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Original Article

Relationship between viral load and pregnancy outcomes among hepatitis B carriers

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ABSTRACT

Objective: Pregnant hepatitis B carriers may have a higher risk of adverse pregnancy outcomes. Current evidences are conflicting regarding the relationship between hepatitis B virus (HBV) and various pregnancy complications, owing to the inclusion of women with different viral activity. This study is to evaluate the relationship between hepatitis B e antigen (HBeAg) status/HBV DNA level and pregnancy outcomes among pregnant hepatitis B carriers in Hong Kong.

Materials and methods: This was a retrospective analysis of a prospective multicenter observational study carried out in Hong Kong between 2014 and 2016. Pregnant HBV carriers were recruited. HBeAg was tested. HBV DNA level was quantified at 28–30 weeks of gestation. The rates of gestational diabetes mellitus (GDM), gestational hypertension, pre-eclampsia, preterm prelabour rupture of membranes (PPROM), preterm birth, low birth weight (LBW), macrosomia and mode of delivery were recorded.

Results: 679 pregnancies were analyzed. 23.3% of women were seropositive for HBeAg. The mean viral load (SD) at 28–30 weeks of gestation was 3.6 (2.5) $\log_{10}$IU/ml. No statistically significant differences were found in the rates of GDM, gestational hypertension, pre-eclampsia, PPROM, preterm birth, LBW, macrosomia and mode of delivery among women with different viral load levels ($\leq$2 $\log_{10}$IU/ml, 2.01–6 $\log_{10}$IU/ml and >6 $\log_{10}$IU/ml). Positive maternal HBeAg status was not associated with pregnancy complications compared to seronegative women.

Conclusion: Seropositive HBeAg status or a higher level of HBV DNA during pregnancy did not pose a significant negative impact to the pregnancy outcomes.

Introduction

Hepatitis B virus (HBV) infection remains the commonest form of chronic hepatitis with an estimated global prevalence of 3.5%. Around 257 million people are chronically infected worldwide [1]. Although universal neonatal vaccination has effectively decreased the prevalence of HBV, pregnant HBV carriers are frequently encountered. In Hong Kong, the local prevalence of pregnant HBV carriers decreases steadily from 11.3% in 1990 to 4.0% in 2019 [2]. HBV carriers are in chronic inflammatory state by ongoing HBV replication, which could increase the risk of adverse pregnancy outcomes [3].

The relationship between maternal HBV infection and pregnancy outcomes appears conflicting. Some studies suggest an increased risk of miscarriage, preterm prelabour rupture of membranes (PPROM), preterm birth, gestational diabetes mellitus (GDM), gestational hypertension, Caesarean delivery and macrosomia [3–14]. Other studies, however, do not support these association [15–17]. The heterogeneous result could be attributed to the diverse study population with a wide range of HBV disease activity. Active viral replication is reflected by positive hepatitis B e antigen (HBeAg) status or elevated HBV DNA level but they were seldom analyzed in relation to the pregnancy outcomes. A retrospective study showed high viral loads (>17,515IU/ml) had an increased rate

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of composite adverse perinatal outcome including preterm birth, fetal growth restriction, small for gestational age, oligohydramnios and pre-eclampsia [18].

Antenatal HBV DNA quantification becomes crucial to HBV pregnant carriers to identify newborn at risk of immunoprophylaxis failure. Knowledge about the relationship between HBV DNA level and pregnancy outcomes could identify potential high-risk women and offer suitable antenatal care. The aim of this study was to evaluate the relationship between between HBeAg status/HBV DNA levels and pregnancy outcomes among pregnant hepatitis B carriers in Hong Kong.

Materials and methods

This was a secondary retrospective analysis of a prospective study conducted from January 2014 to December 2016 at antenatal units in five public hospitals in Hong Kong (Kwong Wah Hospital, Pamela Youde Nethersole Eastern Hospital, Queen Mary Hospital, Queen Elizabeth Hospital and Tuen Mun Hospital). Hepatitis B surface antigen (HBsAg) was tested in all pregnant women at the booking visit and HBV carriers were identified by positive HBsAg status. All women gave a written informed consent and were enrolled under protocols approved by the Institutional Review Board.

