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Hepatitis E virus infection increases the risk of obstetric complications and perinatal adverse outcomes in pregnant women with chronic hepatitis B virus infection

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Abstract. – OBJECTIVE: Hepatitis E virus (HEV) infection may occur in pregnant women who had chronic hepatitis B virus (HBV) infection. This study aimed to evaluate whether HEV–HBV co-infection increases the risk of obstetric complications and perinatal adverse outcomes in pregnant women.

PATIENTS AND METHODS: We investigated the clinical data of 3,251 pregnant women with chronic HBV infection. The obstetric complications and perinatal adverse outcomes were compared between patients with HEV-HBV co-infection and patients who had pure chronic HBV infection.

RESULTS: Of the 3,251 pregnant women with chronic HBV infection, 98 patients (3%) had HEV-HBV co-infection. Compared with healthy controls, there is an increased risk of obstetric complications in pregnant women with pure HEV infection [odds ratio (OR)= 3.99, $p < 0.001$], pure chronic HBV infection (OR = 2.76, $p < 0.001$), and HEV-HBV co-infection (OR = 5.41,$p < 0.001$). The rate of obstetric complications and perinatal adverse outcomes is significantly higher in pregnant women with HEV-HBV co-infection compared with those with pure chronic HBV infection or those with pure HEV infection (all $p< 0.05$). The HEV-HBV co-infection is the most significant risk factor for perinatal adverse outcomes (OR = 15.47, $p < 0.001$), followed by pure HEV infection (OR = 10.22, $p < 0.001$), and pure HBV infection (OR = 5.82, $p < 0.001$).

CONCLUSIONS: HEV infection increases the risk of obstetric complications and perinatal adverse outcomes in pregnant women with chronic HBV infection.

Key Words:
Chronic hepatitis B, Hepatitis E virus, Pregnancy, Obstetric complication, Adverse perinatal outcome.

Introduction

Globally, viral hepatitis has a high prevalence rate. Despite the availability of effective vaccines and treatment strategies, the threat of chronic hepatitis B virus (HBV) infection remains serious. Globally, more than 250 million people have chronic HBV infection[1]. In particular, previous data[2] have suggested that chronic HBV infection is associated with severe symptoms and adverse clinical outcomes for pregnant women. Hepatitis E Virus (HEV) is probably the most common cause of acute hepatitis worldwide. It has been regarded for a long time as a disease limited to developing countries. Recently, the refinement of diagnostic techniques and migratory flows has led to the identification of an increased number of HEV infections in developed countries[3]. Four HEV genotypes have been identified[3] across the world, with different epidemiological burdens and a wide range of clinical presentations.

In several areas, HBV and HEV are highly prevalent, and there is a risk of co-infection. Investigations of serum epidemiology conducted in endemic countries showed that the overlap of HBV and HEV infections accounted for about 3-10%[4]. Although most acute HEV infections

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tend to be sub-clinical, self-limiting, and mild, the overlap of HBV and HEV infections can present additional risks, which frequently leads to severe complications and poor outcomes[5]. In addition, during the second and third trimesters of pregnancy, there is a high risk of developing symptomatic disease following HEV infection, which can progress to acute liver failure[6,7].

Dual infections with HEV and HBV can occur in pregnant women. Several studies[8,9] regarding maternal and fetal adverse outcomes with HEV and HBV co-infections have been reported, but these studies were not widely representative due to small sample sizes. Therefore, taking advantage of the large number of 3,251 pregnant women with chronic HBV infection in a tertiary hospital in China, we explored the prevalence of HEV-HBV co-infection in pregnant women with chronic HBV infection and evaluated whether HEV-HBV co-infection increases the risk of obstetric complications and perinatal adverse outcomes.

Patients and Methods

Patients

This retrospective study included 3,251 pregnant women with chronic HBV infection who accepted maternal-childcare services and delivered between January 2011 and December 2021 in Shanghai Public Health Clinical Center, a regional tertiary hospital for infectious diseases in Shanghai, China. The inclusion criteria were the following: (1) pregnant women, (2) HBsAg positive > six months. The exclusion criteria were the following: (1) co-infection with human immunodeficiency virus (HIV), (2) co-infection with hepatitis A virus, hepatitis C virus (HCV), or hepatitis D virus, (3) alcohol consumption ≥ 20 g/day for more than five years, (4) non-alcoholic fatty liver disease, (5) autoimmune liver disease, (6) cholestatic or vascular liver disease, (7) lack of clinical data necessary for the study. The study was approved by the Clinical Research Ethics Committee of Shanghai Public Health Clinical Center (No. 2022-S075-01). The procedures were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2013).

