Chronic Hepatitis B Infection is Associated with Decreased Risk of Preeclampsia: A Meta-Analysis of Observational Studies

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Abstract

Background/Aims: Preeclampsia is a complex multi-system obstetric syndrome and remains one of the leading causes contributing to maternal and perinatal mortality and morbidity. Previous epidemiological studies regarding the association between chronic hepatitis B virus (CHB) infection and the risk of preeclampsia have reported inconsistent results. Therefore, we conducted a meta-analysis to investigate the association between CHB infection and preeclampsia. Methods: The electronic database was searched until January 1st, 2016. Relevant studies reporting the association between CHB infection and the risk of preeclampsia were included and for further evaluation. Statistical analysis was performed using Stata 10.0 (Stata Corp.). Results: Three observational cohort studies and eight case-control studies, including 11566 preeclampsia patients, were identified. A significant negative association between CHB infection and preeclampsia was observed (odds ratio = 0.77, 95% confidence interval, 0.65–0.90, P=0.002, fixed-effect model). Conclusions: Findings from our meta-analysis indicate that CHB infection may decrease the risk of preeclampsia in Asian population. Future prospective cohorts in different countries with larger sample sizes are warranted to ascertain the causality and pathophysiological studies are required to explore the possible biological mechanisms involved.

Introduction

Hepatitis B viral (HBV) infection is a worldwide public health problem and can be found in around 10% among the Asian populations [1]. Therefore, female HBV infection may be one of the commonest infections during pregnancy.

Preeclampsia is a complex multi-system obstetric syndrome affecting about 5~10% of pregnant women and remains one of the leading causes contributing to maternal and perinatal mortality and morbidity. Several epidemiological studies that investigated the...
incidence of preeclampsia by ethnicity/race observed the prevalence of preeclampsia is approximately 50% lower in the Asian population when compared with Caucasians [2-5]. Although genetic differences might play an important role [6, 7], whether a high rate of chronic hepatitis B virus (CHB) infection in the Asian population may influence the incidence of preeclampsia[8, 9], have not been examined before.

Compared with the generally increased adverse pregnancy outcomes associated with maternal HBV infection, such as gestational diabetes mellitus, preterm birth, and fetal growth restriction [10-13], several studies observed a negative association between CHB infection and preeclampsia [12-14]. However, the limited published studies on this issue have yielded inconclusive and inconsistent results [11, 15-23]. Therefore, whether Chronic HBV infection might be associated with a decreased rate of preeclampsia remains an important but unresolved question.

To answer this question, we conducted a systematic review of the literature and a meta-analysis to explore whether maternal CHB infection was associated with a decreased risk of preeclampsia.

Materials and Methods

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [24].

Data sources and search strategy

Two independent investigators searched PubMed and Embase databases before January 1st, 2016, using the combinations of terms “virus” or “viral” or “hepatitis B” or “hepatitis B surface antigen (HBsAg)” and “pregnancy outcome” or “prenatal outcome” or “perinatal outcome” or “preeclampsia” or “pregnancy hypertension”. We sifted through potentially relevant articles, firstly by titles and abstracts, and then we retrieved the full texts of articles for detailed review. Further, we scanned the reference lists of the articles that met the inclusion criteria in our analysis, and searched for those articles or citations in the Web of Knowledge, Google Scholar and Google to obtain additional studies.

Inclusion and exclusion criteria

Articles were included if they reported a quantitative association between CHB infection during pregnancy and the risk of preeclampsia among pregnant women versus a non-CHB control groups. For studies that enrolled overlapping pregnant women, only more recently published studies and/or those with larger sample sizes were included. Studies included in this analysis defined CHB infection status during pregnancy by the presence or absence of hepatitis B surface antigen (HBsAg) in blood during the first prenatal care visit, on admission to the labour ward, or before delivery. PE diagnosis was performed according to the recommended clinical practice. No language restrictions were used for study inclusion in this meta-analysis.

Data extraction

A form designed a priori was used to extract the information from the included studies. Two independent investigators performed the data extraction. A third investigator examined the results, and a consensus was considered as agreement between at least two out of the three investigators. PE was the primary outcome measure. The following information was recorded: first author’s last name; year of publication; study location; number of CHB participants with or without preeclampsia; scoring of Newcastle-Ottawa Quality Assessment Scale (NOS); covariates adjusted for in the analysis; diagnostic criteria of preeclampsia.

