Maternal age and educational level modify the association between chronic hepatitis B infection and preterm labor

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Abstract

Background To investigated whether maternal age and educational level could modify the association of chronic hepatitis B virus (HBV) infection with preterm labor.

Methods A retrospective cohort study was performed on the pregnant women delivered from June 2012 to August 2017 at Wuhan Medical Care Center for Women and Children, Wuhan, China. Multivariate logistic regression analysis was used to measure the association between maternal HBV infection and preterm labor.

Results 2050 HBsAg-positive pregnant women and 2050 HBsAg negative women were included into this study. In the stratified analyses, positive HBsAg status was associated with the increased risk of preterm labor in women aged <30 years, having low educational level, with an odds ratio of 1.65(95% CI 1.07-2.54) and 2.59(95% CI 1.41-4.76), respectively. After adjusting other covariables, we observed maternal HBV infection (OR 1.60, 95% CI 1.03-2.49) was still associated with risk of preterm labor in mothers with age <30. Similarly, the significant association of HBV infection (OR 2.49, 95% CI 1.34-4.63) with preterm labor remained in low educated women.

Conclusions Our results indicated that HBV infection was associated with high risk of preterm labor, but maternal age and educational level could modify this association. Further studies are warranted to clarify the possible mechanisms behind such modifiable action.

Background

Hepatitis B virus (HBV) infection is one of the most common health problems, causing high mortality and heavy economic burden worldwide [1–3]. China has the world's largest burden of hepatitis B virus infection, with an estimated 90 million people with chronic hepatitis B infection [4–6]. The prevalence of HBV infection in population at different ages varies widely in China [5, 7]. The women of childbearing age have been estimated at 5.2–6.7% [8, 9], which are the main source of hepatitis B transmission. However, most pregnant women with HBV infection are chronic carriers, indicated by positive serum hepatitis B surface antigen (HBsAg) status. Therefore, whether HBV carriers could negatively influence the pregnancy outcomes becomes a critical issue.

Preterm labor (PTB, delivery prior to 37 weeks' gestation) is the leading cause of neonatal morbidity and mortality in high-resource countries [10]. Its complications are estimated to be accounted for approximately 35% annual neonatal deaths [11], and surviving preterm babies have an increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications [12, 13]. Finding from previous studies showed that preterm labor is associated with several maternal risk factors [14], pregnancy history and characteristics, and many genetic, environmental, and social factors [15, 16]. Among these factors, maternal viral infection is an important risk factor of preterm labor, mainly due to activation of the inflammation pathway by viral factors [17, 18]. A large number of studies have explored the impact of maternal chronic HBV infection on preterm labor, but their research results are inconsistent.

Some studies suggest maternal HBV infection is associated with an increased risk of preterm labor [19–21]. However, some studies found no such association [22, 23].

Maternal age and educational level are general demographic characteristics, and the most frequently studied factors influencing health. Maternal age and educational level are common factors that have been related both to HBV infection and preterm labor [24–26]. The accumulated evidence indicated that the population with different ages had various degree of infection risk after exposure to hepatitis B virus [27, 28]. Even in women with HBV infection, age is still associated with HBV DNA level and hepatitis B e antigen (HBeAg) status, and young women are more likely to have a high HBV viral load and HBeAg positivity than older women [29]. Additionally, effects of maternal age on preterm labor has long been noticed by investigator. Advanced maternal age significantly increased the risk of preterm labor [30]. Similarly, maternal educational level could influence the HBV infection status and preterm labor risk. Low schooling level is significantly associated with HBV infection and preterm labor [25, 26]. But whether maternal age and educational level could modify the relationship between HBV infection and preterm labor, it is unclear.

In this hospital-based retrospective cohort study, we examined the association between chronic HBV infection and risk of preterm labor, and explored if maternal age or educational level could modify the association between HBV infection and risk of preterm labor.

