A higher rate of adverse pregnancy outcome in HBsAg-positive pregnant woman

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Abstract

Objective

The aim of this study was to study the relationship between adverse pregnant outcomes(APO) with chronic hepatitis B virus (HBV) infection 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 outcomes of pregnant women with HBsAg(+) or HBsAg(-). Further, among HBsAg(+) pregnant women, We compared of the outcomes of pregnant women with HBeAg(+) group or HBeAg(-) group, HBV DNA above 2×10e^{5}IU/mL group or HBV DNA below 2×10e^{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 HBV DNA above 2×10e^5 IU/mL were higher than those in HBV DNA below 2×10e^5 IU/mL 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,1.033-1.917) 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 appearance 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, some existing studies have shown that there is a correlation between pregnancy complicated with HBV infection and the occurrence of APO. We reviewed the relevant literature along a timeline (Table 1). Interestingly, previous studies were mostly negative [9, 10, 11], while recent studies were mostly positive [12, 13, 14, 15]. Given potential publication bias, exact conclusions are not known.

Table 1
A review of previous related studies

Researcher	Time	Method	Sample size	factors	OR	95%CI
li J G P et al	1988	case-control study	120	All negative	-	-
Wong S et al	1999	retrospective cohort study	7105	All negative	-	-
Safir A et al	2010	retrospective cohort study	186619	Preterm delivery	1.5	1.2-1.9
				perinatal mortality	1.8	1.1-2.9
				Congenital malformation	1.4	1.1-1.9
Lao T T et al	2013	retrospective cohort study	86537	Pregnancy-induced hypertension	0.79	0.66-0.95
Wan Z et al	2018	case-control study	3225	Pregnancy-induced hypertension	2.20	1.30-3.73
				fetal distress;	1.40	1.09-1.78
				macrosomia;	1.68	1.19-2.37
Cai Q et al	2019	Prospective cohort study	3416	Intrahepatic cholestasis pregnancy	1.70	1.67-2.49
Zheng, S et al	2021	retrospective cohort study	14115	premature delivery	1.77	1.046-2.997

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 $2\times10e^5$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

Research on factors

Core exploration factor: HBsAg; HBeAg; HBV DNA load

Potential confounding factors: Age; BMI; Number of pregnancies; History of miscarriage; Fetus's sex; Scar uterus; Histories of abnormal pregnancy

Adverse pregnancy outcomes (APO):

(1) Pregnancy-induced hypertension (PIH): blood pressure ≥140/90mmHg detected for the first time during pregnancy.

(2) Gestational diabetes mellitus (GDM): abnormal glucose metabolism first discovered during pregnancy.

(3) Intrahepatic cholestasis of pregnancy (ICP): the level of total bile acid was ≥10μmol/L for the first time during pregnancy

(4) Stillbirth (STI): intrauterine death of the fetus occurs when the gestation cycle is >20 weeks

(5) Premature delivery (PD): the fetus delivered <37 weeks.

(6) Low birth weight (LBW)/Fetal macrosomia (FM): baby birth weight <2500g/ baby birth weight ≥4000g

(7) Meconium contamination(MC): confirmed by amniotic fluid examination and ultrasound examination.

(8) Neonatal hyperbilirubinemia (NH): jaundice appeared within 24 hours after birth, serum bilirubin value > 102μmol/L(6mg/D1); Or serum bilirubin concentration: term infants > 220.6μmol/L(12.9mg/d1), premature infants > 255μmol/L(15mg/d1); Or serum bilirubin increased by more than 85μmol/L(5mg/d1). Or jaundice lasts more than 2 weeks, or shows progressive aggravation.

(9) Congenital malformations (CM): abnormal morphology, structure, function or metabolism of the fetus caused by genetic or environmental factors.

(10) Postpartum hemorrhage (PH): blood loss >500 mL within 24 h after vaginal delivery or blood loss >1000 mL after artificial cesarean section.

(11) Placenta previa (PP): the gestation cycle is >28 weeks, the placenta is lower than the fetal exposure part, attached to the lower segment of the uterus, the lower margin reaches or covers the cervical opening.