Assessment of methodological quality

Two independent investigators assessed the quality of each study included using the Newcastle-Ottawa Quality Assessment Scale (NOS) [25]. Studies of low, intermediate and high quality were defined with NOS scores of 1–3, 4–6 and 7–9 in the meta-analysis, respectively (Table 1).
**Statistical Analysis**

The pooled odds ratio (OR) with 95% confidence intervals (CIs) between CHB infection and preeclampsia was used to estimate the effect sizes. The ORs were combined in a meta-analysis using a fixed-effects model when heterogeneity observed among studies was absent to moderate. When heterogeneity was high ($I^2 > 50\%$), a random-effects model was used. Heterogeneity among these studies was evaluated by two parameters. $P < 0.10$ for the Cochran’s $Q$ test or $I^2 > 50\%$ for Higgins statistic were regarded statistically significant heterogeneity [26]. The publication bias was investigated by two methods. Visual detection was used to analyze the funnel plots. Quantitative analysis was performed by the Egger’s regression asymmetry test [27]. Subgroup analysis was performed with respect to study type, study location, maternal age, parity, smoking, history of chronic disease and history of adverse pregnancy in order to explore the influence of these factors on the association. Statistical analysis was performed using Stata version 10.0 (Stata Corp).

**Results**

**Selection flow and Study characteristics**

The detailed search procedures are demonstrated in Fig. 1. Full texts of 13 identified articles were retrieved for further assessment. Two of these articles were excluded because they did not meet the inclusion criteria (one study that did not have a control group and one study that investigated hypertension only during pregnancy). Finally, the remaining 11 independent articles were used for this meta-analysis. Of all the including studies, three cohort studies and eight case control studies evaluated the ORs for incidence of preeclampsia (Table 1). Among the studies included, nine was conducted in Asia, one in Europe and one in North America, According to the NOS, all studies were of high quality.
Results of the Meta-analysis

The pooled OR from 3 cohort and 8 case control studies is demonstrated in Fig. 2. Meta-analysis of these 11 studies involving 11566 preeclampsia patients suggested a negative association between CHB infection and preeclampsia (summary OR = 0.77, 95% CI = 0.65 to 0.90) without significant heterogeneity among these studies (Q = 12.63, I² = 20.8%, P = 0.25).
Subgroup Analysis
An analysis of the results according to study type, region, maternal age, parity, smoking, previous history of chronic diseases and adverse pregnancy outcomes is summarized in Table 2. Stratification according to region showed that women with HBV infection in Asian countries have a lower risk for preeclampsia (OR 0.70, 95% CI 0.58-0.84) without significant heterogeneity.

Publication Bias
Funnel plot with respect to the association between CHB infection and preeclampsia did not demonstrate asymmetry which was typically associated with publication bias; Egger’s regression asymmetry test suggested a low probability of publication bias (P = 0.16) (Fig. 3).

| Table 2. Subgroup analysis of the association between chronic hepatitis B infection and preeclampsia. PE: Preeclampsia; CHB: chronic hepatitis B infection |
|----------------------------------|---------------|-----------|------|--------------|-------|
| Study type                       | Studies       | PE/CHB    | PE/control | OR    | 95% (CI)    | I² (%) |
| Cohort study [11,17,19]          | 3             | 16/1611   | 371/23213 | 0.73  | 0.44-1.22   | 0.00   |
| Case-control study [2, 12-16, 18, 20] | 8             | 140/12687 | 11039/400003 | 0.77 | 0.65-0.92 | 42.40 |
| Region                           |               |           |            |       |             |        |
| Asia [11-16, 19-21]              | 9             | 125/13445 | 1535/118844 | 0.70  | 0.58-0.84   | 0.00   |
| Non-Asia [19, 20]                | 2             | 31/853    | 9875/304372 | 1.13  | 0.79-1.62   | 0.00   |
| Maternal age                     |               |           |            |       |             |        |
| Matched [11-16, 19-21]           | 8             | 130/12473 | 11192/407904 | 0.75  | 0.63-0.90   | 32.40 |
| Not matched [11, 17, 18]         | 3             | 26/1825   | 218/15312 | 0.84  | 0.54-1.31   | 7.30   |
| Parity                           |               |           |            |       |             |        |
| Matched [16, 18]                 | 2             | 11/407    | 9/423     | 1.24  | 0.52-2.97   | 34.20 |
| Not matched [11-15, 17, 19-21]   | 9             | 145/13891 | 11401/422793 | 0.75  | 0.64-0.89   | 10.60 |
| Smoking                          |               |           |            |       |             |        |
| Matched [20]                     | 1             | 30/814    | 9715/296218 | 1.13  | 0.78-1.63   | -      |
| Not matched [11-19, 21]          | 10            | 126/13484 | 1695/126998 | 0.70  | 0.58-0.85   | 0.00   |
| History of chronic diseases      |               |           |            |       |             |        |
| Matched [12, 14, 17, 19, 20]     | 5             | 112/11577 | 10973/403538 | 0.78  | 0.64-0.94   | 47.70 |
| Not matched [11, 13, 15, 16, 18, 21] | 6            | 44/2721   | 437/19678 | 0.74  | 0.53-1.03   | 0.00   |
| History of adverse pregnancy outcomes |           |           |            |       |             |        |
| Matched [19]                     | 1             | 1/39      | 160/8154 | 1.31  | 0.18-9.64   | -      |
| Not matched [11-18, 20-21]       | 10            | 155/14259 | 11250/415062 | 0.76  | 0.65-0.90   | 27.20 |

