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Original Research

Adverse Pregnancy Outcomes and Prognostic Factors in Hepatitis B Virus Patients with Intrahepatic Cholestasis During Pregnancy

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Abstract

Background: We conducted this study to investigate adverse pregnancy outcomes of hepatitis B virus infection coexistng with intrahepatic cholestasis in pregnant women, along with identifying associated risk factors. **Methods**: We retrospectively collected study data from Beijing Youan Hospital in China spanning January 2014 to December 2021. The study included 220 patients, divided into two groups: Group I consisted of 110 patients with hepatitis B virus infection and intrahepatic cholestasis during pregnancy, while Group II comprised 110 patients with hepatitis B virus infection alone. Maternal demographics, laboratory values, obstetric complications, and adverse pregnancy outcomes were collected and analyzed between Groups I and II. To investigate the features of hepatitis B virus infection with intrahepatic cholestasis in pregnancy patients further, we also evaluated risk factors of adverse pregnancy outcomes in Group I. **Results**: Adverse pregnancy outcomes, including preterm birth (<37 weeks (w)), postpartum hemorrhage, meconium-stained amniotic fluid, neonatal asphyxia, neonate intensive care unit admission and small for gestational age rates were significantly increased for Group I compared with Group II ($p < 0.05$). In hepatitis B virus infection patients with intrahepatic cholestasis during pregnancy, elevated total serum bile acids independently correlated with six adverse pregnancy outcomes. **Conclusions**: Pregnant patients with both hepatitis B virus infection and intrahepatic cholestasis experienced a higher occurrence of adverse pregnancy outcomes compared to those with Hepatitis B virus infection alone. Total serum bile acids were an independent risk factor for adverse pregnancy outcomes in Hepatitis B virus infection with intrahepatic cholestasis during pregnancy. **Clinical Trial Registration**: The study was registered with https://classic.clinicaltrials.gov/ (no.: zx10201201).

Keywords: adverse pregnancy outcomes; hepatitis B virus infection; intrahepatic cholestasis in pregnancy; prognostic factors; total serum bile acids

1. Introduction

Chronic infection with hepatitis B virus (HBV) is a public health problem in many countries. Chronic HBV infection in pregnant patients can result in virus transmission to the neonate during delivery. Accordingly, most studies have focused on mother-to-child HBV transmission, which remains the primary pathway of HBV infection [1–3]. Data about outcomes of HBV infection in pregnancy are limited, and only a few studies have reported that HBV infection may increase the occurrence of maternal complications such as miscarriage and gestational diabetes mellitus (GDM) [4–6]. Administering telbivudine during the second or third trimester of pregnancy to mothers with high viral loads is effective in reducing perinatal transmission. Women with HBV had an increased risk for preterm birth. Individuals with both HBV and hepatitis C virus co-infection had an increased risk for antepartum haemorrhage. Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in pregnancy and is characterized by pruritus, elevated total serum bile acids (TBAs), and elevated liver enzymes. Many studies showed that ICP is associated with an increased risk of preterm birth, meconium-stained amniotic fluid (MSAF), asphyxia, or respiratory distress syndrome (RDS) [7,8]. Recently, GDM and pre-eclampsia were reported to be associated with ICP [9–11]. The down-regulation of inducible nitric oxide synthase and up-regulation of neuropeptide Y in ICP may play a significant role in poor fetoplacental vascular perfusion and adverse pregnancy outcomes [12]. ICP may increase the incidence of shorter gestational days and non-vaginal delivery methods such as cesarean section but reduce the incidence of premature rupture of membranes and fetal macrosomia [13]. We found that elevated TBAs occurred in some pregnant HBV patients, but there have been no systematic studies involving sucah patients. Severe cholestasis is associated with neonatal morbidity which antenatal testing may not predict [14]. Therefore, our study aimed to investigate adverse pregnancy outcomes (APOs) in patients with both HBV and ICP (HBCP), as well as identify associated risk factors these APOs in HBCP patients.