(12) Premature rupture of membrane (PROM): spontaneous rupture of membranes occurs before delivery.

(13) Fetal distress (FD): fetal heart rate <120/min or >160/min, late deceleration of fetal heart, variable deceleration and lack of deceleration at baseline

(14) Oligohydramnios (OLI): amniotic fluid <300mL; Maximum amniotic fluid depth ≤ 2.0cm, amniotic fluid index ≤5cm.

Study Design and Participant Population

From January 2017 to December 2019, after meeting the inclusion and exclusion criteria and signing informed consent, all 740 HBsAg(+) people were included as the exposed group. When HBsAg(+) people was included, all HBsAg(-) people that met the standard were randomly selected as the control group in accordance with 1:1 taking the workload into consideration.

The inclusion criteria:

(1)12-14 weeks of pregnancy

(2)If HBsAg is positive, it should be positive for more than 6 months, and they have to take tenofovir disoproxil fumarate (TDF) regularly.

The exclusion criteria:

(1)Co-infection with hepatits C virus (HCV), hepatitis D virus (HDV), human immunodeficiency virus (HIV), epstein-barr virus(EBV), human herpes virus (HHV),cytomegalovirus (CMV), rubella virus (RUV)

(2)Common female reproductive system infections such as HPV, genital/ureaplasma urealyticum, group B streptococcus infection

(3)Toxoplasma infection

(4)Smoking or Drinking in pregnancy

(5)Evidence of hepatocellular carcinoma or liver decompensation

(6)A history of Diabetes, high blood pressure, heart disease or renal dysfunction.

After the follow-up, a total of 29 HBsAg(+) pregnant women were excused or lost to follow-up, while 65 HBsAg(-) pregnant women 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(+) and 675 HBsAg(-) mothers were studied. 151 of the 711 HBsAg(+) women also had high loads of HBV DNA (over 2×10^5 IU/mL), 189 of the 711 HBsAg(+) women had HBeAg(+). 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.

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

Comparison of maternal characteristics and adverse pregnancy outcomes between HBsAg(+) and HBsAg(-) groups

No statistically significant differences in the percentage of age, prenatal weight, parity, history of abortion, newborn sex were observed between the two groups ($P > 0.05$) (Table 2).

Table 2

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

	HBsAg(-)N=675		HBsAg(+)N=711		P
	n	%	n	%	
Baseline					
AgeH	100	14.8%	129	18.1%	0.096
BMIH	170	25.2%	161	22.7%	0.279
NopF	330	48.9%	333	46.9%	0.454
HomY	239	35.4%	249	35.0%	0.871
FsB	371	55.0%	387	54.4%	0.820
APO					
PIH	15	2.2%	15	2.1%	0.849
GDM	80	11.9%	124	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%	157	22.1%	0.001
FD	21	3.1%	53	7.5%	0.001
OLI	54	8.0%	100	14.1%	0.001
STI	11	1.6%	4	0.6%	0.051
PD	24	3.5%	46	6.5%	0.010
LBW	38	5.6%	63	8.9%	0.018
FM	13	2.0%	25	3.5%	0.086
MC	42	6.2%	73	10.3%	0.006
NH	80	11.9%	144	20.3%	0.001
CM	0	0%	3	0.4%	0.096

* Age≥35Y (AgeH); BMI≥28kg/m^2 (BMIH); Number of pregnancies: first pregnancy (NopF); History of miscarriage: yes (HomY); fetus's sex: boy (FsB); pregnancy-induced hypertension (PIH); 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)

Compared with the HBsAg-negative, maternal HBsAg carriers had higher appearance 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%), all these differences were statistically significant(*P*<*0.05*). And no statistically significant differences in the appearance of PIH (2.1% vs 2.2%), 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 2).