Variables Extracted from Medical Records

Available data were collected from the electronic medical records. The extracted demographic data included age, pregnancy history, family history, pre-pregnant body mass index (BMI), gestational diabetes mellitus (GDM), subclinical hypothyroidism, and anti-HBV therapy history. The extracted laboratory tests included HBV serological markers, HBV DNA, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamyltransferase (γ-GT), cholinesterase, total bilirubin (TBIL), direct bilirubin, total protein, albumin (ALB), total bile acid (TBA), cholesterol, triglycerides, fasting glucose, creatinine, prothrombin activity (PTA), international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time, leukocyte count, hemoglobin, platelet count, neutrophil count, and lymphocyte count. Maternal and neonatal outcomes were noted in the delivery records. The extracted information included delivery mode (eutocia/cesarean), sex of newborn, body weight, breech delivery, fetal macrosomia, oligohydramnios, postpartum hemorrhage, premature rupture of membranes, spontaneous abortions, low birth weight infant, premature delivery, fetal distress, neonatal asphyxia, newborn admitted to neonatal intensive care unit (NICU) and stillbirth.

Definitions

Pregnant women with acute hepatitis E were identified by two consecutive positive tests for anti-HEV IgM. Pregnant women with chronic HBV infection were confirmed by positive HBsAg for more than six months. Liver failure was diagnosed based on a bleeding tendency with an INR ≥ 1.5 or PTA ≤ 40% or rapidly increased jaundice with total bilirubin 10 times greater than the upper limit of normal or daily progression of ≥ 17.1 μmol/L[10]. Obstetric complications included oligohydramnios, postpartum hemorrhage, premature rupture of membranes, and meconium contamination[11]. Perinatal adverse outcomes included spontaneous abortion, low birth weight infant (full-term fetus < 2.5 kg), premature delivery, fetal distress, neonatal asphyxia, admission to NICU, and stillbirth[11].

Statistical Analysis

Variables were expressed as mean ± SD or median (IQR) for numerical variables and as frequency and percentage for categorical variables. The Student's *t*-test was used for comparisons between normal distribution continuous variables, the Mann-Whitney U-test was used for comparisons between non-normal distribution continuous variables, and the Chi-squared test was used for