HBeAg was tested at recruitment and HBV DNA level was quantified at 28–30 weeks of gestation, using the COBAS TaqMan HBV Monitor Test coupled with the COBAS Ampliprep extraction system (Both Roche Diagnostics, Branchburg, NJ), with a lower limit of detection of 100 copies/mL (~17.2 IU/ml) and upper limit of 990,000,000 copies/mL (~170,103,092 IU/ml) (1 IU = 5.82 copies). Both pregnant women and their obstetricians were blinded to both HBeAg and HBV DNA results. Women with antiviral treatment during pregnancy, absence of HBV DNA result at 28–30 weeks, co-infection with human immunodeficiency virus, miscarriage, termination of pregnancy, stillbirth or multiple pregnancy were excluded. GDM was defined if one or more of the following criteria were met following a fasting 75-g oral glucose tolerance test: fasting plasma glucose ≥5.1 mmoL/l, 1-h plasma glucose ≥10.0 mmol/L or 2-h plasma glucose ≥8.5 mmol/L. Gestational hypertension was defined as blood pressure ≥140/90 mmHg on at least two occasions 4 h apart developing after 20 weeks of gestation in previously normotensive women. Pre-eclampsia was defined as gestational hypertension with ≥300 mg proteinuria in 24 h or two readings of ≥2+ protein on urine dipstick analysis. PPROM was defined as membranes rupture before 37 + 0 weeks of gestation. Low birth weight (LBW) was defined as birth weight ≤2500 g and macrosomia was defined as birth weight ≥4000 g.

Results were presented as mean [standard deviation (SD)] or median [interquartile range (IQR)] or n (%). Women involved in this study were allocated to three groups based on their HBV viral load (≤2 $\log_{10}$IU/ml, 2.01–6 $\log_{10}$IU/ml and >6 $\log_{10}$IU/ml). The differences of obstetrical outcome between women in different viral load groups were investigated by Chi-square. Chi-square test was used to assess the risk of having pregnancy complications according to their HBeAg status. In terms of missing data handling, women who had missing values other than HBV viral load were still included in this study, however, they were removed in the analysis if they have missing value in the specific condition. The mean (SD), median (IQR) and n (%) were also calculated after the removal of missing data. P values of less than 0.05 were considered to indicate statistical significance. SPSS for Mac version 26.0 (IBM Corp.) was used to perform statistical analyses.

Results

A total of 750 HBsAg seropositive women were recruited in the study, 71 pregnancies were excluded due to no maternal HBV DNA testing (n = 42), use of antiviral treatment (n = 16), withdrew consent (n = 8), miscarriage or termination of pregnancy (n = 4) and stillbirth (n = 1). A total 679 pregnancies were available for analysis. Table 1 summarized the basic demographics and obstetric characteristics of these women. 23.3% (158/679) of women were seropositive for HBeAg. The mean viral load (SD) at 28–30 weeks of gestation was 3.6 (2.5) $\log_{10}$IU/ml. 5.7% of women had preterm delivery and 2.9% of them had PPROM. 65.7% (462/679) of women delivered vaginally. The rates of adverse pregnancy complications were 6.6% for LBW, 2.8% for macrosomia, 22.9% for GDM, 3.3% for gestational hypertension and 2.5% for pre-eclampsia.

Table 2 shows the rates of pregnancy complications in relation to different maternal HBV DNA levels at 28–30 weeks. There were no significant differences in the rates of GDM, gestational hypertension, pre-eclampsia, PPROM, preterm birth, vaginal delivery, LBW and macrosomia among women with different viral load levels (≤2 $\log_{10}$IU/ml, 2.01–6 $\log_{10}$IU/ml and >6 $\log_{10}$IU/ml).