Comparison of adverse pregnancy outcomes between HBeAg(+) and HBeAg(-) groups as well as HBV DNA above 2×10e ^{5} IU/mL and HBV DNA below 2×10e^5 IU/mL

First, HBsAg-positive pregnant women were classified into two groups: group 1 (HBV DNA above 2×10e^5 IU/mL) and group 2(HBV DNA below 2×10e^5 IU/mL). Appearance of ICP in HBsAg-positive pregnant women in group 1 and group 2 were 10.6% and 2.5%, respectively. Similarly, appearance of GDM were 23.2% and 16.1%, respectively. Significantly higher appearance of ICP and GDM were found in group 1 compared to group 2(*P*<*0.05*) (Table 3).

Table 3
The appearance of pregnancy outcomes with different viral load in HBsAg(+) pregnant women

APO	HBVDNA<2×10e^{5}IU/mL N=560		HBVDNA≥2×10e^{5}IU/mL N=151		P
	n	%	n	%	
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	114	20.4%	30	20.1%	0.944

*gestational diabetes mellitus (GDM); intrahepatic cholestasis of pregnancy (ICP); premature rupture of membrane (PROM); Fetal distress (FD); oligohydramnios (OLI); Fetal distress (FD); Low birth weight (LBW); Meconium contamination (MC); Neonatal hyperbilirubinemia (NH);

Second, HBsAg-positive pregnant women were classified into two groups: group3 (HBeAg-positive) and group 4 (HBeAg-negative). Appearance of ICP in Group3 was approximately four times higher than Group 4(*P*<*0.05*) (Table 4).

Table 4
The appearance of adverse pregnancy outcomes with different HBeAg states in HBsAg(+) pregnant women

APO	HBeAg(-) N=522		HBeAg(+) N=189		P
	n	%	n	%	
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	108	20.7%	37	19.5%	0.728

*gestational diabetes mellitus (GDM); intrahepatic cholestasis of pregnancy (ICP); premature rupture of membrane (PROM); Fetal distress (FD); oligohydramnios (OLI); Fetal distress (FD); Low birth weight (LBW); Meconium contamination (MC); Neonatal hyperbilirubinemia (NH);

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 appearance of ICP, with an OR value of 5.801(95% CI 2.237-15.04) (*P□0.05*), while 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(*P□0.05*) (Table 5).

Table 5
Single factor regression analysis of intrahepatic cholestasis during pregnancy

		None-ICP N=1351		ICP N=35		χ^2	P	OR	95%CI
		n	%	n	%				
Age	<35Y	1128	83.5%	29	82.9%	0.010	0.920	1.046	0.429-2.550
	≥35Y	223	16.5%	6	17.1%				
BMI	18.5-23.9	349	25.8%	11	30.3%	0.375	0.829	-	-
	24.0-27.9	678	50.2%	17	48.5%				
	≥28	324	24.0%	7	21.2%				
Nop	None	704	52.1%	19	54.3%	0.066	0.797	0.916	0.467-1.796
	first pregnancy	647	47.9%	16	45.7%				
Hom	None	873	64.6%	25	71.4%	0.690	0.406	0.731	0.348-1.535
	Yes	478	35.4%	10	28.6%				
SU	None	1123	83.1%	28	80.0%	0.237	0.627	1.232	0.532-2.853
	Yes	228	16.9%	7	20.0%				
HOAP	None	1277	94.5%	35	100%	-	#0.255	0.974	0.965-0.98
	Yes	74	5.5%	0	0%				
PIH	None	1321	97.8%	35	100%	-	#1.000	-	-
	Yes	30	2.2%	0	0%				
HBsAg	Negative	665	49.2%	5	14.3%	16.617	<0.001	5.801	2.237-15.04
	Positive	686	50.8%	30	85.7%				

Similarly, 206 were GDM patient in pregnant women, Age, NOP, HOM and HBsAg carriage were associated with the increased appearance 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) (*P□0.05*). And there was no significant difference in BMI, SU, HOAP and PIH between pregnant women with GDM and without GDM(*P□0.05*) (Table 6).