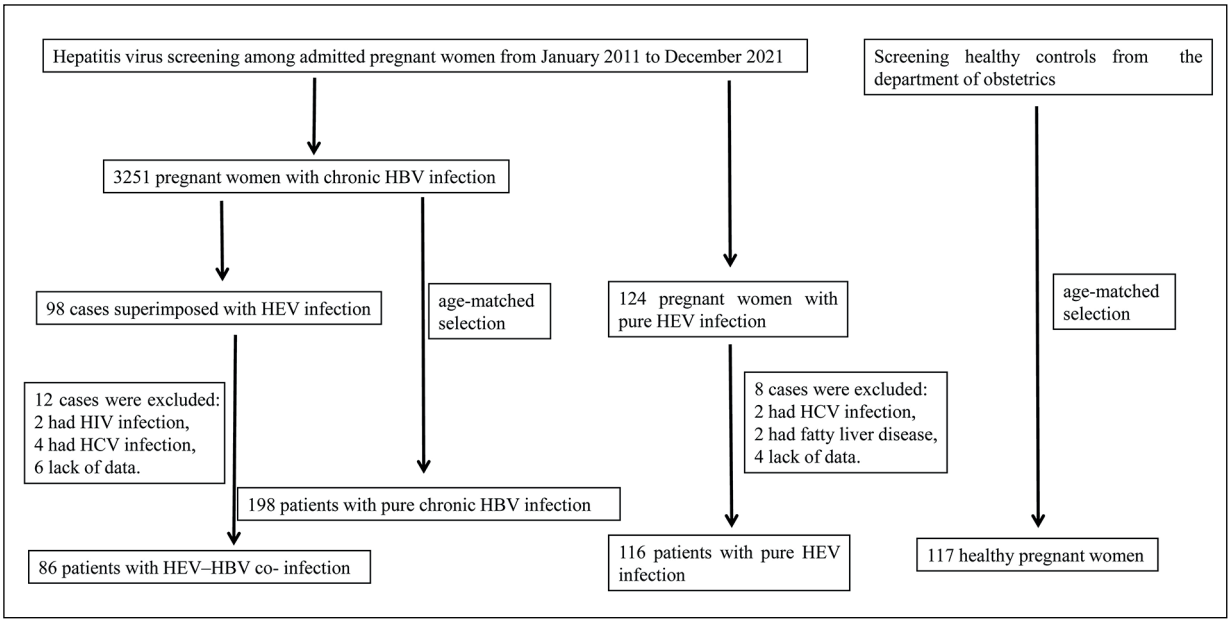

Figure 1. Flow diagram of the study population.

comparisons between categorical variables. Multivariate logistic analysis through the use of odds ratios (ORs) to estimate the relative risk for perinatal complications and perinatal adverse outcomes. A two-sided $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA).

Results

Prevalence of HBV-HEV Co-infection in Patients with Chronic HBV Infection

Among 3,251 HBsAg-positive pregnant women, 98 patients were infected with HEV. The prevalence of HBV-HEV co-infection was 3.01% (98/3251). Among 98 patients with HBV-HEV co-infection, 12 patients were excluded (2 for HIV co-infection, 4 for HCV co-infection, and 6 for lack of data), and 86 patients were included. As a contrast, an age-matched selection was used to recruit 198 patients with pure chronic HBV infection, 116 patients with pure HEV infection, and 117 healthy pregnant women from the non-infectious maternity ward (Figure 1).

Characteristics of the Study Population

Characteristics of the study population are presented in Table I. Patients in the HEV group were older than those in the HBV group (30 *vs.* 28 years, $p = 0.046$). Patients in the HEV group, HBV group, or HEV-HBV group had higher pre-pregnant BMI than patients in the healthy group (21.5, 21.1, 21.0, 20.1, respectively; $p = 0.021$). Patients in the HEV-HBV group, HBV group, or HEV group had a higher prevalence of gestational diabetes mellitus compared with patients in the healthy group (16.6%, 14.7%, 13.8%, and 3.4%, respectively; $p < 0.01$). All HEV infections occurred in the second or third trimester, especially in the third trimester (62.2% in patients with HEV infection and 68.6% in patients with HEV-HBV co-infection). Fulminant liver failure occurs only in the HEV-HBV group and HEV group. The prevalence of fulminant liver failure in the HEV-HBV group is significantly higher than that in the HEV group (5.8% *vs.* 3.5%, $p < 0.01$) (Table I).

Laboratory Tests of the Study Population

Laboratory tests of the study population are presented in Table II. Patients in the HBV group had significantly higher HBeAg positivity rate (75.3% *vs.* 43.0%, $p < 0.001$) but significantly lower rate of HBV DNA $\geq 5 \times 10^5$ IU/mL (8.6% *vs.* 36.7%, $p < 0.001$) compared to patients in HEV-HBV group (Table II). Patients in the HEV group had higher ALT, AST, GGT, and ALB levels compared to patients in the HBV group ($p < 0.001$). However, no significant differences were found in TBIL levels between the three groups (Table II). Moreover, TBA, creatinine, PTA, and PT levels were significantly different among the different hepatitis-virus-infected groups ($p < 0.05$).

Table I. Characteristics of the study population.

	HEV group (n=116)	HBV group (n=198)	HEV-HBV group (n=86)	Healthy group (n=117)	*p*
Age	30 (27-34)	28 (26-31)	30 (26-33)	28 (25-32)	0.046
Elderly maternal, n (%)	32 (25.6)	8 (4.0)	14 (16.3)	10 (8.6)	< 0.001
BMI before pregnancy	21.5 (21.1-23.0)	21.1 (19.8-22.9)	21.0 (21.0-22.6)	20.1 (18.6-22.9)	0.021
Primipara, n (%)	72 (62.1)	129 (65.2)	47 (54.7)	49 (41.9)	< 0.001
History of abortion, n (%)	31 (26.7)	58 (29.3)	30 (34.9)	26 (22.2)	0.240
Gestational diabetes mellitus, n (%)	16 (13.8)	29 (14.7)	16 (16.6)	4 (3.4)	< 0.001
Trimester of HEV infection, n (%)					
Second	38 (32.8)	/	27 (31.4)	/	0.838
Third	78 (62.2)	/	59 (68.6)	/	
Fulminant hepatic failure	4 (3.5)	0 (0)	5 (5.8)	/	< 0.001

HEV, hepatitis E virus; HBV, hepatitis B virus; BMI, Body Mass Index.