2. Materials and Methods

Our study data were collected retrospectively between January 2014 and December 2021 from Beijing Youan Hospital, a liver disease general hospital that specializes in treating hepatopathy in China. All patients in our study

were managed by liver specialists and experts in fetal-maternal medicine. Chronic HBV infection was indicated by positive serum hepatitis B surface antigen (HBsAg) status for more than 6 months and persistently normal levels of alanine aminotransferase (ALT; 7–40 U/L) and aspartate aminotransferase (AST; 13–35 U/L) before pregnancy, with normal TBAs (<10 µmol/L) during pregnancy. HBCP patients had chronic HBV infection and elevated TBA levels more than twice the upper limit of normal with or without pruritus during pregnancy. Our study protocol was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the institutional ethics committee. The study was registered with https://classic.clinicaltrials.gov/ (no.: zx10201201). All patients provided written informed consent in our study.

All enrolled participants also fulfilled the following criteria: (1) having complete pregnancy data; (2) absence of preexisting chronic diseases, including hypertension, diabetes mellitus, and heart, kidney, hematologic and autoimmune diseases; (3) exclusion of other infectious diseases such as hepatitis C virus infection, human immunodeficiency virus or active syphilis; cytomegalovirus, herpes simplex virus, immunoglobulin M antibodies against toxoplasma, or rubella virus; (4) no evidence of other liver diseases such as autoimmune liver diseases, nonalcoholic fatty liver diseases or gallstones, or alcoholic liver diseases by history, trans-abdominal ultrasound or liver function tests; (5) not pregnant with twins or other multiples; and (6) no miscarriage before 12 weeks.

A total of 220 patients, including 110 HBCP patients (Group I) and 110 HBV patients (Group II), were enrolled in the study. Among Groups I and II, there were 70 patients who accepted antiviral treatment during pregnancy and 40 patients who did not take antivirals separately. All patients were followed up until 6 weeks after giving birth or termination of pregnancy. In Group I, all patients received treatment with ursodeoxycholic acid (UDCA; 10–15 mg/kg per day) upon diagnosis. Serum TBAs, ALT, AST, total bilirubin (TBIL; normal range, 5–20 µmol/L), unconjugated bilirubin (DBIL; 1.7–10 µmol/L), gamma-glutamyl transpeptidase (GGT; 7–45 U/L), and alkaline phosphatase (ALP; 35–100 U/L) levels were analyzed weekly. Fetal monitoring by an ultrasound examination and Echo-Doppler detection was conducted weekly. Maternal demographics, laboratory values, obstetric complications, and APOs were collected and analyzed between Groups I and II. To investigate the features of HBCP patients further, we also evaluated risk factors of APOs in Group I.

Obesity was defined as a body mass index (BMI) of >25 kg/m^2 at the first antenatal visit. Obstetric complications included pregnancy-induced hypertension (PIH) (including gestational hypertension and preeclampsia), premature rupture of membranes (PROM), GDM, preterm birth (<37 weeks (w), <34 w, and <32 w), postpartum hemorrhage, and placental abruption. Analysis of APOs included one or more of the following: maternal: (1) preterm birth (<37 w); or (2) postpartum hemorrhage; and neonatal: (1) MSAF (contamination of the amniotic fluid reaching III degree); (2) fetal loss (including late abortion, intrauterine death, induced labor and perinatal death); (3) neonatal asphyxia (<7 scores at 5 min); (4) aspiration syndrome; (5) neonatal respiratory distress syndrome (NRDS); (6) neonate intensive care unit (NICU) admission; (7) pneumonia; (8) hyperbilirubinemia; (9) hypoglycemia; (10) encephalopathy; (11) birth defects; or (12) small for gestational age (SGA) neonate, defined as birth weight <10th percentile without anatomical abnormalities.

Statistical analysis was performed using SPSS version 20 (IBM, Armonk, NY, USA). Results are presented as the median or mean ± standard deviation (SD) and categorical data as percentages. The χ^2 test or Fisher's exact test was used for categorical variables. Multivariable logistic regression analysis was performed to determine the odds ratios (ORs) and 95% confidence interval (95% CI), and to identify potential correlations between risk factors and APOs. A probability of <0.05 was considered statistically significant.

