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Prevalence and outcomes of hepatic flare in hepatitis B carriers during pregnancy

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Introduction: The aim of this study was to examine the prevalence and severity of hepatic flare among pregnant women with chronic hepatitis B (CHB) and to assess pregnancy and neonatal outcomes.
Methods: Records of all hepatitis B surface antigen-positive pregnant women who had their first antenatal visit between January 2017 and December 2018 and had a live birth in the Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Hong Kong were retrospectively reviewed. Hepatic flare was defined as an alanine aminotransferase (ALT) ≥2 times the upper limit of normal, which is 19 U/L for females. Pregnancy and neonatal outcomes between those with and without hepatic flare were compared.
Results: 6.3% of pregnant women with CHB had hepatic flare, with ALT level ranging from 39 to 179 IU/L. None of the women had hyperbilirubinemia or liver failure. In those with hepatic flare, the median hepatitis B virus DNA level was 5.77 $\log^{10}$ IU/mL. The rate of postpartum haemorrhage was higher in those with hepatic flare (19.4% vs 10.8%, p=0.024).
Conclusion: 6.3% of pregnant women with CHB had hepatic flare. The rate of postpartum haemorrhage was higher in those with hepatic flare. Monitoring of liver function is recommended in pregnant women with CHB and hepatic flare.

Keywords: Hepatitis B; Pregnancy

Introduction

Worldwide, 257 million people are estimated to be chronically infected with hepatitis B virus (HBV)[1], which can lead to cirrhosis and liver cancer. In Hong Kong, the seroprevalence of HBV is 7.8% in the general population[2] and 4.5% among antenatal women[3]. Although most pregnant women with chronic hepatitis B infection (CHB) are generally well, cases of hepatic flares[4-9] or acute liver failure[4,7,8] have been reported. Current opinions on the impact of HBV on pregnancy and perinatal outcomes are conflicting[10-15]. CHB is associated with gestational diabetes mellitus, antepartum haemorrhage, preterm labour, preterm premature rupture of membrane, lower Apgar score, and postpartum haemorrhage (PPH)[12-15]. Pregnant women with severely abnormal liver function are more likely to have postpartum haemorrhage, puerperal infection, premature birth, and fetal death[7,14].

In Hong Kong, all pregnant women are screened for hepatitis B surface antigen (HBsAg). Since October 2016, liver function test (LFT) has been routinely carried out for pregnant women positive for HBsAg in the Queen Elizabeth Hospital, Hong Kong. Those with hepatic flares are referred to hepatologists for assessment and monitoring of liver function. HBV DNA levels are checked, and antivirals may be prescribed. Nonetheless, the rate and consequence of hepatic flare in Hong Kong pregnant women remain unknown. These data can guide monitoring and management during pregnancy and counselling for pregnant women with CHB. Thus, the present study aimed to determine the prevalence and severity of hepatic flare in pregnant women with CHB and to assess the maternal and perinatal outcomes.

Methods

This study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee (reference: REC (KC/KE)-20-0109/ER-2). Records of all HBsAg-positive pregnant women who had their first antenatal visit between January 2017 and December 2018 and had a live birth in the Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Hong Kong were identified using the ICD codes. Data collected included demographics, laboratory results, medical history, and antenatal, intrapartum, and postpartum records. Those with multiple comorbidities, multiple pregnancies, or incomplete data (eg, LFT not performed or delivered elsewhere) were excluded, as were those with hepatic flare secondary to known alcoholic liver disease, other viral hepatitis, drug-induced hepatic injury, or other liver diseases.

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Hepatic flare was defined as an alanine aminotransferase (ALT) level ≥2 times the upper limit of normal[16], which is 19 U/L for females[17]. Its severity was determined based on the ALT level, any episode of liver decompensation (including ascites, variceal bleeding, or hepatic encephalopathy), and bilirubin and HBV DNA levels.

