

Study on the Relationship Between Hepatitis B Virus Infection in Pregnant Women and Adverse Pregnancy Outcomes

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Research Article

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Abstract

Objective: Aim to the relationship between adverse pregnant outcomes with chronic hepatitis B virus (HBV) infection in pregnant women. Simultaneously, assess the incidence of adverse pregnancy outcomes (APO) among different serum HBV status in pregnant women.

Method: From 2017 to 2019, we studied HBsAg (+) pregnant women and HBsAg (-) who gave birth at our hospital in Guangzhou City, China. We compared of the incidence of pregnant women with HBsAg(+) or HBsAg(-). Further, among HBsAg(+) pregnant women, We compared of the incidence of pregnant women with HBeAg(+) group or HBeAg(-) group, high HBV DNA loads (HBV DNA $\geq 2 \times 10^5$ IU/mL) group or low HBV DNA loads (HBV DNA $< 2 \times 10^5$ IU/mL) group, respectively. Finally, multivariate logistic regression analysis was used to evaluate the independent association between HBV infection and the risk of developing APO.

Result: First, Our research Indicates that the rates of gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy (ICP), premature rupture of membrane (PROM), Fetal distress (FD), Oligohydramnios, Premature delivery (PD), Low birth weight (LBW), Meconium contamination (MC), Neonatal hyperbilirubinemia(NH) in HBsAg(+) group were higher than those in HBsAg(-) group ($P < 0.05$). Second, among 711 HBsAg(+) pregnant women, the rates of GDM and ICP in high loads of HBV DNA were higher than those in low loads of HBV DNA group ($P < 0.05$). Similarly, The rates of ICP in HBeAg(+) group were higher than those in HBeAg(-) group. Further, through multivariable logistical regression model analysis, we observed maternal HBsAg carrier (OR, 6.758; 95% CI, 2.358-19.369) had an independent risk for ICP. Similarly, HBsAg carrier(OR, 1.101; 95% CI, 1.066-1.137) ,advanced age (OR, 1.407; 95% CI,1.016-1.137) and abortion(OR,1.446; 95% CI, 1.062-1.969) had independent risk for GDM.

Conclusions: Chronic HBV infection can increase the rate of host adverse pregnancy outcomes (APO). The maternal viral load and HBeAg status were significantly associated with the incidence of GDM and ICP. Maternal HBsAg carrier had an independent risk for GDM and ICP.

Introduction

Chronic hepatitis B (CHB) remains an important public health problem, with approximately 240 million HBV-infected individuals worldwide^[1,2]. Among those with CHB infection, approximately 15–40% will further develop more harmful complications such as cirrhosis, liver failure or even hepatoma^[3]. According to the World Health Organization (WHO) statistical report, China is one of the major endemic areas for CHB infection, where the prevalence of CHB in individuals under 60 years old is 7.2%^[4]. Many studies show that the infection rate of hepatitis B virus is at a high level in Chinese fertile women, around 6.7–8%^[5,6]. Previous studies on CHB infection in pregnant women mostly focused on vertical mother-to-child transmission (vMTCT), and viral load was considered to be the biggest risk factor affecting vMTCT. However, there were few studies on whether CHB infection had an impact on the occurrence of APO^[7,8].

Besides the impact of CHB on vMTCT, existing studies have shown that there is a correlation between pregnancy complicated with HBV infection and the occurrence of APO. HBV infection increases the risk of complications such as PD and GDM^[9,10,11]. But, some scholars do not support this view^[12,13]. Therefore, whether pregnancy with CHB infection increases the risk of APO is full of controversy.

In addition, existing studies on pregnant patients with HBV infection and APO are insufficient. First, most studies analyze APO from a single aspect (HBsAg positive, HBeAg positive, or DNA viral load); Secondly, in terms of DNA viral load analysis, the lower limit of clinical detection (100IU/ml) is mostly used as the grouping basis, lacking clinically common indicators with high viral load (over 2×10^5 IU/mL). Furthermore, because the influencing factors of APO are complex and diverse, most studies have not further evaluated the other related influencing factors except HBV infection for APO. Finally, most of the studies were based on methods such as case-control studies and retrospective cohort studies, lacking prospective clinical observation studies.

Considering the above deficiencies, this article conducted a prospective hospital-based cohort study. The objective was to further confirm the influence of HBsAg, viral load and HBeAg in early pregnancy on APO. To explore the risk factors for APO; To further guide clinical management of pregnant women with HBV infection, and to provide ideas and basis for other related studies.