Comparison of Maternal-Neonatal Outcomes

Maternal-neonatal outcomes in various research groups are presented in Table III. The prevalence of cesarean section in the HEV-HBV group is 79.1%, which is significantly higher compared to the HEV group (65.5%), the HBV group (54.0%), and the healthy group (45.3%) ($p < 0.001$). HEV-HBV group also had a significantly higher prevalence of breech delivery compared to the HBV group, HEV group, and healthy group (10.5%, 3.0%, 1.7%, and 1.7%, respectively; $p < 0.001$). Compared to healthy women, patients with hepatitis virus infection showed a significantly higher prevalence of obstetric complications. Patients with HEV infection (HEV group or HEV-HBV group) had a higher prevalence of oligohydramnios, postpartum hemorrhage, and premature rupture of membranes compared with patients without HEV infection (HBV group or healthy group). The prevalence of meconium contamination was highest in the HEV-HBV group, compared to the HBV group, HEV group, and healthy group (22.1%, 17.7%, 14.7%, and 4.3%, respectively; $p < 0.01$). Spontaneous abortions and stillbirths only occurred in pregnant women with HEV infection (HEV group or HEV-HBV group) (Table III).

Risk Factors for Obstetric Complications and Adverse Perinatal Outcomes

Risk factors for obstetric complications and perinatal adverse outcomes are presented in Table IV. Multivariate logistic regression results showed that HEV-HBV co-infection was the most significant risk factor for obstetric complications (OR = 5.41, $p < 0.001$), followed by pure HEV infection (OR = 3.99, $p < 0.001$), and pure HBV infection (OR = 2.76, $p < 0.001$). Multivariate logistic regression results also revealed that HEV-HBV co-infection was the most significant risk factor for adverse perinatal outcomes (OR = 15.47, $p < 0.001$),

Table II. Laboratory data of the study population.

	HEV group (n=116)	HBV group (n=198)	HEV-HBV group (n=86)	*p*-value
HBeAg positivity	/	149 (75.3)	37 (43.0)	< 0.001
HBV DNA ≥ 5×10^5 IU/mL	/	17 (8.6)	36 (36.7)	< 0.001
ALT (IU/L)	22 (10-146)	14 (10-21)	20 (12-127)	< 0.001
AST (IU/L)	24 (15-81)	19 (16-25)	25.5 (19-79)	< 0.001
GGT (IU/L)	15 (9-30)	9.13 (7-14)	12 (9-25)	< 0.001
TBIL (μmol/L)	7.0 (5.0-10.9)	6.8 (5.3-8.9)	7.4 (5.9-11.1)	0.099
ALB (g/dL)	34.6 ± 4.0	32.6 ± 2.9	34.1 (32.1-37.0)	< 0.001
TBA (IU/L)	4.3 (2.5-9.1)	4.3 (2.7-7.1)	6.4 (3.6-17.6)	< 0.001
Creatinine (μmol/L)	42.8 (37.9-49.7)	45.5 (40.1-51.8)	47.6 (41.9-53.5)	< 0.001
PTA (%)	107.1 ± 16.7	112.1 ± 13.4	107.5 (96.0-116.0)	< 0.001
PT (s)	13.0 ± 1.4	12.8 ± 1.1	12.8 (12.3-13.4)	< 0.001

HEV, hepatitis E virus; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TBIL total bilirubin; ALB, albumin; TBA, total bile acid; PTA, prothrombin activity; PT, prothrombin time.

Table III. Maternal-neonatal outcomes in various research groups.

