ORIGINAL PAPER / OBSTETRICS

Adverse pregnancy outcomes and mother-to-child transmission in patients with hepatitis B virus infection and intrahepatic cholestasis of pregnancy

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ABSTRACT

Objectives: The aim of this study was to investigate adverse pregnancy outcomes (APOs) and mother-to-child transmission (MTCT) of intrahepatic cholestasis in pregnancy (ICP) in hepatitis B virus infection (HBV) patients.

Material and methods: We performed a retrospective study at Beijing Youan Hospital in China from January 2010 through May 2017. A total of 232 patients were enrolled, including 106 HBV-infected ICP patients (Group H + C), 20 ICP patients (Group C) and 106 HBV-infected patients (Group H). Characteristics, APOs and MTCT rate of HBV were compared between groups. Group H + C was subdivided into 3 groups according to total bile acid (TBA) values and gestational age at diagnosis (GA). APOs were also compared within Group H + C according to TBA values and GA.

Results: There was no difference in live birth delivery mode and APOs between Groups H + C and C. Compared with Groups H, no difference was in live birth and MTCT rates of HBV. However, cesarean section delivery and APOs rates were higher in Group H+C (p < 0.05). Compared with Group H, adverse maternal outcomes such as postpartum hemorrhage and premature birth were more likely to occur in Group H + C (p < 0.001). Adverse fetal outcomes, the proportions of amniotic fluid reaching III degrees (AFIII), NICU admission, neonatal asphyxia and SGA were significantly higher among Group H + C than Group H (p < 0.05). Contamination of the AFIII rate increased with increasing TBA (p < 0.05). The rate of preterm birth and small for gestational age (SGA) was more common in GA 28–32 w compared with GA < 28 w and > 33 w (p < 0.01).

Conclusions: H + C patients had more APOs than HBV patients, but the difference was not significant when compared with ICP patients. Although we did not find any difference in MTCT rate between H + C and HBV patients, active treatment to prevent neonatal asphyxia and HBV infection should be considered. Therefore, it is necessary to emphasize maternal and fetal monitoring during pregnancy and delivery.

Key words: adverse pregnancy outcomes; mother-to-child transmission; intrahepatic cholestasis in pregnancy; hepatitis B virus infection

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is an important global health problem with a high infection rate. HBV infection triggers an autoimmune response, leading to hepatic cell damage and even cholestasis [1, 2]. Infections acquired by vertical transmission, also called mother-to-child transmission (MTCT), during pregnancy or perinatal periods have been recognized as the most important cause of chronic HBV infection [3–5]. Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and elevated total bile acid (TBA) level [6, 7]. ICP is relatively benign to women, however, it can have severe consequences for the fetus and is associated with adverse fetal outcomes, such as preterm delivery, fetal distress and meconium-stained amniotic fluid (MSAF) [8, 9]. Specific hormone level changes during pregnancy place extra burden on the liver and liver damage aggravates [10]. Moreover, elevated serum TBA is observed in some HBV patients. However, there are inadequate data regarding the clinical characteristics of ICP in HBV patients. Therefore, the aim of this study was to investigate adverse pregnancy outcomes (APOs) and MTCT of ICP in HBV patients.
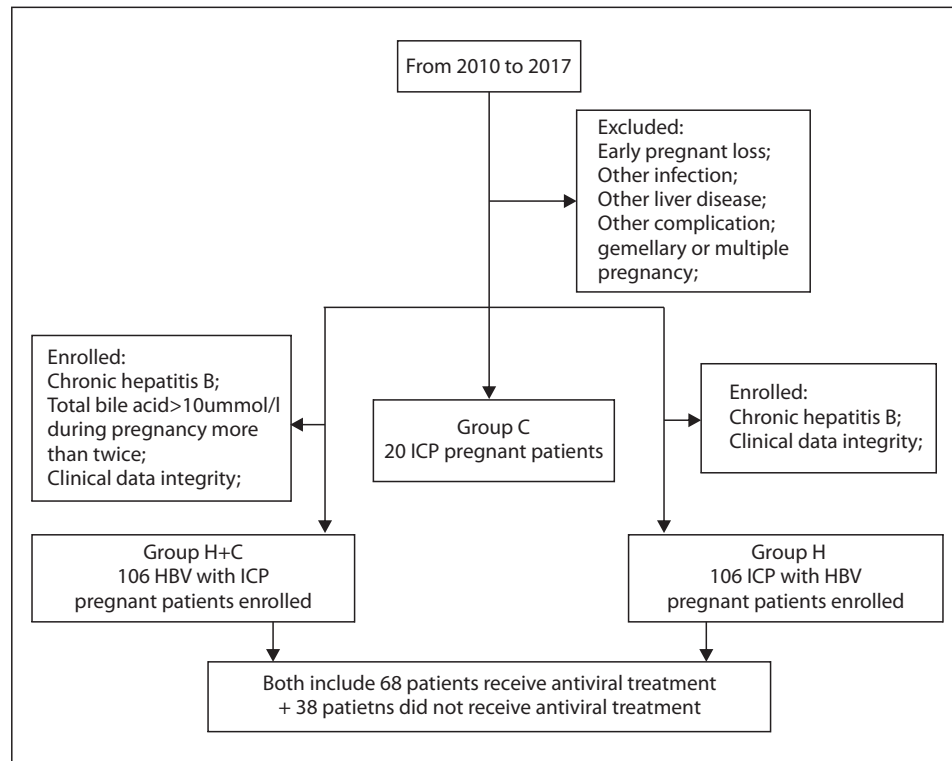
Objectives