3. Results

A comparison between the demographic and clinical data in patients with HBCP and HBV is presented in Table 1. The rate of demographic characteristics such as unigravida, age, *in vitro* fertilization and embryo transfer (IVF-ET) management, obesity, and live birth were similar in both groups ($p > 0.05$). Compared with Group II for live births, Group I showed a marked increase in the cesarean section rate (57.27% *vs.* 39.09%, $p < 0.01$) and lower vaginal birth rate (38.18% *vs.* 60%, $p < 0.05$).

Table 2 describes the laboratory values in the study. There was no difference between the groups for ALP ($p > 0.05$). However, the mean levels of TBAs, ALT, AST, TBIL, DBIL, and GGT in Group I were higher than those in Group II ($p < 0.01$).

Obstetric complications for all patients are summarized in Table 3. Six patients were diagnosed with PIH (5.45%), including one with gestational hypertension (0.91%) and five with preeclampsia (4.55%) in Group I, which was not different compared with Group II ($p > 0.05$). In our cohort there were 26 cases of preterm birth (<37 w), including five cases <32 w and 34 w. The premature birth rate (<37 w) (26/110, 23.64%) and postpartum hemorrhage rate (12/110, 10.91%) in Group I were higher than those in Group II (2/110, 1.82%; 3/110, 2.73%), respectively; both $p < 0.01$). There was no significant difference between the two groups for other obstetric complications such as GDM, PROM and placental abruption ($p > 0.05$).

The APOs for the two groups are reported in Table 4. Overall, almost all APOs in our study occurred in Group I. Adverse maternal pregnancy outcomes including preterm birth (<37 w) and postpartum hemorrhage, which were re-

Table 1. Demographic and clinical data.

Characteristics	Group I (N = 110)		Group II (N = 110)		*p*
	n	%	n	%	
Unigravida	78	70.91	65	59.09	0.066
Multigravida	32	29.09	45	40.91	0.066
Age (Y)	29.14 ± 4		30.11 ± 4.46		
IVF-ET	5	4.54	3	2.73	0.719
Obesity	8	7.27	5	4.54	0.391
Live birth	105	95.45	109	99.09	0.214
by vagina†	42	38.18	66	60.00	0.015
by cesarean section‡	63	57.27	43	39.09	0.007

Obesity: Body Mass Index (BMI) >25 kg/m^2.

IVF-ET, *in vitro* fertilization and embryo transfer; Y, years.

p: Group I *vs*. Group II.

†: Group I < Group II, $p < 0.05$.

‡: Group I > Group II, $p < 0.05$.

Table 2. Laboratory values of patients (mean ± SD).

Serum parameters, mean ± SD	Group I	Group II	*p*
TBA (μmol/L)†	53.89 ± 44.55	6.23 ± 1.88	<0.001
ALT (U/L)†	92.48 ± 85.51	22.19 ± 12.99	<0.001
AST (U/L)†	76.14 ± 68.35	23.21 ± 8.13	<0.001
TBIL (μmol/L)†	14.16 ± 17.37	9.66 ± 4.35	0.009
DBIL (μmol/L)†	6.05 ± 11.46	3.01 ± 1.11	0.007
GGT (U/L)†	25.64 ± 20.34	12.87 ± 11.29	<0.001
ALP (U/L)	98.74 ± 42.50	91.97 ± 58.30	0.325

SD, standard deviation; TBA, total serum bile acids (<10 μmol/L); ALT, alanine transaminase (7–40 U/L); AST, glutamic-oxaloacetic transaminase (13–35 U/L); TBIL, total bilirubin (5–20 μmol/L); DBIL, unconjugated bilirubin (1.7–10 μmol/L); GGT, gamma-glutamyl transpeptidase (7–45 U/L); ALP, alkaline phosphatase (35–100 U/L).

p: Group I *vs.* Group II.