Pregnancy outcomes between those with and without hepatic flare were compared, including rates of antepartum complications (antepartum haemorrhage, pre-eclampsia, gestational diabetes mellitus, intrauterine growth restriction, and preterm premature rupture of membrane), delivery gestational age, rate of preterm delivery, intrapartum and postpartum outcomes (rate of induction of labour, mode of delivery, blood loss, and PPH [blood loss of >500 mL[18]]), and neonatal outcomes (rate of fetal distress, birth weight, Apgar score at 5 minutes, and neonatal intensive care unit admission).

Statistical analysis was performed using SPSS (Mac version 26; IBM Corp, Armonk [NY], US). Continuous variables were analysed using the t-test and categorical variables using the Chi-squared test or Fisher's exact test. A p value of <0.05 was considered statistically significant.

Results

Of 661 (5.8% of the total) pregnant women with CHB, 169 were excluded owing to no LFT performed (n=8), miscarriages or termination of pregnancy (n=30), lost to follow-up or delivery in other hospitals (n=117), or twin pregnancies (n=14). None of these cases had other known underlying liver disease or multiple comorbidities. The remaining 492 women were included for analysis (Figure). The median gestational age when the LFT was taken was 21 weeks. There were more nulliparous women in the hepatic flare group (61.3% vs 42.2%, p=0.042, Table 1).

31 (6.31%) pregnant women with CHB had hepatic flare at booking, with an ALT level ranging from 39 to 179 (median, 50) IU/L. Of them, 27 (87%) had ALT ≥2 times the upper limit of normal and four (12.9%) had ALT ≥5 times the upper limit of normal. All women had normal bilirubin levels (5.23±2.54 μmol/L), and none had liver failure during pregnancy.

Of the 31 women with hepatic flare, 23 (74.2%) had HBV DNA checked, with levels ranging from 17.7 IU/mL to >9 $\log_{10}$ IU/mL (median, 5.77 $\log_{10}$ IU/mL). The level was ≥5.3 $\log_{10}$ IU/mL in 15 (65%) women and ≥7 $\log_{10}$ IU/mL in nine (39%) women. There was no correlation between ALT and HBV DNA levels (r=0.005, p=0.982). Antiviral drugs were initiated in 21 (4.2%) women to prevent maternal-to-child transmission. Of them, 13 had hepatic flare and eight had HBV DNA levels >5.3 $\log_{10}$ IU/mL.

Women with hepatic flare had a higher rate of PPH (19.4% vs 10.8%, p=0.024) but a similar volume of blood loss during delivery (342 mL vs 307 mL, p=0.402), and had a higher Apgar score at 5 minutes (8.61 vs 8.31, p=0.017) but a similar rate of having an Apgar score <7 at 5 minutes (0% vs 1.1%, p=0.721) [Table 2].