Methods

Study population

A hospital-based retrospective cohort study was performed on singleton pregnancies delivered from June 2012 to August 2017 at Wuhan Medical Care Center for Women and Children, Wuhan, China. The annual delivery rate of this hospital was around 5000. The majority of the parturients are local residents, >98% of whom are ethnic Han. All pregnant women conducted a routine screening for HBsAg and the antibodies to HCV, HIV and TP by enzyme-linked immunosorbent assay (ELISA) at first antenatal visit. All HBsAg-positive women aged 18 or older with singleton pregnancy, who did not have current and previous medical complications (including diabetes mellitus, hypertension, psychiatric illness, HCV, HIV or TP infection), were assigned to HBsAg-positive group. A total of 2050 HBsAg-positive women were eligible for the study. For each case, a control without HBsAg, matched for age and parity, was identified and randomly chosen from electronic databases using the same criteria mentioned.

The present study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology. The written informed consent of all subjects had been obtained before participating the study.

Data collection and samples collection

The clinical records of participants in the two groups were retrieved for data extraction. The maternal demographic and clinical information, including age, ethnicity, educational level, height, pre-pregnancy weight, gestational weight gain (GWG), history of pregnancy (including gravidity, parity, miscarriage, induced abortion and stillbirth), and gestational age were obtained from the obstetric records. Pre-pregnancy body mass index (BMI) was calculated as the ratio of pre-pregnancy weight (kg) divided by height (m^2). Pregnancy women with years of education ≤9 was considered having low educational level, otherwise, the women had high educational level. Gestational age was based on the interval between the date of last menstrual period and the date of delivery. Preterm labor was defined as delivery with gestational week less than 37.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) and analyzed by Student's t-tests. Categorical data were expressed as percentages and compared by chi-square tests. Stratified analyses were used to identify effects of maternal age and educational level on the association between HBV infection and preterm labor. The homogeneity of the odds ratios for HBV infection across each stratum of age and educational level was assessed by Breslow-day test. Using a likelihood ratio test in the logistic regression model, multiplicative interaction was tested to evaluate interactions between maternal age and educational level and HBV infection. Multivariable logistical regression was used to measure the independent association between HBV infection and preterm labor stratified by maternal age and educational level. Statistical significance was assessed at the 5% level (two-tail test). All analyses were performed using SPSS software version 18.0 (SPSS, Chicago, IL, USA).

Results

In total, 2050 HBsAg-positive women and 2050 HBsAg-negative women were identified during June 2012 to August 2017. Characteristics of two groups are shown in Table 1. The distribution of maternal educational level exists significant difference between two groups, HBsAg-positive women were more likely to have a high educational level, compared with HBsAg-negative mothers. But there was no significant difference in maternal age, ethnicity, pre-pregnancy BMI, gestational weight gain (GWG), gravidity, parity, history of miscarriage, history of induced abortion, or history of stillbirth between HBsAg-positive group and HBsAg-negativegroup.

To determine the interaction between maternal age, educational level and HBsAg status, stratified analyses by HBsAg status were performed according to maternal age, educational level, i.e. age or <30 years, educational level classified as low educational level, high educational level. As shown in Table 2, positive HBsAg status was associated with the increased risk of preterm labor in women aged <30 years, having low educational level, with an odds ratio of 1.65(95% CI 1.07–2.54) and 2.59(95% CI 1.41–4.76), respectively. Subsequently, Breslow-day test shown that there existed significant differences in the ORs for HBsAg carriage across each stratum of maternal age (P = 0.023), educational level (P = 0.002). In

addition, multiplicative interactions between maternal age (P = 0.039), educational level (P = 0.003) and HBV infection was identified in the logistic regression model after adjusting age, education level, pre-pregnancy BMI, GWG, HBsAg status.

Because the interactions between maternal age, educational level and HBsAg carrier were identified in stratified analyses. We performed multiple regressions between HBsAg status and preterm labor stratified by maternal age and educational level. HBsAg and other risk factors (including maternal age, educational level, pre-pregnancy BMI and GWG) affecting the presence of preterm labor, were included into multivariable logistical regression analyses. Among the pregnancy women with age <30, HBsAg carrier (OR 1.61, 95% CI 1.04–2.51) were associated with the increased incidence of preterm labor, after adjustment for other associated covariates (Table 3). Pregnancy women with high educational level (OR 0.60, 95% CI 0.37–0.97) have a decreased risk of preterm labor. But in other subgroups with age ≥30, the association between HBV carrier and preterm labor did not reach significant difference.