The aim of this study was to investigate APOs and MTCT of ICP in HBV patients.

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Figure 1. Flowchart of patients enrollment

MATERIAL AND METHODS
Study design and participant population

We performed a retrospective cohort study of all patients who were managed at Beijing Youan Hospital in China from January 2010 through May 2017. Our hospital is a tertiary hospital, with liver specialists and fetal-maternal medicine specialists who diagnose and treat patients with hepatopathy and infectious disease during pregnancy from other community hospitals in China. HBV infection was diagnosed as serum hepatitis B surface antigen (HBsAg) positivity status for > 6 months and persistently normal levels (≤ 40 U/L) of alanine transaminase (ALT) and aspartate aminotransferase (AST) before and at study entry before pregnancy with or without elevated total bilirubin and pruritus during pregnancy. ICP was diagnosed by presence of pruritus and serum TBA level more than twice the normal level (> 10 μmol/L) without a rash; the maximum serum TBA level during pregnancy was documented. Patients with both HBV infection and ICP satisfied both the HBV and ICP standards described above.

Women were excluded when they met any of the following criteria. (1) Patients with twin or other multiple pregnancy. (2) Patients co-infected with human immunodeficiency virus, active syphilis or hepatitis C virus infection, or immunoglobulin M antibodies against Toxoplasma, rubella virus, cytomegalovirus or herpes simplex virus. (3) Patients with other liver diseases such as gallstones, alcoholic liver diseases, nonalcoholic fatty liver diseases or autoimmune liver diseases according to history, transabdominal ultrasound and/or liver function tests. (4) Patients who had preexisting chronic diseases including diabetes mellitus, hypertension, heart and kidney diseases, asthma, severe hematologic diseases and autoimmune diseases. (5) ALT/AST > 10 times the upper limit (40 U/L) or total bilirubin >3 times the upper limit (21 μmol/L) of the normal value. (6) Patients lacking complete pregnancy data. (7) Patients whose pregnancy ended before 12 weeks.

A total of 232 pregnant women were enrolled in this study, including 106 HBV-infected ICP patients (Group H + C), 20 ICP patients without HBV infection (Group C) and 106 HBV-infected patients without ICP (Group H) (Fig. 1). Groups H + C and H each had 68 patients who received antiviral treatment and 38 patients who did not receive antiviral treatment during pregnancy. Characteristics, APOs and MTCT rate of HBV were compared between groups. We also subdivided Group H + C into 3 groups according to TBA values and gestational age at diagnosis (GA). Based on maximum TBA levels, Group H + C patients were categorized into mild TBA (10–39.99 mmol/L), moderate TBA (40–99 mmol/L) and severe TBA (≥ 100 mmol/L) groups. According to GA, Group H + C patients were divided into the following groups: < 28 w, 28–33 w and > 33 w. APOs were also compared within Group H + C according to TBA values and GA.

The study protocol was approved by the institutional ethics review committee and registered with ClinicalTrials.gov (no. zx10201201). The study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from each patient in our study. All participants were followed until delivery and during the postpartum period for 6 weeks, and their children were followed up for at least 7 months.