†: Group I > Group II, $p < 0.05$.

ported above in Group I, were higher than those in Group II ($p < 0.05$). For adverse neonatal outcomes, MSAF, neonatal asphyxia, NICU admission, and SGA rates in Group I were significantly increased compared with Group II (30% *vs*. 10.91%; 1.82% *vs*. 3.64%; 9.09% *vs*. 1.82%; 15.45% *vs*. 2.73%, respectively; all $p < 0.05$). Additionally, the percentages of those with fetal loss, aspiration syndrome, NRDS, pneumonia, hyperbilirubinemia, hypoglycemia, encephalopathy, and birth defects were similar between the patients in Groups I and II ($p > 0.05$).

To evaluate the risk factors statistically, we extracted the baseline data at the time of conception, including demographic data, laboratory values, and obstetric complications between Groups I and II. Single factor analysis showed statistically significant differences between the two groups for the following variables: TBAs, ALT, AST, TBIL, DBIL, and GGT. Accordingly, these variables were further analyzed using a multivariable logistic regression model to evaluate risk factors for the following six APOs: preterm birth (<37 w), postpartum hemorrhage, MSAF, neonatal asphyxia, NICU admission, and SGA. TBAs were found to be an independent risk factor for APOs in HBCP patients (Table 5).

4. Discussion

Cholestasis, classified as either intrahepatic or extrahepatic, is a barrier to bile formation or flow. Inhibiting or restricting bile flow leads to high TBA levels. Extrahepatic cholestasis is usually caused by biliary obstruction such as stones, tumors, and cysts; patients with this condition were excluded from our study [15]. Intrahepatic cholestasis may be caused by hepatocyte dysfunction or obstructive lesions at the end of the intrahepatic bile duct [16]. Our study focused on the effect of intrahepatic cholestasis on APOs resulting from HBV during pregnancy. HBV causes chronic inflammatory liver diseases, which can lead to hepatocellular damage and intrahepatic cholestasis. Intrahepatic cholestasis also aggravates liver damage. Additionally, changes in hormone levels during pregnancy can increase the burden on the liver and aggravate liver disease

Table 3. Maternal obstetric complications.

Obstetric complications	Group I (N = 110)		Group II (N = 110)		*p*
	n	%	n	%	
PIH	6	5.45	3	2.73	0.496
Gestational hypertension	1	0.91	2	1.82	>0.99
Preeclampsia	5	4.55	1	0.91	0.214
PROM	15	13.64	15	13.64	>0.99
GDM	22	20.00	13	11.82	0.097
Premature birth					
<32 w	5	4.55	0	0	
<34 w	8	7.27	2	1.82	0.052
<37 w[†]	26	23.64	2	1.82	<0.001
Postpartum hemorrhage[†]	12	10.91	3	2.73	0.016
Placental abruption	2	1.82	1	0.91	>0.99

PIH, pregnancy-induced hypertension; PROM, premature rupture of membrane; GDM, gestational diabetes mellitus; w, week.

p: Group I *vs.* Group II.

[†]: Group I > Group II, $p < 0.05$.

[17,18]. However, the mechanism of intrahepatic cholestasis in HBV patients remains unclear.

ICP is a pregnancy-associated liver disease that is characterized by elevated TBAs. Numerous studies have reported that ICP is associated with a poor perinatal outcomes such as preterm delivery, MSAF, and fetal distress [19,20]. Only one study exclusively explored pregnancy outcomes, primarily focusing on fetal outcomes witjin the context of HBCP patients [21]. Thus, we conducted our study to estimate the APOs for HBCP patients and to determine the risk factors for APOs in HBCP patients. To the best of our knowledge, our study is the largest and the most systematic study about HBCP patients, and is the first to estimate risk factors for APOs in HBCP patients.