Methods

Study Design and Participant Population

From January 2017 through December 2019, after signing the informed consent, 740 individuals were included in each group of HBsAg(+) and HBsAg(-), and there were 29 HBsAg (+) pregnant women who were lost to follow-up after 6 weeks postpartum, while 65 HBsAg (-) pregnant women who dropped out or lost to follow-up. Finally, we recruited a total of 1386 pregnant women who gave birth at our hospital in Guangzhou, China. Including 711 HBsAg-positive and 675 HBsAg-negative mothers were studied. 151 of the 711 HBsAg-positive women also had high loads of HBV DNA (over 2×10^5 IU/mL), 189 of the 711 HBsAg-positive women had HBeAg-positive. The clinical records of the two groups were retrieved, including age, prenatal weight, parity, history of abortion, newborn sex. From 14 weeks of pregnancy to postpartum week 6, All the mothers were followed.

Eligible participants were pregnant women, 12–14 weeks of pregnancy, who had chronic HBV infection. The exclusion criteria were the following: co-infection with hepatitis C virus (HCV), hepatitis D virus (HDV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), human herpes virus (HHV), cytomegalovirus (CMV), rubella virus (RUV), Smoking or Drinking, evidence of hepatocellular carcinoma or liver decompensation, a history of Diabetes, high blood pressure, heart disease or renal dysfunction.

Detection

HBsAg-positive women were used to Examine HBV serum markers (HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc) were quantified by the Abbott ARCHITECT HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc assays, respectively, (detection limits: 1.00 s/co, 10.00 IU/L, 1.00 s/co, 1.00 s/co and 1.00 s/co, respectively; Abbott Laboratories, Chicago, USA). The HBV DNA load was measured by a real-time PCR-based (detection limit: 100 IU/mL, Da'an Gene Co. Ltd., Sun Yat-Sen University, Guangdong, China).

Statistical Analyses

The baseline characteristics of the patients were reported with the use of descriptive statistics, which includes percentages. In univariate analyses, categorical data were compared by chi-square tests was used to assess the homogeneity of the odds ratios (ORs) and 95% confidence intervals (CIs). logistic regression analysis was used to analyze the association between HBsAg positivity and ICP or GDM. *P* values of less than 0.05 were assessed to be of statistical significance. All analyses was performed using the SPSS version 22.0 software (IBM, NY, USA).

Results

We compared the incidence of adverse pregnancy outcomes under different conditions (Fig. 1), the specific results are as follow.

Maternal features and incidence of adverse pregnancy outcomes with respect to HBsAg status

No statistically significant differences in the percentage of age, prenatal weight, parity, history of abortion, newborn sex use were observed between the two groups ($P > 0.05$) (Table 1). Compared with the HBsAg-negative, maternal HBsAg carriers had higher incidences of adverse pregnancy outcomes, including GDM (17.4% vs 11.9%), ICP (4.1% vs 0.7%), PROM (22.1% vs 14.7%), FD (7.5% vs 3.1%), OLI (14.1% vs 8.0%), PD (6.5% vs 3.5%), LBM (8.9% vs 5.6%), MC (10.3% vs 6.2%), NH (20.3% vs 11.9%). And no statistically significant differences in the incidence of PIH (2.1% vs 2.2%), PE (2.9% vs 1.5%), ECL (0.3% vs 0), PH (1.9% vs 1.3%), PP (1.1% vs 0.4%), STI (0.6% vs 1.6%), FM (3.5% vs 2.0%), CM (0.4% vs 0) were found between the two groups ($P > 0.05$) (Table 1).

Table 1

Comparison of the baseline and incidence of adverse pregnancy outcomes between HBsAg(-) and HBsAg(+) pregnant women