APOs

Adverse maternal outcomes included premature rupture of membranes, gestational diabetes mellitus, pregnancy-induced hypertension (including gestational hypertension and preeclampsia), preterm birth (< 37 w, < 34 w and < 32 w) and postpartum hemorrhage. Adverse fetal outcomes were defined as any of the following: fetal loss (including late abortion, intrauterine death, induced labor and perinatal death), contamination of the amniotic fluid reaching III degrees (AFIII), neonate intensive care unit (NICU) admission, neonatal asphyxia (< 7 at 5 min), aspiration syndrome, neonatal respiratory distress syndrome, ventilator-assisted breathing, endotracheal tube-assisted breathing, pneumonia, hyperbilirubinemia, neonatal hypoglycemia, encephalopathy, birth defects or small for gestational age (SGA; defined as having a birth weight < 10th percentile for gestational age).

HBV serological assay and quantification of HBV viral load

Serum HBsAg and hepatitis B e antigen levels were determined using reagents from Roche Diagnostics and a Cobas e601 analyzer (Roche Diagnostic GmbH, Mannheim, Germany). HBV DNA was quantitatively measured using a real-time PCR assay (Sansure Biotech Inc., Changsha, Hunan, China).

Newborn immunoprophylaxis

All neonates were administered hepatitis B immune globulin (HBIG) (100 IU) and recombinant yeast hepatitis B vaccine (10 μg) as soon as possible after birth, preferably within 24 hours. Neonates then received 200 IU of HBIG at 21 days of age and 2 additional vaccinations at 1 and 6 months of age. Serum HBV DNA and HBV markers from the infants' venous blood were measured at birth (prior to immunoprophylaxis) and again at 7 months of age.

Effect of immunoprophylaxis

Intrauterine infection was defined as positive HBV DNA/HBsAg in infant peripheral blood at birth that was consistently positive at 7 months of age. Intrapartum contamination with HBV referred to transient presence of HBV DNA/HBsAg after delivery, *i.e.*, positive HBV DNA/HBsAg in infant peripheral blood at birth but negative HBV DNA/HBsAg at 7 months of age. Postpartum contamination was defined as negative HBV DNA/HBsAg in infant peripheral blood at birth and positive HBV DNA/HBsAg in infant peripheral blood at 7 months of age. Both intrauterine infection and postpartum contamination indicated failure of newborn immunoprophylaxis.

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) and categorical data are expressed as percentages. Analysis of variance was used to evaluate differences in continuous variables, and the χ2 test or Fisher's exact test was used for categorical variables. All analyses were conducted using SPSS version 20 (IBM, Armonk, NY, USA). A p value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the study population are shown in Table 1. The mean age of patients in Group H + C was 29.02 ± 3.90 years and 71.7% were nulliparous. GA < 28 w in Group H + C occurred most frequently (51, 48.11%), which was higher than that in Group C (3, 15%; p < 0.01). Patients in Group C were more likely diagnosed in GA > 33 w (11, 55%) during pregnancy, however, this was not significantly different than Group H + C (p > 0.05). Group H + C was also subdivided according to TBA levels as follows: mild TBA 52.83%, moderate TBA 36.79% and severe TBA 10.38%, which was not significantly different from Group C (p > 0.05). Moreover, there was no difference in live birth and delivery mode between Groups H + C and C. Comparisons between Groups H + C and H demonstrated no difference in live birth; however, the cesarean section delivery rate was significantly higher (58.49% vs 9.62%) and the vaginal delivery rate was lower (36.79% vs 59.43%) than that of Group H (p < 0.01).

Table 2 describes APOs of all patients in our study. No significant difference was observed in the occurrence of adverse maternal and fetal outcomes between Groups H + C and C (p > 0.05). Notably, patients in Group H + C showed a tendency toward low frequency of most APOs except premature birth (< 32 w), postpartum hemorrhage, pneumonia and encephalopathy, although these differences were not significant. Compared with Group H, adverse maternal outcomes such as postpartum hemorrhage and premature birth were more likely to occur in Group H + C (p < 0.001), while there were no differences of preterm birth < 34 w and < 32 w (p > 0.05). Concerning adverse fetal outcomes, the proportions of AFIII, NICU admission, neonatal asphyxia and SGA were significantly higher among Group H + C than Group H (p < 0.05). There were no statistical differences in other APOs between Groups H + C and C or Groups H + C and H (p > 0.05).