Table 6
Single factor regression analysis of gestational diabetes mellitus

		None-GDM N=1180		GDM N=206		χ^2	P	OR	95%CI
		n	%	n	%				
Age	<35Y	1017	86.2%	140	68.0%	42.619	<0.001	2.952	2.110-4.131
	≥35Y	163	13.8%	66	32.0%				
BMI	18.5-23.9	307	26.0%	52	25.4%	1.595	0.450	-	-
	24.0-27.9	598	50.7%	97	47.2%				
	≥28	275	23.3%	57	27.4%				
Nop	None	601	50.9%	122	59.2%	4.897	0.027	0.713	0.528-0.963
	first pregnancy	579	49.1%	84	40.8%				
Hom	None	785	66.5%	113	54.9%	10.437	0.001	1.634	1.211-2.204
	Yes	395	33.5%	93	45.1%				
SU	None	986	83.6%	164	79.6%	2.010	0.156	1.308	0.902-1.898
	Yes	194	16.4%	42	20.4%				
HOAP	None	1119	94.8%	193	93.7%	0.422	0.516	1.227	0.662-2.273
	Yes	61	5.2%	13	6.3%				
PIH	None	1155	97.9%	201	97.6%	0.090	0.764	1.160	0.439-3.066
	Yes	25	2.1%	5	2.4%				
HBsAg	Negative	589	49.9%	80	38.8%	8.571	0.003	1.567	1.158-2.120
	Positive	591	50.1%	126	61.2%				

*Number of pregnancies (Nop); History of miscarriage (Hom); Scar uterus (SU); histories of abnormal pregnancy (HOAP) pregnancy-induced hypertension (PIH);

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 7). In addition, 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 1.033-1.917) and 1.446 (95%CI 1.062-1.969), respectively (Table 8).

Table 7
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 8
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
*History of miscarriage (Hom);						

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, and 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 appearance of ICP [12], which is consistent with our findings. The reason why CHB infection increases the appearance 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[16]. 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 [17].

It is noteworthy that further analysis in this study found that the appearance of GDM and ICP in HBsAg(+) pregnant women with high viral load ($2\times10e^5$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 [18, 19]. HBeAg is a marker of active HBV replication [20]. There was a strong inflammatory response in HBV infected patients

with HBeAg (+) or high load of HBV DNA [21, 22]. HBV DNA load is an important marker to predict the course of severe complications from HBV immune tolerance [21, 23]. 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 [24]. 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[25].

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[26, 27]. 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[28,29.30]. 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[31]. 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 [32, 33]. In patients with CHB, hepatocytes are constantly destroyed and multiplied. In proliferative hepatocytes, the NTCP expression on cell membrane is decreasing [34]. Moreover, existing research suggest that, ICP is related to PGE2(prostaglandin E2), which will affects the function of natural killer cells [35, 36]; Mutations in genes associated with drug resistance(such as ABCB 11[37],ABCC 2[38],ABCB 4[39, 40],NR1H4 [41]).

In some of APO (e.g., premature delivery and Pregnancy-induced hypertension), this study is different from previous studies [12, 14]. This difference may be due to the fact that the appearance of some adverse pregnancy outcomes may have declined as a result of stricter inclusion and exclusion criteria, such as we control for medication use.

This research has several priorities. First of all, we have strict inclusion and exclusion criteria, and consider the use of drugs. Second, we evaluated the effect of HBV DNA on the incidence of APO, which has certain guiding significance for clinical work.

Our study has some limitations. First of all, we did a hospital-based, single-center study, not a community study, which is not very representative of the population. Second, we did not assess the patient's liver function indicators (such as liver enzymes, etc.). Third, we did not assess the psychological status of pregnant women, nutritional status and other factors that might affect outcome.

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 (Try to keep viral load below 2× $10e^5$ UI/mL). Pregnant women with HBeAg-positive or high viral load should be alert to the occurrence of GDM and ICP. 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' contri ions

Zhi-Hao Huang, Shi Ou-Yang, Ting-Ting Peng, Jun-Chao Qiu, Dong-Dong Yu developed the concept of the study, Hao-Zhen Yan, 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, Hao-Zhen Yan, 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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