Stratified by maternal educational level, a significant association of maternal HBsAg carriage with the incidence of preterm labor was observed (OR 2.49, 95% CI 1.34–4.63) (Table 4) in the low educational level group. However, the association between HBV carrier and preterm labor vanished in the high educational level group. But in the high educational level group, the results of analyses showed that older pregnancy women with age ≥30 (OR 2.53, 95% CI 1.81–3.53) have an increased risk of preterm labor compared with young women with age <30. Simultaneously, significant association between GWG and increased risk of preterm labor were detected in the high educational level group, with an OR value of 0.96 (95% CI 0.94–0.99).

Discussion

Our study found that there existed interactions between the maternal age, educational level and HBV infection and a differential association between HBV infection and preterm labor across different maternal age and educational level was observed. As a result, the maternal age, educational level can mediate the association between chronic hepatitis B infection and preterm labor.

In present study, we found that maternal age, educational level, GWG were associated with the presence of preterm labor in partial subgroup analyses despite the fact that the associations did not always exist. Our findings further proved that preterm labor is multifactorial diseases influenced by maternal characteristics, resulting in a differential risk of preterm labor in various subgroup.

The association between maternal HBV infection and preterm labor has been extensively studied over the past decades [19, 21–23], and modest positive association has been reported in several large cohort study [20]. Similarly, our study showed that HBV infection was associated with high risk of preterm labor in young or low educated women. Findings from previous studies have suggested that factors related to systemic inflammatory responses, such as liver injury (hepatitis, cirrhosis and hepatocellular carcinoma), that promote release of proinflammatory cytokines, have been considered as possible mechanisms for the observed association [31, 32]. Additionally, the long-term accumulation of HBV DNA in the placenta

and trophoblast cells activated the placental inflammatory response and impaired trophoblasts and placental function [33, 34]. This could play a role in the link between HBV infection and preterm labor.

From the stratified analyses, our data suggest a modifying effect of maternal age and educational level on the association between HBV infection and preterm labor in the present study. We found that among pregnant women with age <30, HBV infection significantly increased risk of preterm labor compared with the health groups. Similar results could be seen in low educational level group. But this positive association between HBV infection and preterm labor disappeared in the groups of older or highly educated pregnancy women. The previous study demonstrated that advanced maternal ages were associated with hepatitis B virus load in pregnancy women [30]. Elderly pregnant women tend to have low viral load [29], resulting in relatively mild inflammatory reaction. Additionally, hepatitis B virus DNA load was positive associated HBV infection rates in the placental cell layers [35]. This explains to a certain extent why the association between HBV infection and preterm labor vanished in the older pregnancy women. Published study showed that educational differences in birth outcomes may reflect differences in the way women utilize health care systems [36]. Generally, the pregnancy women with high educational level was positively associated economic income, which is the most important factors for accessibility of high-quality medical services. Moreover, educationally disadvantaged women could be more marginalised and vulnerable in societies compared with highly educated people. Consequently, pregnancy women with low educational level could suffer from more stress from life and work [36]. This may be alternative explanations for a modifying effect of educational level on the associations between HBV infection and preterm labor.

This study has also multiple strengths. Firstly, the present study included the large number of subjects, which makes it possible to explore modification effects of external variables with confounding variables controlled in prospective cohort study. Secondly, this study comprehensively explored the associations between HBV infection and preterm labor in different level of maternal age and education, which provide more evidence for presentation of the targeted preventive strategies for pregnancy women with different characteristics. Thirdly, to our knowledge, this is the first study that has examined the potential modification effects of maternal variables on the association between HBV infection and preterm labor. However, the limitations of our study are also unavoidable. The first and most obvious limitation is that our study is a retrospective study that proves a positive correlation between HBV infection and preterm labor. But its capability of etiological inferences is limited. Therefore, a large-scale prospective study on this causal relationship is needed. Second, we did not collect the data of liver injury including hepatitis, cirrhosis and hepatocellular carcinoma in this study, which could provide evidence for the positive association between HBV infection and preterm labor.

Conclusion

HBV infection is associated with high risk of preterm labor. Advanced maternal age and high educational level could buffer the adverse association between maternal HBV infection and preterm labor. Unfortunately, the apparent moderation effect of maternal age and educational level disappears at the

young or low educational women. More research is needed to explore this possibility, and to identify other modifiable factors (for example, economic income, physical activity, nutritional status during pregnancy) that may alleviate adverse effects of maternal HBV infection on preterm labor.