	HBsAg(-)	HBsAg(+)	P
Baseline			
AgeH	100(14.8%)	131(18.1%)	0.096
BMIH	167(25.2%)	156(22.7%)	0.279
NopF	330(48.9%)	339(46.9%)	0.454
HomY	239(35.4%)	253(35.0%)	0.871
FsB	371(55.0%)	393(54.4%)	0.820
Gestational complications			
PIH	15(2.2%)	15(2.1%)	0.849
PE	10(1.5%)	21(2.9%)	0.071
ECL	0(0%)	2(0.3%)	0.500
GDM	80(11.9%)	126(17.4%)	0.003
ICP	5(0.7%)	30(4.1%)	<0.001
PH	9(1.3%)	14(1.9%)	0.376
PP	3(0.4%)	8(1.1%)	0.162
PROM	99(14.7%)	160(22.1%)	<0.001
FD	21(3.1%)	54(7.5%)	<0.001
OLI	54(8.0%)	102(14.1%)	<0.001
STI	11(1.6%)	4(0.6%)	0.051
PD	23(3.5%)	47(6.5%)	0.010
LBW	37(5.6%)	64(8.9%)	0.018
FM	13(2.0%)	25(3.5%)	0.086
MC	41(6.2%)	74(10.3%)	0.006
NH	78(11.9%)	145(20.3%)	<0.001
CM	0(0%)	3(0.4%)	0.096
* Age \geq 35Y (AgeH); BMI \geq 28kg/m ² (BMIH); Number of pregnancies: first pregnancy (NopF); History of miscarriage: yes (HomY); fetus's sex: boy (FsB); pregnancy-induced hypertension (PIH); pre-eclampsia (PE); eclampsia (ECL); gestational diabetes mellitus (GDM); intrahepatic cholestasis of pregnancy (ICP); postpartum hemorrhage (PH); placenta previa (PP); premature rupture of membrane (PROM); Fetal distress (FD); oligohydramnios (OLI); stillbirth (STI); Premature delivery (PD); Low birth weight (LBW); fetal macrosomia (FM); Meconium contamination (MC); Neonatal hyperbilirubinemia (NH); congenital malformations (CM)			

Incidence of adverse pregnancy outcomes with respect to virological traits of hepatitis B virus infection in pregnant women

First, HBsAg-positive pregnant women were classified into two groups: group 1, high loads of HBV DNA (over 2×10^5 IU/mL) and group 2, low HBV DNA loads. Incidences of ICP in HBsAg-positive pregnant women with high HBV DNA loads and low HBV DNA loads were 10.6% and 2.5%, respectively. Similarly, incidences of GDM were 23.2% and 16.1%, respectively. A significantly higher incidence of ICP and GDM were found in group 1 compared to group 2. These differences were statistically significant (Table 2).

Table 2

The incidence of pregnancy outcomes with different viral load in HBsAg(+) pregnant women

Gestational complications	HBVDNA < 2×10 ⁵ IU/mL	HBVDNA ≥ 2×10 ⁵ IU/mL	P
GDM	90(16.1%)	35(23.2%)	0.042
ICP	14(2.5%)	16(10.6%)	< 0.001
PROM	118(21.1%)	41(27.2%)	0.111
FD	41(7.3%)	12(7.9%)	0.795
OLI	78(13.9%)	23(15.2%)	0.684
PD	37(6.6%)	10(6.7%)	0.976
LBW	55(9.9%)	9(6.0%)	0.146
MC	62(11.2%)	11(7.4%)	0.180
NH	113(20.4%)	30(20.1%)	0.944

Second, HBsAg-positive pregnant women were classified into two groups: group3 (HBeAg-positive) and group 4 (HBeAg-negative). Incidences of ICP in Group3 was approximately four times higher than Group 4. These differences were statistically significant (Table 3).

Table 3

The incidence of adverse pregnancy outcomes with different HBeAg states in HBsAg(+) pregnant women

Gestational complications	HBeAg(-)	HBeAg(+)	P
GDM	90(17.2%)	35(18.5%)	0.693
ICP	13(2.5%)	17(9.0%)	< 0.001
PROM	120(23.0%)	39(20.6%)	0.506
FD	39(7.5%)	14(7.4%)	0.977
OLI	73(14.0%)	28(14.8%)	0.779
PD	35(6.7%)	12(6.5%)	0.914
LBW	50(9.6%)	14(7.6%)	0.405
MC	58(11.2%)	15(8.1%)	0.243
NH	107(20.7%)	36(19.5%)	0.728

Univariate and multivariate logistic regression analyses of factors related to ICP and GDM

Among the 1386 pregnant women enrolled, 35 (2.5%) were ICP patient. HBsAg carriage were observed with the increased incidence of ICP, with an OR value of 5.801(95% CI 2.237–15.04). But in Age (OR 1.046 95%CI 0.429–2.55),BMI, NOP (OR 0.916 95%CI 0.467–1.796),HOM(OR 0.731 95%CI 0.348–1.535),SU (OR 1.232 95%CI 0.532–2.853), HOAP (OR 0.974 95%CI 0.965–0.98) and PIH, there was no significant difference between the mothers with ICP and those without. (Table 4). Similarly, 206 were GDM patient in pregnant women, Age,NOP,HOM and HBsAg carriage were associated with the increased incidence of GDM, with an OR value of 2.952(95%CI 2.11–4.131), 0.713(95%CI 0.528–0.963), 1.643(95%CI 1.211–2.204) and 1.567(95%CI 1.158–2.12). And there was no significant difference in BMI, SU, HOAP and PIH between pregnant women with GDM and without GDM. (Table 5).

