, the relationship between HBV infection and other pregnancy complications and outcomes is controversial. In this study, by comparing the general baseline characteristics of the HBV infection group and the control group, we found that there was no significant difference in the incidence of GDM, PPROM, gestational hypertension, preeclampsia, HELLP, and between the two groups, which is similar to the findings of Bajema et al. [20] ,Reddick et al. [21] Sirilert et al.[22], and Cui et al.[23]. At the same time, the difference in the incidence of miscarriage between the two groups was not statistically significant, which contradicts the previous belief that HBV infection is an independent risk factor for miscarriage by Ai-Ming Cui et al.. The reason for this difference may be attributed to the inclusion of pregnant women from 12–18 weeks and who underwent regular check-ups. Therefore, pregnant women who had miscarriages before 12 weeks were not included in the study. In addition, we also found that the two groups had statistically significant differences in intrahepatic cholestasis during pregnancy ($P < 0.001$). In the meta-analysis conducted by Jiang et al. [24], we found that HBV infection was a high-risk factor for intrahepatic cholestasis during pregnancy. Cai et al.[25] also reached a similar conclusion. As for neonatal outcomes, we found that the two groups had statistically significant differences in birth weight (weight of neonates, LBW, and SGA), which was different from the conclusions of Lao's [26] and Connell's [27] studies.

This study is a single-center retrospective cohort study. There are some limitations of retrospective studies such as selection shifts. However, as a tertiary hospital in Southeast China, the number of patients included in the study is representative, and the results have certain reference value. Nevertheless, further prospective cohort and multicenter research is warranted to expand the research results and promote the research conclusions.

5. Conclusion

In summary, pregnancy combined with HBV infection can increase the risk of PTB before 34 weeks of pregnancy. Pregnant women with HBV infection with HBeAg negative and normal ALT may show increased risk of PTB before 34 weeks. Clinically, pregnant women with HBV infection must be closely monitored, including careful screening of high-risk women. During pregnancy, we must evaluate the condition and provide PTB-related examinations, such as fetal fibronection (fFN) testing and ultrasound measurement, as appropriate. Cervical canal length, abdominal palpation to evaluate uterine contractions, vaginal speculum examination, and cervical dilation monitoring, along with timely preventive cervical cerclage or vaginal progesterone administration for high-risk women help reduce the incidence of adverse outcomes.

6. Abbreviations

HBV, chronic hepatitis B virus; PTB, preterm birth; BMI, body mass index; ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; AST, aspartate aminotransaminase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; TG, triglyceride; CHOL, cholesterol; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; LBW, low birth weight; ICP, intrahepatic cholestasis of pregnancy; PPROM, preterm premature rupture of the membrane; fFN, fetal fibronection.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the data used in our research acquired administrative permissions, consent waiver obtained from the institutional ethics committee of Fujian Provincial Maternity and Children's Hospital. The study was legally approved by the institutional ethics committee of Fujian Provincial Maternity and Children's Hospital and conducted in accord with the guidelines of the Declaration of Helsinki, and the rights of all participants were protected.

Consent for publication

All data was anonymous. Therefore individual consent for publication was not required.

Availability of data and materials

Data were anonymized, and no patient information was included to preserve confidentiality. All data used to reach the aforementioned conclusions is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding statement

This study was supported in part by grants from Guide Fund for the Development of Local Science and Technology from the Central Government (2020L3019), National Health and Family Planning Commission Science Foundation(2019-WJ-04), Fujian Science and Technology Project(2018Y0005), Key Clinical Specialty Discipline Construction of Fujian ,P.R.C ([2015] no. 593).

Authorship contribution statement

S-SZ, QH, J-YY, and H-LZ carried out the field study. H-LZ and R-XC performed the statistical analysis. S-SZ and QH drafted the manuscript. J-YY and H-LZ participated in the study design and coordination and helped to refine the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank all participants in this study and the staff from the Department of Obstetrics, Fujian Provincial Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medicine University for their work on patients enrollment and follow-up.

References

1. Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP: Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev* 2006; 28:112-125.
2. Lao TT, Sahota DS, Law LW, Cheng YK, Leung TY: Age-specific prevalence of hepatitis B virus infection in young pregnant women, Hong Kong Special Administrative Region of China. *Bull World Health Organ* 2014; 92:782-789.
3. Huang Y, Li L, Sun X, Lu M, Liu H, Tang G, Wang D, Hutin YJ: Screening of pregnant women for hepatitis B virus surface antigen (HBsAg) and subsequent management, Qiandongnan prefecture, Guizhou, China, 2010. *Vaccine* 2013; 31 Suppl 9:J62-65.
4. Lao TT: Hepatitis B - chronic carrier status and pregnancy outcomes: An obstetric perspective. *Best Pract Res Clin Obstet Gynaecol* 2020; 68:66-77.
5. Zou L, Wang X, Ruan Y, Li G, Chen Y, Zhang W: Preterm birth and neonatal mortality in China in 2011. *Int J Gynaecol Obstet* 2014; 127:243-247.
6. Elefsiniotis I, Tsoumakas K, Vezali E, Glynou I, Drakoulis N, Saroglou G: Spontaneous preterm birth in women with chronic hepatitis B virus infection. *Int J Gynaecol Obstet* 2010; 110:241-244.
7. Ma XA-O, Sun D, Li C, Ying J, Yan Y: Chronic hepatitis B virus infection and preterm labor(birth) in pregnant women-an updated systematic review and meta-analysis. 2018; 90:93-100.
8. WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. 2015.
9. Zhao Y, Chen Y, Song H, Huang P, Wang L, Liu W, Huang B, Lv F, Huang C, Yan B *et al*: Effects of maternal hepatitis B surface antigen positive status on the pregnancy outcomes: A retrospective