Table 1. Patient characteristics

Characteristics	Group H + C		Group C		Group H		P1	P2
	n = 106		n = 20		n = 106			
	n	%	n	%	n	%		
Unipara	76	**71.70**	18	90.00	63	59.43	0.085	0.06
Multipara	30	**28.30**	2	10.00	43	40.57	0.085	0.06
Age [years]	29.02 ± 3.90		28.3 ± 5.51		30.04 ± 4.40			
Gestational age at diagnosis [weeks]								
< 28 †	51	48.11	3	15.00			0.006	
28–33	19	17.92	6	30.00			0.349	
> 33	36	33.96	11	55.00			0.074	
The degree of bile acid increase								
Mild	56	52.83	7	35.00			0.144	
Medium	39	36.79	9	45.00			0.488	
Severe	11	10.38	4	20.00			0.4	
Live birth	101	95.28	19	95.00	105	99.06	1	0.214
By vagina ‡	39	36.79	6	30.00	63	59.43	0.561	0.001
By cesarean section ‡	62	58.49	13	65.00	42	39.62	0.586	0.006

P1 — Group H + C vs Group C; P2 — Group H + C vs Group H; † — P1 < 0.05; ‡ — Group H + C < Group H, P2 < 0.05; § — Group H + C > Group H, P2 < 0.05

HBV infection of infants in Groups H + C and H are summarized in Figure 2. In Group H + C, 4 infants were positive for HBsAg or HBV DNA from birth to 7 months of age (intrauterine infection), 1 infant was positive for HBsAg at birth but had HBsAg negative conversion at 7 months of age (intrapartum contamination) and 2 infants were negative for HBsAg and HBV DNA at birth but had positive conversion at 7 months (postpartum contamination). Thus, intrauterine infection, intrapartum contamination, postpartum contamination and MTCT rates of HBV were 3.96% (4/101), 1.98% (2/101), 0.99% (1/101) and 4.95% (5/101) in Group H + C, respectively, which were not significantly different from corresponding rates in Group H (p > 0.05).

Table 3 and Figure 3 demonstrate the distribution of APOs in Group H + C according to TBA values and GA. Incidence of AFIII was lower in the mild TBA group than moderate and severe TBA groups and meconium-stained amniotic fluid (MSAF) rate increased with increasing TBA (p < 0.05). The rate of preterm birth in GA 28–32 w was 57.89%, which was higher than both GA < 28 w and > 33 w (p < 0.01). Additionally, SGA was more common in GA 28–32 w compared with GA < 28 w and > 33 w (p < 0.01). Other APOs were not significantly different according to TBA and GA subgroups (p > 0.05).

DISCUSSION

In this study, we descriptively reported the distribution of demographic features, APOs and MTCT rate in HBV-infected ICP patients (H + C patients). Notably, we found that there was no significant difference between H + C and ICP patients in terms of APOs, whereas H + C patients had more APOs than HBV patients. We further evaluated APOs within H + C patients according to TBA values and GA. Interestingly, APOs were more common in GA 28–32 w compared with GA < 28 w and > 33 w (p < 0.01). Furthermore, MSAF rate increased with increasing TBA in H + C patients (p < 0.05). However, no difference in MTCT rates was observed between H + C and HBV patients (p > 0.05).

The exact reason for occurrence of HBV with ICP has not yet been reported. HBV infection may trigger an autoimmune response, leading to hepatic cell damage and even cholestasis [1, 2]. Furthermore, similar to the pathogenesis of ICP, specific hormone level changes during pregnancy place extra burden on the liver, which subsequently aggravates liver damage, impairs bile secretory function and ultimately increases TBA [10]. To date, only one study has focused on fetal outcomes of H + C patients compared with ICP and HBV patients [11]. In that study, H + C patients had more adverse fetal outcomes including fetal distress and neonatal asphyxia. Moreover, MTCT rate of H+C patients was higher than that of HBV patients [11]. However, to our knowledge, there are no reports about pregnancy outcomes including maternal and fetal outcomes in H + C patients. Therefore, our study is the first to report the complete pregnancy outcomes of H + C patients. We observed no significant difference in the occurrence of adverse maternal and fetal outcomes between H + C and ICP patients (p > 0.05). However, adverse maternal outcomes such as postpartum hemorrhage and premature