Table 4
Single factor regression analysis of intrahepatic cholestasis during pregnancy

		None-ICP(n%)	ICP(n%)	χ^2	P	OR	95%CI
Age	< 35Y	1138(83.5%)	29(82.9%)	0.010	0.920	1.046	0.429–2.550
	≥ 35Y	225(16.5%)	6(17.1%)				
BMI	18.5–23.9	340(25.8%)	10(30.3%)	0.375	0.829	-	-
	24.0-27.9	662(50.2%)	16(48.5%)				
	≥ 28	316(24.0%)	7(21.2%)				
Nop	None	710(52.1%)	19(54.3%)	0.066	0.797	0.916	0.467–1.796
	first pregnancy	653(47.9%)	16(45.7%)				
Hom	None	881(64.6%)	25(71.4%)	0.690	0.406	0.731	0.348–1.535
	Yes	482(35.4%)	10(28.6%)				
SU	None	1133(83.1%)	28(80.0%)	0.237	0.627	1.232	0.532–2.853
	Yes	230(16.9%)	7(20.0%)				
HOAP	None	1288(94.5%)	35(100%)	-	*0.255	0.974	0.965–0.98
	Yes	75(5.5%)	0(0%)				
PIH	None	1333(97.8%)	35(100%)	-	*1.000	-	-
	Yes	30(2.2%)	0(0%)				
HBsAg	Negative	670(49.2%)	5(14.3%)	16.617	< 0.001	5.801	2.237–15.04
	Positive	693(50.8%)	30(85.7%)				
*: Fisher #: Chi-square Test Correction formula							
Scar uterus (SU); histories of abnormal pregnancy (HOAP)							

Table 5
Single facto regression analysis of gestational diabetes mellitus

		None-GDM(n%)	GDM(n%)	χ^2	P	OR	95%CI
Age	< 35Y	1027(86.2%)	140(68.0%)	42.619	< 0.001	2.952	2.110–4.131
	≥ 35Y	164(13.8%)	66(32.0%)				
BMI	18.5–23.9	300(26.0%)	50(25.4%)	1.595	0.450	-	-
	24.0-27.9	584(50.7%)	93(47.2%)				
	≥ 28	269(23.3%)	54(27.4%)				
Nop	None	606(50.9%)	122(59.2%)	4.897	0.027	0.713	0.528–0.963
	first pregnancy	585(49.1%)	84(40.8%)				
Hom	None	792(66.5%)	113(54.9%)	10.437	0.001	1.634	1.211–2.204
	Yes	399(33.5%)	93(45.1%)				
SU	None	996(83.6%)	164(79.6%)	2.010	0.156	1.308	0.902–1.898
	Yes	195(16.4%)	42(20.4%)				
HOAP	None	1129(94.8%)	193(93.7%)	0.422	0.516	1.227	0.662–2.273
	Yes	62(5.2%)	13(6.3%)				
PIH	None	1166(97.9%)	201(97.6%)	0.090	0.764	1.160	0.439–3.066
	Yes	25(2.1%)	5(2.4%)				
HBsAg	Negative	594(49.9%)	80(38.8%)	8.571	0.003	1.567	1.158–2.12
	Positive	597(50.1%)	126(61.2%)				

To judge whether HBsAg carriage was an independent risk factor for GDM or ICP, A multivariable logistic regression analysis was used in our study, Maternal HBsAg carriage was an independent risk factor for ICP, with an OR value of 7.758(95%CI 2.358–19.369). (Table 6). But a significant association of age, HOM and maternal HBsAg carriage with the increased risk of GDM was discovered, with an OR value of 1.101 (95%CI 1.066–1.137),1.407 (95%CI 1.066–1.137) and 1.446 (95%CI 1.062–1.969). respectively. (Table 7)

Table 6
Logistic multivariate regression analysis of intrahepatic cholestasis during pregnancy

	B	S.E	Wald	P	OR	95%CI
HBsAg	1.911	0.537	12.647	< 0.001	6.758	2.358–19.369

Table 7
Logistic multivariate regression analysis of gestational diabetes mellitus

	B	S.E	Wald	P	OR	95%CI
Age	0.096	0.016	34.487	< 0.001	1.101	1.066–1.137
Hom	0.342	0.158	4.690	0.030	1.407	1.033–1.917
HBsAg	0.369	0.158	5.476	0.019	1.446	1.062–1.969

Discussion

CHB is still one of the major infectious diseases in the world. Previous studies on HBV infection in pregnant women mainly focus on vMTCT, but there were few studies on whether CHB infection had an impact on the occurrence of APO.