study in Xiamen, China, 2011-2018. *PloS one* 2020; 15:e0229732.

10. Cui AM, Shao JG, Li HB, Shen Y, Chen ZX, Zhang S, Bian ZL, Qin GA-O, Cheng XY: Association of chronic hepatitis B virus infection with preterm birth: our experience and meta-analysis. 2018; 90:93-100.
11. Bierhoff M, Angkurawaranon C, Myat Min A, Gilder ME, Win Tun N, Keereevijitt A, Kyi Win A, Win E, Carrara VI, Brummaier T *et al*: Maternal Hepatitis B Infection Burden, Comorbidity and Pregnancy Outcome in a Low-Income Population on the Myanmar-Thailand Border: A Retrospective Cohort Study. *J Pregnancy* 2019; 2019:11.
12. Liu J, Zhang S, Liu M, Wang Q, Shen H, Zhang Y: Maternal pre-pregnancy infection with hepatitis B virus and the risk of preterm birth: a population-based cohort study. 2017; 5:e624-632.
13. Chen J, Zhang S, Zhou YH, Xu B, Hu Y: Minimal adverse influence of maternal hepatitis B carrier status on perinatal outcomes and child's growth. *J Matern Fetal Neonatal Med* 2015; 28:2192-2196.
14. Tan J, Huang S, He G, Tang L, Ren Y, Zheng J, Liu X, Sun X: Maternal hepatitis B surface antigen carrier status and its impact on neonatal outcomes: a cohort study of 21 947 singleton newborns in China. *J Matern Fetal Neonatal Med* 2017; 30:2219-2224.
15. Chen P, Xie Q, Chen T, Wu J, Wu J, Ruan B, Zhang Z, Gao H, Li L: Hepatitis B virus infection in hilly/mountainous regions of southeastern China: a locality-dependent epidemiology. *BMC Infect Dis* 2017; 17:809.
16. Zhuang X, Cui A, Wang Q, Cheng X, Shen Y, Cai W, Li H, Zhang S, Qin G: Liver Dysfunction during Pregnancy and Its Association of With Preterm Birth in China: A Prospective Cohort Study. *EBioMedicine* 2017; 26:152-156.
17. Green ES, Arck PC: Pathogenesis of preterm birth: bidirectional inflammation in mother and fetus. *Seminars in Immunopathology* 2020; 14:17-34.
18. Wan Z, Zhou A, Zhu H, Lin X, Hu D, Peng S, Zhang B, Du Y: Maternal Hepatitis B Virus Infection and Pregnancy Outcomes: A Hospital-based Case-control Study in Wuhan, China. *J Clin Gastroenterol* 2018; 52:73-78.
19. Elefsiniotis IS, Papadakis M, Vlachos G, Vezali E, Tsoumakas K, Saroglou G, Antsaklis A: Presence of HBV-DNA in cord blood is associated with spontaneous preterm birth in pregnant women with HBeAg-negative chronic hepatitis B virus infection. *Intervirology* 2011; 54:300-304.
20. Bajema KL, Stankiewicz Karita HC, Tenforde MW, Hawes SE, Heffron R: Maternal Hepatitis B Infection and Pregnancy Outcomes in the United States: A Population-Based Cohort Study. *Open Forum Infectious Diseases* 2018; 5.
21. Reddick KL, Jhaveri R, Gandhi M, James AH, Swamy GK: Pregnancy outcomes associated with viral hepatitis. *J Viral Hepat* 2011; 18:e394-398.
22. Sirilert S, Traisrisilp K, Sirivatanapa P, Tongsong T: Pregnancy outcomes among chronic carriers of hepatitis B virus. *Int J Gynaecol Obstet* 2014; 126:106-110.
23. Cui AM, Cheng XY, Shao JG, Li HB, Wang XL, Shen Y, Mao LJ, Zhang S, Liu HY, Zhang L *et al*: Maternal hepatitis B virus carrier status and pregnancy outcomes: a prospective cohort study. 2016;

16:1-8.