Table 2. Adverse pregnancy outcomes of all patients

Pregnancy outcome	Group H + C n = 106		Group C n = 20		Group H n = 106		P1	P2
	n	%	n	%	n	%		
Maternal								
PROM	15	14.15	3	15.00	15	14.15	1	1
GDM	22	20.75	5	25.00	13	12.26	0.899	0.096
PIH	5	4.72	2	10.00	3	2.83	0.679	0.719
Gestational hypertension	0	0	0	0	2	1.89		
Preeclampsia	5	4.72	2	10.00	1	0.94	0.679	0.214
Premature birth								
< 32 w	5	4.72	0	0	0	0		
< 34 w	8	7.55	3	15.00	2	1.89	0.515	0.052
< 37 w [§]	26	24.53	9	45.00	2	1.89	0.061	< 0.001
Postpartum hemorrhage [§]	11	10.38	2	10.00	3	2.83	1	0.027
Fetal								
Fetal loss	5	4.72	2	10.00	1	0.94	0.679	0.214
Late abortion	1	0.94	0	0	0	0		
Intrauterine death	2	1.89	0	0	1	0.94		1
Induced labor	1	0.94	1	5.00	0	0	0.293	
Perinatal mortality	1	0.94	1	5.00	0	0	0.293	
AFIII [§]	32	30.19	10	50.00	12	11.32	0.085	0.001
NICU admission [§]	10	9.43	3	15.00	2	1.89	0.726	0.017
Neonatal asphyxia [§]	13	12.26	5	25.00	4	3.77	0.252	0.023
Aspiration syndrome	6	5.66	2	10.00	1	0.94	0.818	0.124
NRDS	5	4.72	2	10.00	1	0.94	0.679	0.214
Ventilator-assisted breathing	9	8.49	3	15.00	4	3.77	0.621	0.152
Endotracheal tube-assisted breathing	5	4.72	2	10.00	2	1.89	0.679	0.442
Pneumonia	6	5.66	1	5.00	2	1.89	1	0.28
Hyperbilirubinemia	3	2.83	1	5.00	4	3.77	0.504	1
Hypoglycemia	3	2.83	1	5.00	3	2.83	0.504	1
Encephalopathy	2	1.89	0	0	0	0		
Birth defects	7	6.60	1	5.00	4	3.77	1	0.353
SGA [§]	16	15.09	7	35.00	3	2.83	0.072	0.002

PROM — premature rupture of membrane; GDM — gestational diabetes mellitus; PIH — pregnancy-induced hypertension; AFIII — degree of contamination of the amniotic fluid reaching III degrees; NICU admission — neonate intensive care unit admission; NRDS — neonatal respiratory distress syndrome; SGA — small for gestational age; P1 — Group H + C vs Group C; P2 — Group H + C vs Group H; [§] — Group H + C > Group H P2 < 0.05

birth were more likely to occur in H + C patients compared with HBV patients (p < 0.001). One potential explanation is that cholestasis can lead to steatorrhea, which reduces vitamin K absorption, and chronic hepatitis, which causes liver damage (the site for the synthesis of various clotting factors) and eventually leads to hemorrhage [12, 13]. Some reports have shown elevated bile acid (BA) induces vasoconstriction of human placental chorionic veins and increases the sensitivity and expression of oxytocin receptors in the human myometrium, possibly clarifying the mechanism of preterm birth in H + C pregnancies [14, 15]. Interestingly, in a recent nationwide cohort study, ICP was associated with gestational diabetes and pre-eclampsia [16]. We did not find similar results in H + C or ICP patients, perhaps because of the small sample size of our study. Therefore, the effect of H + C on these mentioned complications should be further evaluated in a larger cohort.