We compared laboratory values between HBCP and HBV patients and found that, except for ALP, all biochemical indices in HBCP patients were higher than those in HBV patients ($p < 0.05$). ALP is widely distributed in the human liver, bone, kidney, and placenta, and it can be elevated during pregnancy or rapid bone growth. As was reported for ICP, the most sensitive laboratory abnormality is an increase of TBAs; other laboratory result abnormalities such as ALT, AST, and GGT are found in ICP patients [22]. Elevated bilirubin was found in 10–20% of women with ICP [23]. Our results were consistent with laboratory values reported for ICP patients. Additionally, Kawakita *et al.* [24] found that ICP patients with increased TBA levels were more likely to have higher liver transaminase and TBIL levels. Therefore, we speculate that in HBCP patients, chronic HBV and intrahepatic cholestasis interact with each other, which aggravates liver damage and manifests as higher ALT and AST levels than in HBV patients.

For maternal obstetric complications, preterm birth (<37 w) occurred more frequently in HBCP patients compared with HBV patients, which was consistent with a previous study [21]. Studies have reported that TBAs in ICP patients could increase the sensitivity and expression of oxytocin receptors in the human uterine muscle, which may result in preterm labor. We also found that HBCP patients had a greater tendency toward postpartum hemorrhage compared with HBV patients, which was not addressed in Hu's study [21]. Cholestasis may be complicated by steatorrhea and vitamin K deficiency leading to postpartum hemorrhage [25]. Additionally, other obstetric outcomes in HBCP patients such as PROM and placental abruption did not show any difference compared with HBV patients ($p > 0.05$). Several studies recently reported that GDM and PIH, especially pre-eclampsia, were associated with ICP [9,26–28]. These studies proposed that TBAs may cause endothelial injury in the kidney, triggering the release of reactive oxygen species and promoting the formation of various vasoactive mediators; this process could contribute to the development of PIH in pregnancy [29–31]. However, the proportion of PIH and GDM was not higher in HBCP patients than in HBV patients, and no other study has investigated this prospect in HBCP patients.

The percentage of adverse maternal pregnancy outcomes such as preterm birth and postpartum hemorrhage, and neonatal pregnancy outcomes such as MSAF, neonatal asphyxia, NICU admission, and SGA, were higher in HBCP patients compared with HBV patients ($p < 0.05$). Hu *et al.* [21] found that the rate of MSAF, neonatal asphyxia, and birth defects was 52%, 60%, and 16%, respectively, in HBCP patients, which were all higher than control groups and also higher than that in our HBCP patients. This may be explained by our timely treatment with UDCA. However, the study by Hu *et al.* [21] did not further examine other APOs. In our data, there was no difference between HBCP and HBV patients with respect to birth defects ($p > 0.05$). Many studies on ICP patients, focusing

Table 4. Adverse pregnancy outcomes.

Adverse pregnancy outcomes	Group I (N = 110)		Group II (N = 110)		*p*
	n	%	n	%	
Maternal					
Premature birth†					
<37 w	26	23.64	2	1.82	<0.001
Postpartum hemorrhage†	12	10.91	3	2.73	0.016
Neonatal					
MSAF†	33	30.00	12	10.91	<0.001
Fetal loss	5	4.55	1	0.91	0.214
Late abortion	1	0.91	0	0	
Intrauterine death	2	1.82	1	0.91	>0.99
Induced labor	1	0.91	0	0	
Perinatal mortality	1	0.91	0	0	
Neonatal asphyxia†	13	11.82	4	3.64	0.023
Aspiration syndrome	6	5.45	1	0.91	0.124
NRDS	5	4.55	1	0.91	0.214
NICU admission†	10	9.09	2	1.82	0.018
Pneumonia	6	5.45	2	1.82	0.28
Hyperbilirubinemia	3	2.73	4	3.64	>0.99
Hypoglycemia	3	2.73	3	2.73	>0.99
Encephalopathy	2	1.82	0	0	
Birth defects	7	6.36	4	3.64	0.353
SGA†	17	15.45	3	2.73	0.001

NICU admission, neonate intensive care unit admission; NRDS, neonatal respiratory distress syndrome; MSAF, meconium-stained amniotic fluid; SGA, small for gestational age.

p: Group I *vs.* Group II.

†: Group I > Group II, $p < 0.05$.

Table 5. Risk Factors of Adverse Pregnant Outcomes.