	HEV group (n=116)	HBV group (n=198)	HEV-HBV group (n=86)	Healthy group (n=117)	*p*
Delivery mode, n (%)					
Eutocia	29 (25.0)	91 (46.0)	16 (18.6)	64 (54.7)	< 0.001
Cesarean	76 (65.5)	107 (54.0)	68 (79.1)	53 (45.3)	< 0.001
Infant body weight (g)	3,200 (2,880-3,475)	3,265 (3,000-3,545)	3,202 (2,900-3,552)	3,230 (2,990-3,530)	0.068
Breech delivery	2 (1.7)	6 (3.0)	9 (10.5)	2 (1.7)	< 0.001
Fetal macrosomia	5 (4.3)	6 (3.0)	6 (7.0)	4 (3.4)	0.466
Obstetric complications, n (%)					
Oligohydramnios	25 (21.6)	22 (11.1)	19 (22.1)	10 (8.6)	< 0.001
Postpartum hemorrhage	11 (9.5)	10 (5.1)	7 (8.1)	1 (0.9)	< 0.05
Premature rupture of membranes	23 (19.8)	20 (10.1)	18 (20.9)	12 (12.3)	< 0.05
Meconium contamination	17 (14.7)	35 (17.7)	19 (22.1)	5 (4.3)	< 0.01
Adverse perinatal outcomes, n (%)					
Spontaneous abortions	10 (8.6)	0 (0)	1 (1.2)	0 (0)	< 0.001
Low birth weight infant	14 (12.1)	8 (4.0)	14 (16.3)	2 (1.7)	< 0.001
Premature delivery	24(20.7)	13 (6.6)	9 (10.5)	3 (2.6)	< 0.001
Fetal distress	22 (19.0)	20 (10.1)	17 (19.8)	3 (2.6)	< 0.001
Neonatal asphyxia	13 (11.2)	10 (5.1)	10 (11.6)	0 (0)	< 0.01
Admitted to NICU	10 (8.6)	2 (1.0)	3 (3.5)	0 (0)	< 0.001
Stillbirth	1 (0.9)	0 (0)	2 (2.3)	0 (0)	0.098
Maternal death	0	0	0	0	/

HEV, hepatitis E virus; HBV, hepatitis B virus; NICU, neonatal intensive care unit.

followed by pure HEV infection (OR = 10.22, $p < 0.001$), and pure HBV infection (OR = 5.82, $p < 0.001$).

Discussion

HEV and HBV are hyperendemic in China, where dual infection is common[4]. HEV super-infection in patients with chronic HBV infection might result in acute exacerbation of liver disease and even lead to mortality. However, in several special populations, such as pregnant women, the data of overlapping infection are rarely reported. According to previous studies[7,12], HEV and HBV infection are associated with obstetric complications and poor prognosis among pregnant women. Yet, the incidence of HEV-HBV co-infection among pregnant women is not known, nor whether maternal HEV-HBV co-infection affects pregnancy outcome. In this study, we analyzed data from 3,251 pregnant women with chronic HBV infection to answer the questions.

The frequency of hepatitis E was found to be only 3% in pregnant women with chronic HBV infection, which indicated that the incidence of HEV-HBV co-infection was low in pregnancy compared with that in general chronic HBV infection population[4,13]. Despite the population being generally susceptible to HEV, exposure to HEV in pregnant women all occurred in the second or third trimester. This phenomenon might be related to the changes in hormone levels during pregnancy. Specifically, steroid hormones might play a role in HEV infection through their properties of immunosuppression and inducing lymphocyte apoptosis[14,15]. Pregnant women with HEV-HBV co-infection were found to be older than those with pure HBV infection, which suggests that HEV can easily infect women with advanced maternal age.

We also observed high BMI among hepatitis-virus-infected women, which suggests that obese pregnant women are more likely to be infected with HBV or HEV. The results were not surprising, since excess fat has been reported[16,17] to function synergistically with liver damage induced by HBV and HCV. An interaction between HEV and obesity has also been reported in a previous study by Viera-Segura et al[18], who found a higher rate of positive anti-HEV and HEV RNA in obese patients. A higher incidence of GDM was also seen in pregnant women with viral hepatitis compared with healthy controls, which suggests that HEV or HBV infection might be a risk factor for the development of GDM. There are several theories to support the association between hepatitis B and GDM[19-21]. In our study, we also found an increased incidence of GDM in

Table IV. Risk factors for obstetric complications and adverse perinatal outcomes.