In terms of adverse fetal outcomes, the proportions of AFIII, NICU admission, neonatal asphyxia and SGA were significantly higher among H + C patients than HBV patients,
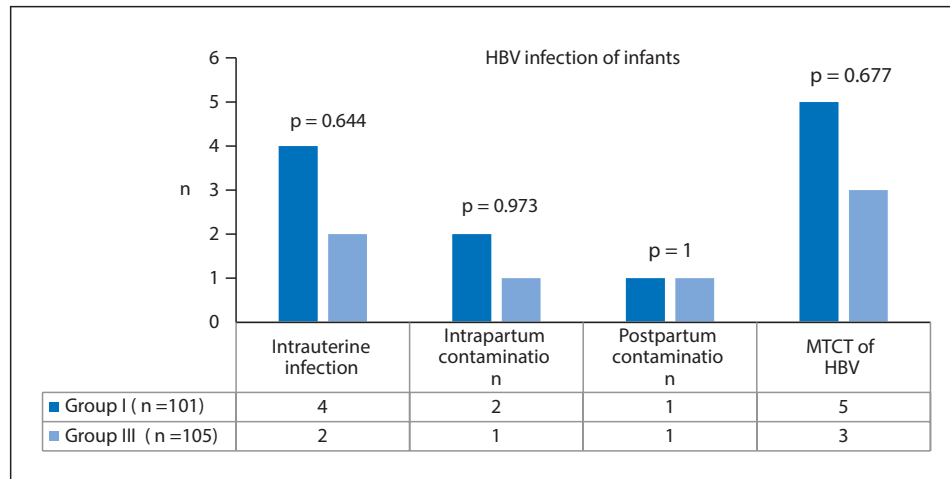
Figure 2. HBV infection of infants; P: Group H + C vs Group H

which is consistent with findings from a previous study [11]. The underlying mechanisms of these complications are still obscure. However, several studies reported that BA was linked with a higher risk of MSAF, fetal distress and fetal death in ICP patients [17–21]. BAs can contract placenta chorionic veins, damage fetal cardiomyocytes and induce lung injury, leading to surfactant depletion, surfactant dysfunction and lung inflammation and eventually resulting in the occurrence of fetal distress, asphyxia and death [9, 22, 23]. Furthermore, elevated BA has been suggested to increase colonic motility, resulting in MSAF [9, 24]. There was no difference in live birth and delivery mode between H + C and ICP patients. However, H + C patients had a significantly higher cesarean section delivery rate and lower vaginal delivery rate than HBV patients, although there was no difference in terms of live birth. The higher rate of NICU admission and neonatal asphyxia may account for the higher cesarean section delivery rate, and the higher preterm birth rate may explain the higher SGA rate in H + C patients than in HBV patients.

Prognostic factors for APO in ICP patients have been evaluated. Early onset of elevated TBA and high levels of TBA (> 40 μmol/L) are considered predictors of composite APOs such as preterm delivery, increased risk of meconium staining and low Apgar scores in ICP [25–28]. Therefore, to investigate APOs of H + C patients further, we divided H + C patients into 3 subgroups according to TBA values and GA. We found increased MSAF rate with increasing TBA occurred more often in H + C patients (p < 0.05), which is in line with previous studies about the effect of TBA on ICP patients [25, 26]. This observation highlights the relationship between high TBA value and APOs and suggests that we should enhance monitoring and provide early treatment for high TBA in H + C patients. Additionally, the occurrence of preterm birth and SGA in GA 28–32 w was higher

than those in GA < 28 w and > 33 w (p < 0.01). Although this finding is inconsistent with previous studies that found early onset of elevated TBA is associated with APO in ICP patients, we speculate relatively early onset of elevated TBA may lead to APO. Additionally, other APOs were not significantly different among TBA and GA subgroups. These findings highlight the need for further investigation of the association between GA and risk for APOs in H + C patients.

We also considered whether high TBA would affect MTCT in H + C patients as MTCT is regarded as the primary pathway of infection in HBV patients. Vaccination failure has been shown to occur most frequently in subjects born to mothers with higher HBV DNA levels, even with immunoprophylaxis intervention [29, 30]. Recently, in China, HBV patients were treated with nucleoside analogs such as lamivudine and telbivudine during late pregnancy, which significantly decreased maternal serum HBV DNA levels and reduced MTCT rate [31, 32]. In the present study, approximately 64% of H + C and HBV patients received antiviral treatment during pregnancy, and no significant difference in MTCT rate was observed between H + C and HBV patients. Thus, our results suggested TBA did not enhance MTCT in H + C patients, contrary to findings of a previous study [11]. Further large prospective trials are required to confirm the role of high TBA on MTCT.