A seropositive HBeAg status was not associated with pregnancy complications compared to seronegative women (Table 3).

Discussion

Our findings suggested active HBV replication during pregnancy, as reflected by HBV DNA levels or HBeAg status, did not pose a significant negative impact to pregnancy outcomes. This information is important to reassure the obstetricians and the women that additional antenatal surveillance appears unnecessary in women with higher viral load.

There were only few studies using HBeAg or HBV DNA as a parameter to assess pregnancy outcomes. Sirilert et al. did not

Table 1
Basic maternal demographics and obstetric characteristics (n = 679)[a].

Viral load at 28–30 weeks ($\log_{10}$IU/ml), mean (SD)	3.6 (2.5)
Age (years), mean (SD)	32.7 (4.5)
Gravida, median (IQR)	2 (1, 3)
Parity, median (IQR)	0 (0, 1)
Nulliparity, n (%)	382 (56.3)
Body mass index (kg/m^2), mean (SD)	22.2 (3.2)
Smoker, n (%)	40 (5.9)
Drinker, n (%)	14 (2.1)
Education level	
Secondary or lower, n (%)	429 (64.8)
Tertiary or above, n (%)	233 (35.2)
Positive HBeAg, n (%)	158 (23.3)
Gestational diabetes mellitus, n (%)	150 (22.9)
Gestational hypertension, n (%)	21 (3.3)
Pre-eclampsia, n (%)	16 (2.3)
Preterm pre-labour rupture of membranes n (%)	20 (2.9)
Gestational age at delivery (mean, weeks)	39.1 (1.5)
Preterm delivery <37 weeks, n (%)	40 (5.7)
Preterm delivery <34 weeks, n (%)	9 (1.0)
Mode of delivery	
Normal Vaginal delivery, n (%)	418 (61.5)
Forceps, n (%)	9 (1.3)
Vacuum extraction, n (%)	35 (5.2)
Elective Caesarean section, n (%)	118 (17.4)
Emergency Caesarean section, n (%)	99 (14.6)
Birth weight (grams), mean (SD)	3124.4 (442.8)
≤2500 g, n (%)	45 (6.6)
≥4000 g, n (%)	18 (2.8)

[a] The demographic information was calculated after the removal of missing data in each factor.

Table 2
Pregnancy complications with different maternal HBV DNA levels[a].

	HBV DNA level			P value
	≤2 log_{10}IU/ml n = 253	2.01–6 log_{10}IU/ml n = 276	>6 log_{10}IU/ml n = 150	
Gestational diabetes mellitus, n (%)	54 (22%)	68 (25.6%)	28 (19.3%)	0.328
Gestational hypertension, n (%)	8 (3.4%)	10 (3.9%)	3 (2.1%)	0.631
Pre-eclampsia, n (%)	6 (2.5%)	6 (2.3%)	4 (2.8%)	0.960
Preterm pre-labour rupture of membranes, n (%)	8 (3.2%)	9 (3.3%)	3 (2%)	0.738
Preterm delivery <37 weeks, n (%)	12 (4.7%)	20 (7.2%)	8 (5.3%)	0.449
Preterm delivery <34 weeks, n (%)	3 (1.2%)	6 (2.2%)	0 (0%)	0.168
Vaginal delivery (including instrumental delivery), n (%)	177 (70%)	181 (65.6%)	104 (69.3%)	0.519
Birth weight, (grams), mean (SD)	3138.3 (422.5)	3127.7 (473.4)	3094.9 (418.7)	0.629
≤2500 g, n (%)	15 (5.9%)	20 (7.2%)	10 (6.7%)	0.831
≥4000 g, n (%)	7 (2.8%)	8 (2.9%)	3 (2%)	0.850

[a] The Chi-square test was performed after the removal of missing data in each factor.

Table 3
The pregnancy complications and maternal HbeAg status[a].