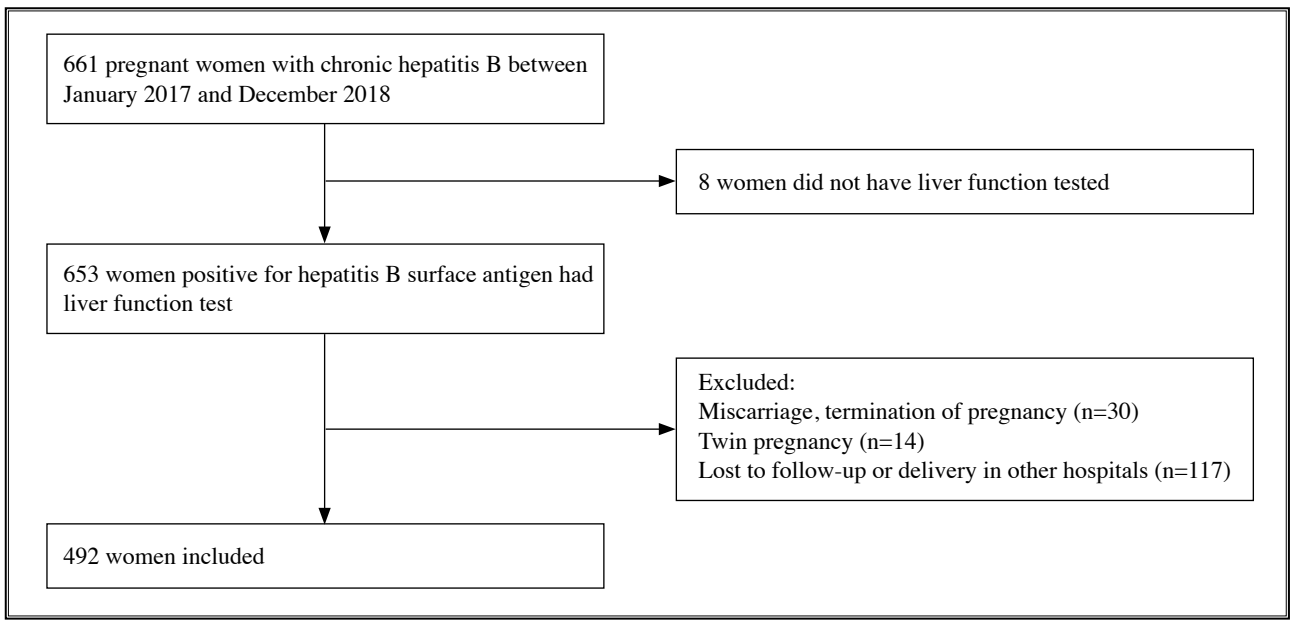

Figure. Flowchart of inclusion of pregnant women with chronic hepatitis B and hepatic flare

Table 1. Pregnant women with chronic hepatitis B stratified by the presence of hepatic flare

Demographic	Without hepatic flare (n=461)	With hepatic flare (n=31)	p Value
Maternal age, y	33.52±4.05	33.29±4.18	0.756
Advanced maternal age	182 (39.5)	9 (29)	0.262
Body mass index, kg/m^2	21.63±3.32	22.68±3.88	0.092
Nulliparous	195 (42.3)	19 (61.3)	0.042
Smoking	18 (3.9)	1 (3.2)	0.849
Drinking	1 (0.2)	0 (0)	0.937
Substance abuse	3 (0.7)	0 (0)	0.822
Education level			0.900
Primary	10 (2.2)	1 (3.2)	
Secondary	245 (53.1)	17 (54.8)	
Tertiary	206 (44.8)	13 (41.9)	

* Data are presented as mean ± standard deviation or No. (%) of pregnant women

Table 2. Pregnancy and neonatal outcomes of pregnant women with chronic hepatitis B stratified by the presence of hepatic flare

Pregnancy and neonatal outcome	Liver function test		p Value
	Normal (n=461)	Abnormal (n=31)	
Antepartum haemorrhage	24 (5.2)	1 (3.2)	0.522
Pre-eclampsia	8 (1.7)	1 (3.2)	0.446
Gestational diabetes	70 (15.2)	7 (22.6)	0.304
Intrauterine growth restriction	14 (3.0)	1 (3.2)	0.629
Preterm premature rupture of membrane	8 (1.7)	0 (0)	0.592
Preterm delivery	30 (6.5)	1 (3.2)	0.711
Gestational age, weeks	38.45±1.69	38.32±1.45	0.679
Induction of labour	196 (42.5)	18 (58.1)	0.091
Mode of delivery			
Vaginal	284 (61.6)	15 (48.4)	0.133
Instrumental	33 (7.2)	5 (16.1)	
Caesarean section	144 (31.2)	11 (35.5)	
Blood loss	307.26±10.41	341.94±38.17	0.402
Postpartum haemorrhage	50 (10.8)	6 (19.4)	0.024
Birth weight, g	3155.32	3085.48	0.405
Fetal distress	12 (2.6)	1 (3.2)	0.603
Apgar score at 5 min	8.31	8.61	0.017
Apgar score <7 at 5 min	5 (1.1)	0 (0)	0.721
Neonatal intensive care unit admission	65 (14.1)	4 (12.9)	0.553

* Data are presented as mean ± standard deviation or No. (%) of pregnant women

Discussion

In the present study, the incidence of hepatic flare was 6.3%, which is lower than the 9% to 14% reported from other studies[4-6]. The timing of LFT, which was usually in the second trimester, may account for the lower incidence, as the risk of hepatic flare is highest in the first trimester and then gradually decline during pregnancy[5,19]. The LFT was performed only once at booking and was not repeated if it was normal; flare up in later gestations could have been missed.