To our knowledge, our study is thus far the first and largest study to report APOs of H + C patients systematically. Nevertheless, there are some limitations associated with the present study that must be addressed. First, we conducted a retrospective study, therefore, some patients did not have serial BA measurements. As a result, we could only evaluate outcomes based on maximum documented BA level and not trending BA levels. Second, we did not include multiple centers with diverse ethnicities and did not have a healthy group as our control group. Therefore,

Table 3. The distribution of adverse pregnant outcomes with TBA values and gestational age at diagnosis

| Pregnancy outcome	TBA (µmol/L)						Gestational age at diagnosis [weeks]					
	Mild		Moderate		Severe		< 28		28–33		> 33	
	n = 56		n = 39		n = 11		n = 51		n = 19		n = 34	
	n	%	n	%	n	%	n	%	n	%	n	%
Maternal												
PROM	10	17.86	4	10.26	1	9.09	8	15.69	4	21.05	3	8.82
GDM	10	17.86	11	28.21	1	9.09	10	19.61	4	21.05	8	23.53
PIH	3	5.36	2	5.13	0	0	2	3.92	1	5.26	2	5.88
Gestational hypertension	0	0	0	0	0	0	0	0	0	0	0	0
Preeclampsia	3	5.36	2	5.13	0	0	2	3.92	1	5.26	2	5.88
Premature birth												
< 32 w	2	3.57	2	5.13	1	9.09	3	5.88	2	10.53	0	0
< 34 w	2	3.57	5	12.82	1	9.09	3	5.88	5	26.32	0	0
< 37 w[†]	9	16.07	14	35.90	3	27.27	11	21.57	11	57.89	4	11.76
Postpartum hemorrhage	5	8.93	4	10.26	2	18.18	5	9.80	4	21.05	2	5.88
Fetal												
Fetal loss	2	3.57	0	0	3	27.27	4	7.84	1	5.26	0	0
Late abortion	1	1.79	0	0	0	0	1	1.96	0	0	0	0
Intrauterine death	1	1.79	0	0	1	9.09	2	3.92	0	0	0	0
Induced labor	0	0	0	0	1	9.09	1	1.96	0	0	0	0
Perinatal mortality	0	0	0	0	1	9.09	0	0	1	5.26	0	0
AFIII[‡]	13	23.21	12	30.77	7	63.64	14	27.45	9	47.37	9	26.47
NICU admission	4	7.14	5	12.82	1	9.09	6	11.76	2	10.53	2	5.88
Neonatal asphyxia	4	7.14	7	17.95	2	18.18	6	11.76	5	26.32	2	5.88
Aspiration syndrome	2	3.57	3	7.69	1	9.09	3	5.88	2	10.53	1	2.94
NRDS	2	3.57	2	5.13	1	9.09	3	5.88	1	5.26	1	2.94
Ventilator-assisted breathing	2	3.57	6	15.38	1	9.09	3	5.88	4	21.05	2	5.88
Tracheal intubation assisted breathing	2	3.57	2	5.13	1	9.09	3	5.88	1	5.26	1	2.94
Pneumonia	3	5.36	3	7.69	0	0	4	7.84	0	0	2	5.88
Hyperbilirubinemia	1	1.79	1	2.56	1	9.09	3	5.88	0	0	0	0
Hypoglycemia	2	3.57	1	2.56	0	0	2	3.92	0	0	1	2.94
Encephalopathy	1	1.79	1	2.56	0	0	1	1.96	0	0	1	2.94
Birth defects	4	7.14	3	7.69	0	0	3	5.88	2	10.53	1	2.94
SGA[†]	6	10.71	8	20.51	2	18.18	8	15.69	6	31.58	2	5.88

TBA — total bile acid; [†] — in gestational age at diagnosis (GD) subgroup, n% 28–33 w > (< 28) w and (> 33) w, p < 0.05; [‡] — in TBA subgroup, n% Severe > Medium > Mild, p < 0.05

our single-center study may have bias and our results may be not generalizable. Third, early onset of elevated TBA and high TBA levels (> 40 µmol/L) have been described as predictors of composite APOs. Although we divided H + C patients into 3 subgroups according to TBA values and GA, logistic regression analysis was not performed to identify APOs of H + C patients. Fourth, we found high preterm birth and cesarean section delivery rates. However, we did not divide preterm birth into iatrogenic and spontaneous preterm birth. Fifth, although the efficacy of ursodeoxycholic acid (UDCA) therapy is uncertain, it is currently the only therapy that has shown some results. As we administered UDCA treatment to all H + C and ICP patients, we did not discuss this matter. Finally, the relatively small number of APOs is likely explained by the low incidence of these complications, which may result in some findings to be nonsignificant.