Predictors	For obstetric complications		For adverse perinatal outcomes	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Total patients (n=517)				
Age, y (continuous)	1.03 (0.99-1.08)	0.104	1.04 (0.99-1.09)	0.092
Status of virus hepatitis				
Healthy pregnant women	Reference	Reference	Reference	Reference
HEV infection	3.99 (2.21-7.22)	< 0.001	10.22 (5.75-21.31)	< 0.001
HBV infection	2.76 (1.59-4.79)	< 0.001	5.82 (2.22-15.30)	< 0.001
HEV-HBV co-infection	5.41 (2.85-10.25)	< 0.001	15.47 (5.65-42.21)	< 0.001
HEV-HBV co-infection pregnant women (n=86)				
Age, y (continuous)	1.02 (0.93-1.12)	0.717	0.10 (0.88-1.14)	0.976
HBeAg positive, n (%)	2.20 (0.60- 8.14)	0.237	0.18 (0.16-0.36)	0.032
HBV DNA (IU/mL)				
HBV DNA < 500	Reference	Reference	Reference	Reference
500 ≤ HBV DNA < 5*10^5	0.60 (0.13-2.82)	0.524	0.07 (0.03-0.68)	0.245
HBV DNA ≥ 5*10^5	0.55 (0.10-3.10)	0.468	0.76 (0.28-2.11)	0.604
Anti-HBV therapy, n (%)	0.54 (0.12-2.38)	0.416	0.02 (0.00-0.19)	< 0.001
Pure HBV infection pregnant women (n=198)				
Age, y (continuous)	1.01 (0.94-1.09)	0.704	1.08 (0.98-1.18)	0.119
HBeAg positive, n (%)	0.34 (0.16-0.71)	0.004	0.61 (0.25-1.49)	0.278
HBV DNA (IU/mL)				
HBV DNA < 500	Reference	Reference	Reference	Reference
500 ≤ HBV DNA < 5*10^5	1.41 (0.56-3.57)	0.466	0.74 (0.23-2.37)	0.608
HBV DNA ≥ 5*10^5	2.87 (0.75-11.00)	0.124	2.61 (0.61-11.20)	0.198
Anti-HBV therapy, n (%)	0.73 (0.30-1.74)	0.471	0.35 (0.11-1.09)	0.070

HEV, hepatitis E virus; HBV, hepatitis B virus; OR, odds ratio.

women infected with HEV. However, the underlying mechanism remains unclear.

Although HEV infection worsened illness in pregnant women, the rate of fulminant hepatic failure was low, and no deaths were registered in our study. However, according to a previous study by Reddick et al[21], HEV showed a high maternal mortality rate during pregnancy. The conflicting result might be due to genotypic differences in HEV. Previous research[21] indicated that poor outcomes, including fulminant hepatic failure and death, were associated with genotypes 1 and 2, while mild illness was associated with genotypes 3 and 4. In China, serological investigation[22] showed that genotype 4 HEV infection was dominant. Therefore, there were no deaths in our study, which is consistent with a previous study[23] in which HEV genotypes 1 and 2 (more virulent) in pregnancy showed a fulminant course, while HEV genotypes 3 and 4 were rare.

Logistic regression models showed that HEV infection, HBV infection, and HEV-HBV co-infection were significantly associated with an increased risk of perinatal complications and adverse perinatal outcomes. Several immunological changes during gestation (including hormonal changes, proinflammatory processes decrease whereas anti-inflammatory processes increase and then depress cell-mediated immunity), which might activate hepatitis virus and lead to the progression of hepatitis E and B, were considered[15]. Nevertheless, spontaneous hepatitis B flares were mild and self-limited in our study, and no patient developed liver failure. This was consistent with a previous study[24] in which hepatitis B flares leading to severe clinical decompensation were infrequent in pregnant women. Previous research by Nasir et al[4] reported that HEV super-infection could aggravate the clinical outcome of HBV infection. Our research confirmed this and demonstrated that HEV-HBV co-infection could progress to liver failure among pregnant women.