	HBeAg negative (n = 521)	HbeAg positive (n = 158)	p-value
Gestational diabetes mellitus, n (%)	123 (24.5%)	27 (17.6%)	0.079
Gestational hypertension, n (%)	18 (3.7%)	3 (2%)	0.435
Pre-eclampsia, n (%)	11 (2.3%)	5 (3.3%)	0.552
Preterm pre-labour rupture of membrane, n (%)	16 (3.1%)	4 (2.5%)	1.000
Vaginal delivery, (including instrumental delivery), n (%)	352 (67.6%)	110 (69.6%)	0.627
Preterm delivery <37 weeks, n (%)	31 (6%)	9 (5.7%)	0.905
Preterm delivery <34 weeks, n (%)	9 (1.7%)	0 (0%)	0.126
Birth weight, (grams), mean (SD)	3134.1 (449.8)	3092.6 (418.6)	0.303
≤2500 g, n (%)	35 (6.7%)	10 (6.3%)	0.863
≥4000 g, n (%)	14 (2.7%)	4 (2.5%)	1.000

[a] The Chi-square test was performed after the removal of missing data in each factor.

reveal an increased risk of GDM in HBV carriers compared to non-carriers, however, a significant higher risk was found in seropositive HBeAg carriers than seronegative carriers [10]. This emphasizes the difference in the risk profile of HBV carriers with different disease activities, and highlights the potential pitfall when they are grouped together for analysis. However, we cannot identify an increased risk of GDM in women with different viral loads.

Wan et al. demonstrated second trimester maternal viremia was associated with increased preterm birth rate, while data on GDM was not available [12]. A systematic review of 22 observational studies found increased risk of preterm birth among seropositive (21%) and seronegative (16%) HBV carriers, compared with non-infected women [8]. One study found no difference in the risk of preterm birth among 44 HBV carriers with different viral loads. The mean HBV DNA was 6716IU/ml and only one was seropositive for HBeAg, which would represent women with low level of disease activity [19]. We did not find an increased preterm birth rate in women with higher viral load. The preterm birth rate of 5.7% in our cohort is lower than that published in previous local report (6.5%), which could be due to the exclusion of women who had preterm birth before the HBV DNA testing at 28–30 gestational weeks and these women may have a very high viral load [20]. Small sample size of women having higher vial load could be another reason. The association between preterm birth and elevated HBV DNA is particularly crucial since the fetuses of these women are also at risk of immunoprophylaxis failure, requiring maternal antiviral treatment from 28 to 32 gestational weeks. Preterm birth may therefore shorten the duration of antiviral treatment leading to suboptimal viral load suppression at delivery and persistent neonatal HBV infection. Therefore, HBV DNA quantification during early pregnancy and initiate antiviral treatment may be required in women with high viral load and risk of preterm birth.

The strengths of our study are, first, prospective in nature and the double blinded HBV DNA result to both the obstetrician and the HBV infected women that would avoid bias in obstetric management. Second, the multicenter study increases the generalizability of our result to other population. Limitations of our study are the study design of HBV DNA quantification at 28–30 weeks so that assessment of early pregnancy loss prior to this gestation with HBV DNA level was not possible. Furthermore, liver function test was not tested which could be another factor affecting the pregnancy outcomes. We did not analyze the data with each log of HBV DNA because the number of subjects in each subgroup was small, a study of larger sample size involving more women of higher viral load could confirm the absence of elevated risk of pregnancy complications even in women with active viral replication. Finally, we did not use non-infected women as the control group but women of low HBV DNA level (<100IU/ml) were used for comparison of pregnancy complications. We believe the risk of adverse pregnancy outcomes in this group is low and similar to general obstetric women, given the inactive disease status. However, the risk of a higher rate of pregnancy complications in HBV carriers, compared to non-infected women, cannot be excluded by this study.

Conclusion

Seropositive HBeAg or high level of HBV DNA during pregnancy did not pose a significant negative impact to the pregnancy outcomes.

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Declaration of competing interest

All authors have disclosed no conflicts of interest.

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