24. Jiang R, Wang T, Yao Y, Zhou F, Huang X: Hepatitis B infection and intrahepatic cholestasis of pregnancy: A systematic review and meta-analysis. *Medicine (Baltimore)* 2020; 99:e21416.
25. Cai Q, Liu H, Han W, Liu L, Xu Y, He Y, Li Q, Zhang M, Hu A, Zheng Y: Maternal HBsAg carriers and adverse pregnancy outcomes: A hospital-based prospective cohort analysis. *J Viral Hepat* 2019; 26:1011-1018.
26. Lao TT, Sahota DS, Suen SS, Law LW, Leung TY: Maternal HBsAg status and infant size--a Faustian bargain? *J Viral Hepat* 2012; 19:519-524.
27. Connell LE, Salihu HM, Salemi JL, August EM, Weldeselasse H, Mbah AK: Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. *Liver Int* 2011; 31:1163-1170.

Figures

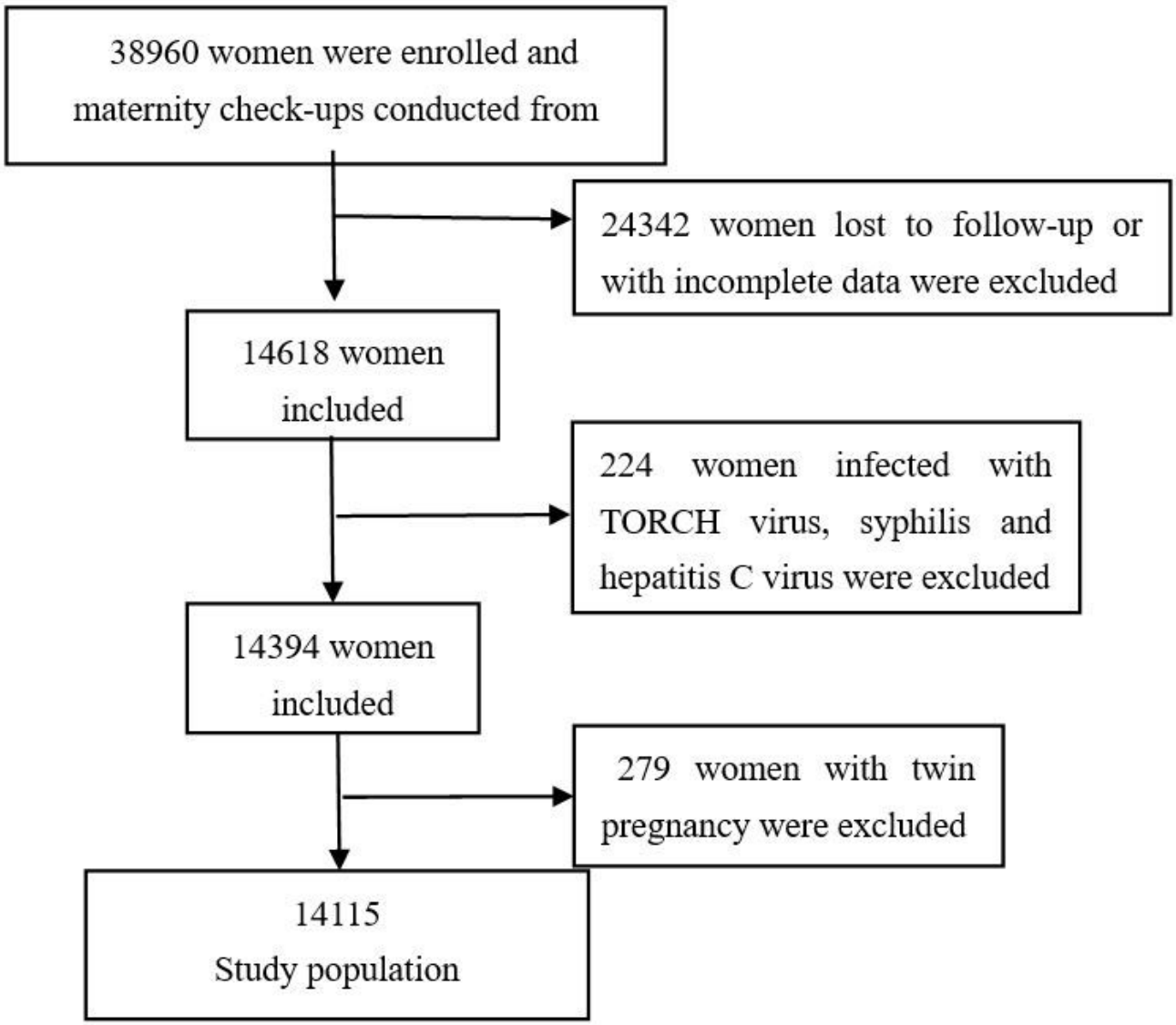

Figure 1

Flowchart of participant selection for the study cohort. TORCH virus includes Toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex virus and other viruses