Maternal risk factor	Adverse Pregnant Outcomes		
	Odds ratio (OR)	95% CI	*p* value
TBA†	1.013	1.001–1.026	0.038
ALT	1.013	0.998–1.028	0.099
AST	0.981	0.961–1.000	0.053
TBIL	1.017	0.933–1.109	0.695
DBIL	1.028	0.932–1.135	0.577
GGT	1.008	0.987–1.029	0.458

95% CI, 95% confidence interval.

p: Group I *vs.* Group II.

†: Group I > Group II, $p < 0.05$.

on adverse fetal outcomes, have reported that ICP is associated with an increased risk of MSAF, asphyxia, or RDS [32,33]. Evidence of a possible pathogenic role of TBAs, which increases colon motility and triggers MSAF, is based on *in vitro* and laboratory animal studies [23]. Moreover, TBAs can induce lung injury, leading to surfactant depletion; vasoconstriction of placental chorionic veins may account for fetal distress and asphyxia [34]. Additionally, the higher preterm birth rate may be a possible explanation for a higher rate of SGA in HBCP patients.

There was higher incidence of APOs such as premature birth, postpartum hemorrhage, MSAF, neonatal asphyxia, NICU admission, and SGA in HBCP patients. To administer treatment in a timely manner and to improve pregnancy outcomes, our study also assessed risk factors for APOs, including TBA level, ALT, AST, TBIL, DBIL, and GGT, using a multivariable logistic regression analysis. We found that only TBAs were an independent risk factor for these APOs. Many studies on ICP patients have reported a high TBA level (>40 µmol/L), which has been associated with an increased risk of MSAF, preterm delivery, and fetal distress [35–37]. Rook *et al.* [38] reported that ICP patients who had a TBA level ≥100 µmol/L had a 60% chance of experiencing an APO, whereas patients with a TBA level from 40–99.9 µmol/L and 10–39.9 µmol/L had a lower chance (19% and 29%, respectively). How TBAs affect APOs was previously discussed. Although the efficacy of UDCA therapy is uncertain, it remains the first-line and only therapy used in clinical practice. Therefore, once TBA levels are elevated in HBV patients, fetal monitoring should be increased, UDCA therapy should be given in a timely manner, and pregnancy should be terminated when necessary.

5. Conclusions

The main limitation was the retrospective nature of our data collection and our single-center study, which limits the generalizability of our results. Second, we found that HBCP patients had a higher preterm birth rate. However, we did not divide preterm births into iatrogenic and spontaneous preterm births because we also found a higher cesarean section delivery rate in HBCP patients. Additionally, all our HBCP patients received UDCA treatment, which may affect the objectivity of the results. Finally, our sample size was relatively small, and we did not group TBAs according to the degree of their increase, and APOs associated with different degrees of TBA increase requires further analysis. The small sample size of our treatment group limited the ability to detect statistically significant differences, necessitating further research and follow-up in the future.

Abbreviations

HBV, hepatitis B virus; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; TBAs, otal serum bile acids; MSAF, meconium-stained amniotic fluid; RDS, respiratory distress syndrome; APOs, adverse pregnancy outcomes; HBCP, hepatitis B virus with intrahepatic cholestasis of pregnancy; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid; TBIL, total bilirubin; DBIL, unconjugated bilirubin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; BMI, body mass index; PIH, pregnancy-induced hypertension; PROM, premature rupture of membranes; NRDS, neonatal respiratory distress syndrome; NICU, neonate intensive care unit; SGA, small for gestational age; SD, standard deviation; ORs, odds ratios; IVF-ET, *in vitro* fertilization and embryo transfer.

Availability of Data and Materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Author Contributions

YZ designed the research study. HW and ZZ analyzed the data. YZ, HW and ZZ revised the manuscript critically for important intellectual content. CZ had substantial contributions to the design of the work and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by Beijing Youan Hospital, Capital Medical University Human Research Protection Program (2015-32). Informed consent was obtained from the patient.

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Conflict of Interest

The authors declare no conflict of interest.

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