For pregnant women with HEV-HBV co-infection, multivariate logistic regression showed that HBeAg positivity ($p = 0.237$) and anti-HBV therapy ($p = 0.416$) were not significant contributors to obstetric complications (Table IV). However, for adverse perinatal outcomes, both HBeAg negativity and absence of anti-HBV therapy were risk factors (HBeAg positive OR = 0.18, $p = 0.032$; an-

ti-HBV therapy OR = 0.02, $p < 0.001$, respectively). For patients with pure HBV infection, HBeAg negativity was also a risk factor for obstetric complications (HBeAg positive OR = 0.34, $p = 0.004$). Anti-HBV therapy might have a protective role in adverse perinatal outcomes, as it showed a trend for significant difference (OR = 0.35, $p = 0.070$) (Table IV).

For the management of pregnant women with chronic HBV infection, previous studies[25,26] focused on mother-to-child transmission and blocking, which considered that HBeAg positivity and high HBV DNA load acted as risk factors for mother-to-child transmission and advocated antiviral therapy in these populations. Previous literature[27,28] has also concluded that the immune active phase during pregnancy and higher HBV DNA levels might cause adverse perinatal and neonatal outcomes among pregnant women with chronic HBV infection. However, little is known regarding the association of HBV-related factors with poor maternal and infant outcomes in the HEV-HBV co-infection population. In our study, the perinatal complications and adverse outcomes of patients with HBsAg positivity were significantly higher than those in HBsAg-negative cases and were significantly increased in combination with HEV infection. A previous study by Chen et al[5] showed that patients with HBeAg-negative CHB were the most vulnerable to symptomatic HEV infections and identified independent predictors for adverse outcomes in the co-infected non-pregnant populations. In the study, we confirmed this among pregnant women, in whom HBeAg negativity acted as an independent risk factor for adverse perinatal outcomes. Besides, anti-HBV treatment could significantly reduce the adverse clinical outcomes (liver failure and mortality) in both pure HBV infection and HEV-HBV co-infection[5].

In this study, we studied HEV seroprevalences in patients with HBV infection to understand the consequences of HEV superinfection in a Chinese population. We compared the data of this study with data from different areas where HBV and HEV infections are hyperendemic. Hoan et al[29] studied HEV seroprevalences in patients with HBV infection in a Vietnamese population and found that seroprevalences of anti-HEV IgG among HBV infection patients and controls corresponded to 45% and 31%, respectively ($p = 0.034$). This study performed by Hoan et al[29] indicated a high prevalence of HEV infection in Vietnamese HBV patients and showed that HEV superinfection might influence the outcome and progression of HBV-related liver disease. McGivern et al[30] reported the prevalence and impact of HEV infection among persons with chronic HBV infection living in the US and Canada. The authors found that anti-HEV IgG and IgM seroprevalence were 28.5% and 1.7%, respectively. The odds of anti-HEV seropositivity (IgG+ or IgM+) were higher in older participants, males, Asians, less educated people, and those born outside the United States and Canada[30]. Singh et al[31] reported the prevalence of HEV and HBV dual infection in North India (Delhi)[31]. They found that 2.8% (26/927) of HEV and HBV patients were fully infected among serum samples from 1,147 proven HEV infections.

Conclusions

In areas where hepatitis E and B are prevalent, pregnant women are at risk of HEV-HBV co-infection. The interaction of pregnancy and HBV/HEV infection affected the clinical features of pregnant women. HEV-HBV co-infection might be an important risk factor for obstetric complications and adverse perinatal outcomes. It is important to develop and implement necessary interventions to reduce the prevalence of maternal HEV and HBV infection in endemic areas.

Conflict of Interest

All authors have nothing to declare.

Authors' Contributions

Study concept and design: Qiang Li and Liang Chen. Data collection: Chong Chen, Man-Li Wang, Wei-Xia Li, and Xun Qi. Analysis and interpretation of data: Chong Chen, Man-Li Wang, and Wei-Xia Li. Drafting of the manuscript: Chong Chen. Critical revision of the manuscript: Qiang Li and Liang Chen.

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Availability of Data and Materials

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes without breaching participant confidentiality. The supporting data can be provided by the corresponding author upon request.

Ethics Approval

The study was approved by the Clinical Research Ethics Committee of Shanghai Public Health Clinical Center (No. 2022-S075-01). The procedures were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2013).

Informed Consent

Not applicable due to the retrospective nature of the study.

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