CONCLUSIONS

Our study confirmed that H + C patients had more APOs than HBV patients, but the difference was not significant when compared with ICP patients. Therefore, it is necessary to emphasize maternal and fetal monitoring during
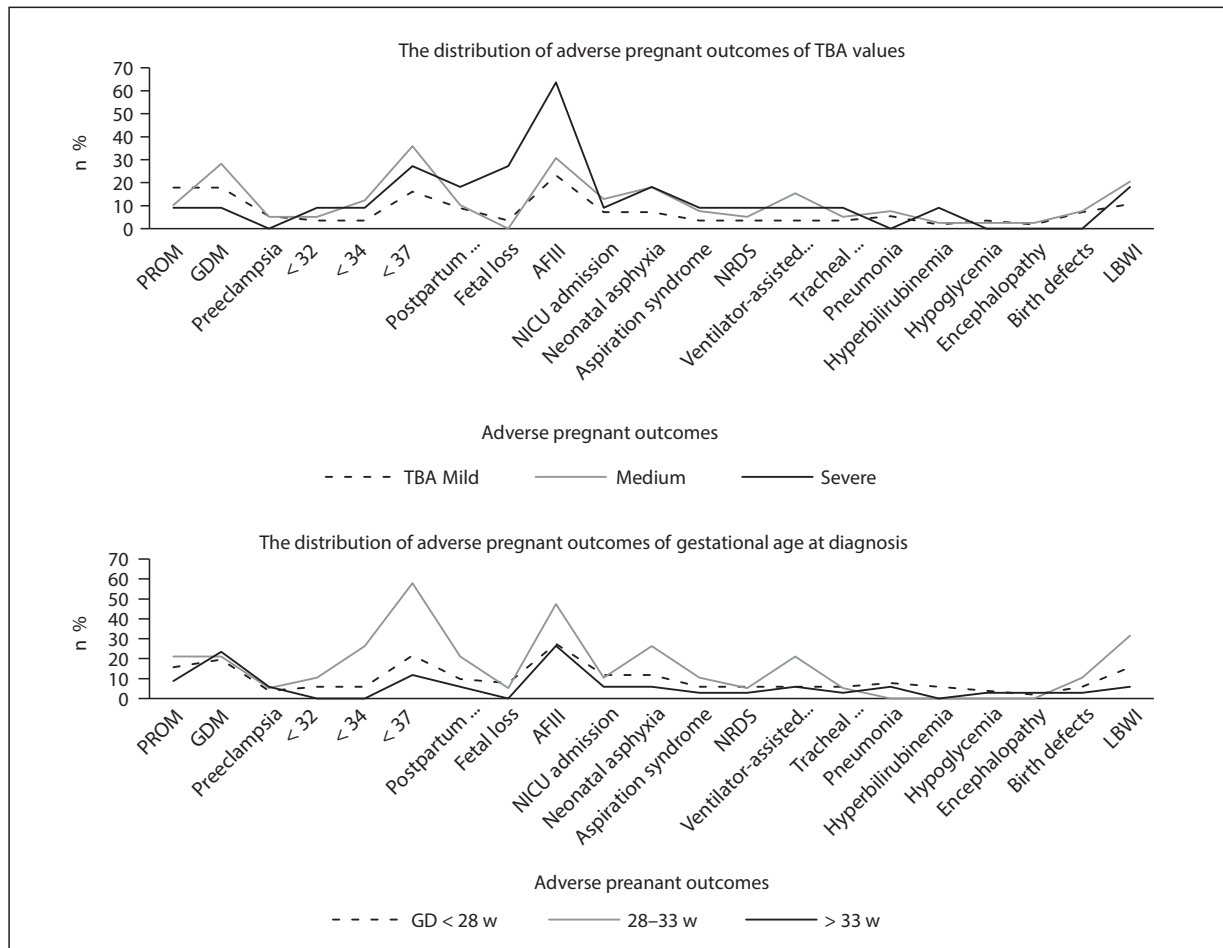
Figure 3. The distribution of adverse pregnant outcomes with TBA values and gestational age at diagnosis (GD); PROM — premature rupture of membrane; GDM — gestational diabetes mellitus; NRDS — neonatal respiratory distress syndrome; LBWI — low birth weight infant

pregnancy and delivery. Although we did not find any difference in MTCT rate between H + C and HBV patients, active treatment to prevent neonatal asphyxia and HBV infection should be considered. To fully investigate the characteristics of H + C patients, a larger multi-center prospective study may be necessary.

Conflict of interest

All authors declare no conflict of interest.

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