In the second and third decades of life, transition from the immune tolerance phase to the immune-active phase of perinatally acquired HBV is common. Spontaneous HBeAg seroconversion is frequently accompanied by an increase in the ALT level[20]. In addition, pregnancy increases spontaneous HBeAg seroconversion[21,22]. Routine LFT for pregnant women may identify those in the immune-active phase of CHB. Immune modulation occurs during pregnancy in order to tolerate paternal semi-allogeneic tissues and prevent fetus rejection[23]. As HBV infection is predominantly an immune-mediated disease[24], immune and hormonal changes during pregnancy facilitate viral activity and is responsible for hepatic flare during pregnancy[5,7]. This may explain why more nulliparous women, who are more likely to have immune maladaptation[25], have hepatic flare.

Pregnant women with high viral load are more likely to have hepatic flare[5]. Viraemic mothers have significantly higher ALT level[26]. However, there was no correlation between ALT and HBV DNA levels (r=0.005, p=0.982), although half of pregnant women with hepatic flare had HBV DNA level >5.3 $\log^{10}$ IU/mL. This may be due to the small sample size with HBV DNA level tested, as HBV DNA levels were not checked in most pregnant women with normal ALT level. However, eight women without hepatic flare were found to have high viral loads and were prescribed with antivirals for prevention of maternal-to-child transmission. Checking HBV DNA level routinely in all pregnant women with CHB can identify those with high viral load, even if they do not have flare, so that antenatal antivirals can be prescribed. Since August 2020, HBV DNA level has been assessed for all pregnant women with CHB in our hospital.

The risk of PPH increases in pregnant women with CHB[15]. During hepatic flare, hepatic cells are damaged, affecting the synthesis of the coagulation factor. In women with hepatic flare, the rates of induction of labour and instrumental delivery were higher, which may account for the higher incidence of PPH.

Obstetric causes of hepatic flare such as pre-eclampsia and acute fatty liver of pregnancy are difficult to be differentiated from HBV flare during antenatal period[27]. These obstetric causes may also result in increased use of induction of labour or instrumental delivery. However, there was no difference in neonatal outcomes, including the rate of prematurity, birth weight, rate of fetal distress, and neonatal intensive care unit admission.

The treatment goals for CHB in pregnancy are to monitor for any maternal flare and prevent maternal-to-child transmission[21,28]. Checking ALT level in HBV-infected pregnant women at booking visits is recommended to screen for possible flare and determine severity and guide management. For many women, the initial diagnosis of HBV infection is made during pregnancy. LFT at booking can determine the severity of liver condition and exclude any unrecognised severe conditions such as liver cirrhosis. Monitoring of liver function in pregnancy can identify pregnant women with hepatic flare who may need antivirals.

The findings of the present study can be used to guide counselling of pregnant women with CHB. Severe hepatic flare with complications can be fatal. Monitoring is advised, and use of antivirals may be indicated. The risk of PPH in those with hepatic flare should be aware. Blood tests for platelet count and coagulation should be performed; any coagulopathy should be reversed.

There are limitations to our study. First, LFT was performed once only during the first antenatal visit. Changes in the later gestation could have been missed, and the effect of pregnancy on liver disease progress cannot be assessed. Second, other causes of deranged live function were not ruled out such as fatty liver or other viral infections. Third, the effect of antiviral treatment to pregnancy outcome was not evaluated. Fourth, the HBeAg status was not checked, so the phase of HBV disease and the effect of HBeAg could not be assessed.

Conclusion

About 6.3% of pregnant women with CHB had hepatic flare; 12.9% of them had ALT level ≥5 times the upper limit of normal. None had liver decompensation. The rate of PPH was higher in pregnant women with hepatic flare. Monitoring of liver function is recommended in pregnant women with CHB and hepatic flare.

Declaration

The authors have no conflict of interest to disclose.

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