Abbreviations

BMI: body mass index; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; GWG: gestational weight gain; OR: odds ratio; PTB: preterm labor; SD: standard deviation; TP: *treponema pallidum.*

Declarations

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology. The written informed consent of all subjects had been obtained before participating the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the research still being carried on but are available from the corresponding author on reasonable request.

Conflicts interest

All authors of this study report no potential conflicts.

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Author contributions

All authors contributed significantly to this work. Songxu Peng collected the data, did the statistical analysis, and drafted the initial manuscript. Hongyan Chen helped collected the data. Xiu Li assisted with data collection, and revised the manuscript. Yukai Du and Yong Gan designed the study, directed the statistical analysis, and reviewed the manuscript.

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Tables

Table 1 Maternal characteristics and clinical features by HBsAg status among the participants

Characteristics	HBsAg + (n=2050)	HBsAg - (n=2050)	*P*-value
Age (years, mean ± SD)	29.0±4.1	29.0±4.1	1.000
Han nationality	2040(99.5)	2038(99.4)	0.669
Education			**<0.001**
Low educational level	344(16.8)	461(22.5)	
High educational level	1706(83.2)	1589(77.5)	
Pre-pregnancy BMI	20.7±2.6	20.9±2.7	0.311
GWG	16.6±6.2	16.8±7.6	0.363
History of pregnancy			
History of stillbirth	6 (0.3)	5 (0.2)	0.763
History of miscarriage	68(3.3)	86(4.2)	0.139
History of induced abortion	324(15.8)	357(17.4)	0.166
First gestation	1010 (49.3)	1046(51.0)	0.261
Nulliparous	1616(78.8)	1616(78.8)	1.000

Abbreviation: SD, standard deviation; GWG, gestational weight gain.

Table 2 Incidence of preterm labor with respect to HBsAg status in pregnant women, stratified by maternal age, education level.

Factors	PT (%)		OR(95% CI)	*P*-values[a]	P_{mul}
	HBsAg +	HBsAg -			
Age					
<30	4.3(55/1271)	2.7(34/1271)	1.65(1.07-2.54)	**0.023**	**0.039**
≥30	6.8(53/779)	8.0(62/779)	0.84(0.58-1.24)		
Education					
Low educational level	9.0(31/344)	3.7(17/461)	2.59(1.41-4.76)	**0.002**	**0.003**
High educational level	4.5(77/1706)	5.0(79/1589)	0.90(0.66-1.24)		

[a] *P*-values for interaction effect between each risk factor and HBsAg status on PT.

P_{mul} for multiplicative interaction between each risk factor and HBsAg status on PT, adjusting age, education level, pre-pregnancy BMI, GWG, HBsAg status.

Abbreviation: PT, preterm labor; OR, odds ratio; CI, confidence interval.

Table 3 Multiple regressions between HBsAg status and preterm labor stratified by maternal age.

Variable	Age <30		Age ≥30	
	OR (95% CI)	*P*-value	*OR (95% CI)*	*P*-value
HBsAg	1.60 (1.03-2.49)	**0.036**	0.83 (0.57-1.22)	0.346
Education level	0.60 (0.37-0.97)	**0.037**	1.08 (0.67-1.76)	0.746
Pre-pregnancy BMI	1.06 (0.97-1.15)	0.200	1.02 (0.96-1.09)	0.486
GWG	0.97 (0.93-1.00)	0.058	0.99 (0.96-1.02)	0.332

Abbreviation: OR, odds ratio; CI, confidence interval, BMI, body mass index; GWG, gestational weight gain.

Table 4 Multiple regressions between HBsAg status and preterm labor stratified by maternal educational level.

Variable	Low educational level		High educational level	
	OR (95% CI)	*P*-value	*OR (95% CI)*	*P*-value
HBsAg	2.49 (1.34-4.63)	**0.004**	0.88 (0.63-1.21)	0.427
Age	1.46 (0.80-2.69)	0.222	2.53 (1.81-3.53)	**<0.001**
Pre-pregnancy BMI	1.11 (0.99-1.25)	0.070	1.01 (0.96-1.07)	0.677
GWG	1.03 (0.98-1.07)	0.223	0.96 (0.94-0.99)	**0.004**

Abbreviation: OR, odds ratio; CI, confidence interval, BMI, body mass index; GWG, gestational weight gain.