The existing research results show that there is a correlation between HBV infection in pregnancy with APO. HBV infection increases the incidence of PD, GDM, LBW [9,10,11], which is consistent with our findings. The reason why CHB infection increases the incidence of some APO may be related to the effect of HBV virus on liver function of inactivating enzymes and hormones. During pregnancy, women produce more endogenous hormones, which will put a heavier burden on the liver. The virus damages hepatocytes, which leads to a relatively high level of estrogen. High level of estrogen will lead to APO [14]. Furthermore, when the placenta and fetal membranes are infected by HBV, the chorionic vessels will change accordingly, causing the blood circulation of the placenta to drop. Reduced intrauterine blood oxygen supply will also increase the risk of APO [15].

It is noteworthy that further analysis in this study found that the incidence of GDM and ICP in HBsAg(+) pregnant women with high viral load (2×10^5 IU/ml) and HBeAg(+) were higher than their control group. This may be related to the maternal excessive inflammatory response. Existing studies have shown that maternal excess inflammation increases the risk of complications during pregnancy [16,17]. HBeAg is a marker of active HBV replication [18]. There was a strong inflammatory response in HBV infected patients with HBeAg (+) or high load of HBV DNA [19,20]. HBV DNA load is an important marker to predict the course of severe complications from HBV immune tolerance [19,21]. Chronic inflammation caused by HBV is associated with insulin resistance. In HBV infected patients, the insulin resistance level is significantly higher than the normal population [22]. In addition, HBsAg and HBV DNA were found in the pancreas of patients infected with HBV. These suggest that HBV may cause damage to pancreatic tissue, leading to insufficient insulin secretion [23].

Logistic model was established to analyze the influencing factors of APO and it was found that CHB infection could be an independent risk factor for ICP. Many studies also showed that the risk of ICP in pregnant women was higher when HBeAg was positive [24,25]. We think this may be related to the downgrading of the expression of NTCP (sodium taurocholate cotransporting polypeptide). Human NTCP has been identified as a functional receptor for HBV. HBV can mediate the infection through the specific binding of surface antigen [26,27,28]. Meanwhile, NTCP is responsible for the transmembrane transport of sodium and bile acids in liver cells, and is responsible for about 80% of bile acid reuptake [29]. NTCP can transport bile acids to hepatocytes in the enterohepatic circulation and play an important role in the hepatoenteric circulation of cholic acid to maintain the dynamic balance of bile acids. Some studies have suggested that defects in NTCP may lead to intractable hyperbile acidemia [30,31]. In patients with CHB, hepatocytes are constantly destroyed and multiplied. In proliferative hepatocytes, the NTCP expression on cell membrane is decreasing [32]. Moreover, existing research suggest that, ICP is related to PGE2 (prostaglandin E2), which will affects the function of natural killer cells [33,34]; Mutations in genes associated with drug resistance (such as ABCB 11 [35], ABCC 2 [36], ABCB 4 [37,38], NR1H4 [39]).

To sum up, pregnancy with HBV infection is a serious threat to maternal and child health. It is necessary to pay attention to the health education of pregnant women, the HVB DNA in early pregnancy and the regular examination of liver function during pregnancy (especially the related examination of gestational diabetes and cholestasis). Consulting about potential risks as well as focusing on antenatal surveillance for APO in HBV-infected pregnant women may be necessary.

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of The Fifth Affiliated Hospital of Guangzhou Medical University. Written informed consent was obtained from individual or guardian participants.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Zhi-Hao Huang, Shi Ou-Yang, Ting-Ting Peng, Jun-Chao Qiu, Dong-Dong Yu developed the concept of the study, Mei-Ling Liu, Xin-Yue Huang, Guo-Jun Xu participated in its design and coordination and helped draft the manuscript. Ting-Ting Peng, Zhi-Hao Huang, Sheng-Guang Yan contributed to the acquisition and interpretation of data. Shi Ou-Yang, Jun-Chao Qiu provided a critical review and substantially revised the manuscript. All authors read and approved the final manuscript.