Fig. 3. Funnel plot of the association between chronic hepatitis B infection and preeclampsia.
Discussion

While maternal asymptomatic infection with HBV has been associated with increased antepartum hemorrhage [18-21, 28], gestational diabetes mellitus [10, 13, 18, 28], preterm birth [18-23], and fetal growth restriction [20, 21, 28], one intriguing finding was on the occurrence of preeclampsia. Compared with the generally increasing rates of adverse pregnancy outcomes associated with maternal CHB infection [10-13, 22, 23], several epidemiological studies observed a negative association between CHB infection and preeclampsia [9-11], but the limited published studies regarding this issue showed inconclusive and inconsistent results. Our meta-analysis of 11 studies suggested that maternal CHB infection was associated with 23% decreased risk of preeclampsia.

Mounting evidences found that excessive activations of maternal innate and adaptive immune system played a critical role in the pathogenesis of preeclampsia [29, 30]. Previous researches have demonstrated that HBV replication could induce virus specific T-cell tolerance or even T-cell depletion, thus caused relative impaired adaptive immunity in patients with CHB infection [31-34]. Autoimmune diseases are a broad range of diseases characterized by loss of self-tolerance combined with excessive activation of innate and/or adaptive immunity. A recent publication found that unexpected low percentage of CHB infection in patients with autoimmune disorders including Sjogren's syndrome, type 1 diabetes as well as systemic lupus erythematosus in comparison with their healthy matched controls and suggested a putative protective role of HBV infection by enhancing immune-tolerance from autoimmune disease [35]. Taken together, one possible biological interpretation for the lower incidence of preeclampsia in this specific population is the impaired immune response and/or enhanced immune-tolerance caused by maternal HBV infection.

Migration and invasive capacity of trophoblasts were closely associated with proper placental implantation. Impaired spiral artery remodeling caused by inadequate trophoblasts’ migration and invasion was regarded as another critical factor in the pathogenesis of preeclampsia [36, 37]. Recently, several experimental studies demonstrated that hepatitis B virus X (HBV X) protein could enhance cellular invasion and metastasis in hepatocellular carcinoma through several different mechanisms [38-40]. Furthermore, mounting evidence suggested that inadequate matrix metalloproteinases (MMPs) production in placenta could induce invasive dysfunction of trophoblast cells and incomplete remodeling of spiral arteries [41, 42]. A previous study demonstrated that inhibition of MMPs activity in placental decidual co-culture model resulted in impairment of vascular remodeling [42]. Several studies found that HBV X protein could enhance hepatocarcinoma metastasis by up-regulating of MMPs [37, 43]. However, up till now only few publications investigated the influence of HBV infection on the trophoblasts biological function [44, 45]. Knowledge with respect to this field was largely unexplored. Therefore, another possible biological interpretation for the lower incidence of preeclampsia may be the results of increased migration and invasive capacity of trophoblasts as well as over-production of placental MMPs caused by maternal HBV infection.

Recently, accumulating evidence suggested that maternal age at pregnancy and previous history of chronic diseases might be associated with obstetrical outcomes [46-48]. A recent large cohort study found that adolescent pregnancies (pregnant women < 20 years of age) had a significantly lower risk of gestational hypertension [46], while women with advanced maternal age were at a higher risk for preeclampsia than their younger counterpart [47]. In our meta-analysis, results of stratification according to maternal age and previous history of chronic diseases matched groups also indicated that this specific population had a lower risk of preeclampsia. Furthermore, with respect to region, our meta-analysis data showed that women with HBV infection in Asian countries had a lower risk of preeclampsia, which suggested the high rate of female CHB infection in Asian countries might be a contributory factor to the decreased risk of preeclampsia observed in these populations.

To the best of our knowledge, this is the first meta-analysis to synthesize available observational studies exploring the influence of HBV infection on the preeclampsia. However,
some limitations of our study should be emphasized. First of all, eight of the studies included in the current meta-analysis were case-control studies. Evidence from case-control studies could be probably of less accuracy and more influenced by recall bias compared to that from cohort studies. Second, most of the articles included in the meta-analysis were conducted in Asia, only one in America and one in Europe. In addition, one study performed by Lao TT and his colleague [14] in Asian accounting for a 48% weight was contributing the most to the analysis. Therefore, the results of this analysis should be interpreted with caution. The association between HBV infection and decreased risk of preeclampsia should not be extended to Non-Asian population. Third, although tests in the analysis using the Cochrans Q test and Higgins statistic which showed no significant heterogeneity. This test must be viewed with caution as they are low powered for meta-analysis when studies have small sample size or are few in number.

In conclusion, findings from our meta-analysis indicate that CHB infection may decrease the risk of preeclampsia in Asian population. In the future, prospective cohorts in different countries with larger sample sizes are warranted to ascertain the causality and pathophysiological studies are required to explore the possible biological mechanisms involved.

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Disclosure Statement

The authors have no competing interests to declare.

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