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Figures

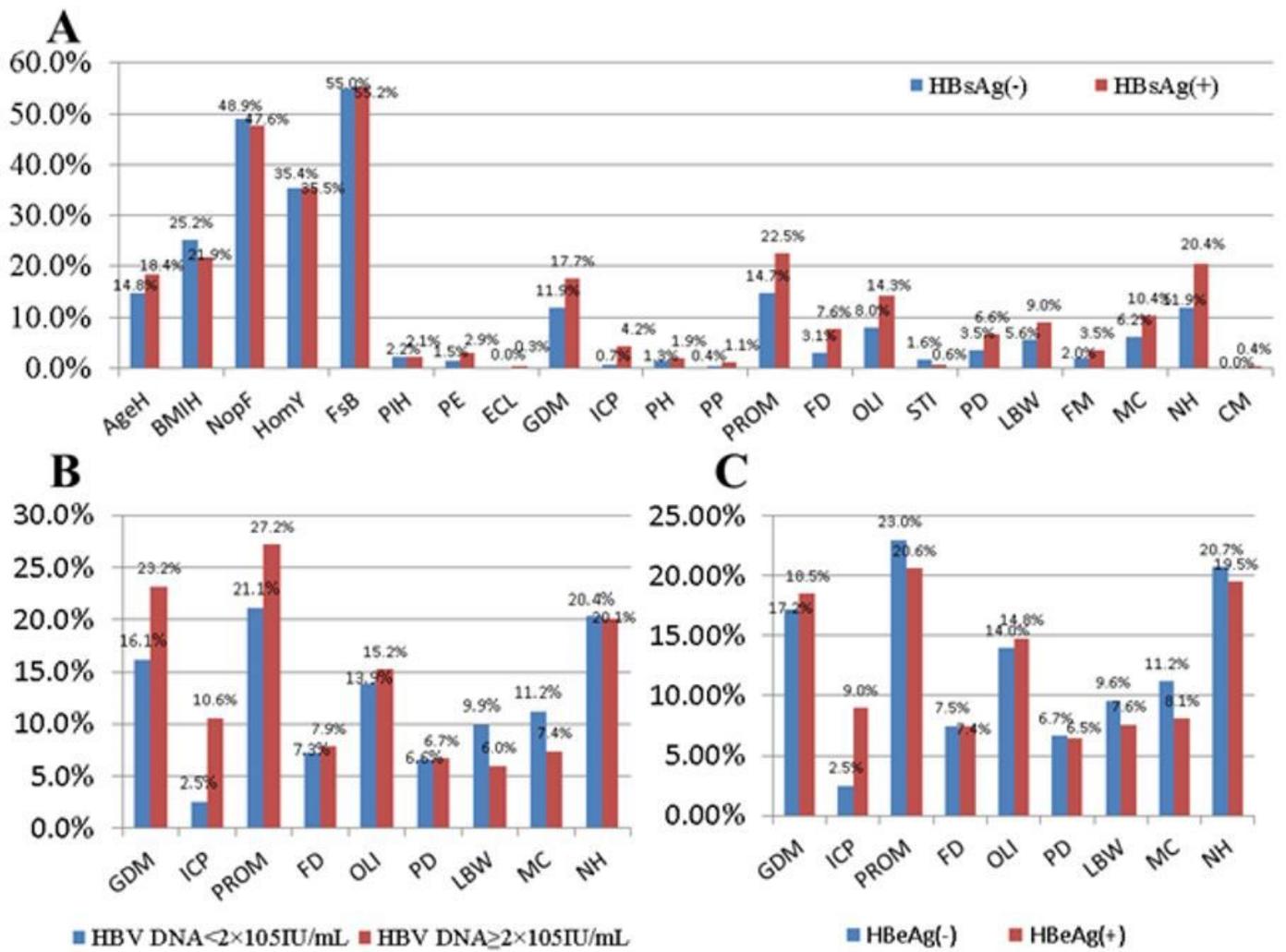


Figure 1

Comparison of the incidence of adverse pregnancy outcomes under different conditions (A) Comparison of the baseline and incidence of adverse pregnancy outcomes between HBsAg(-) and HBsAg(+) pregnant women (B) The incidence of pregnancy outcomes with different viral load in HBsAg(+) pregnant women (C) The incidence of adverse pregnancy outcomes with different HBeAg states in HBsAg(+) pregnant women