Protocol

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Hepatitis B virus infection during pregnancy and the risk of postpartum hemorrhage: a protocol for systematic review and meta-analysis

Kang Zou, BSc[a,b,c], Jingwen Chen, BSc[a,b,c], Jin Guo, PhD[a,b,c], Wanqiang Wei, MSc[a,b,c], Mingyu Liao[a,b,c], Qixin Cai, BSc[d], Yiquan Xiong, MD[a,b,c,*]

Background: Hepatitis B virus (HBV) infection is a significant public health issue worldwide, with a hepatitis B surface antigen (HBsAg) seroprevalence of 3.5%. Maternal HBV infection during pregnancy, a common comorbidity, is associated with an increase in the risk of adverse obstetric and perinatal outcomes. However, the relationship between maternal HBV infection and postpartum hemorrhage (PPH), a leading contributor to maternal morbidity and mortality, is currently uncertain. The aim of this study is to comprehensively clarify the potential impact of maternal HBV on PPH risk.

Methods and Analysis: The authors initially searched five English databases and three Chinese databases from their inception to 26th June 2023. Two reviewers will independently conduct study selection, data extraction, and quality assessment. Cohort and case–control studies investigating the effect of maternal HBV infection on PPH will be included, with study quality assessed using the Newcastle–Ottawa Scale (NOS). Meta-analyses will be performed using a fixed-effects model for $I^2 \leq 50\%$ or a random-effects model otherwise. Several categories of subgroup analyses (e.g. sample size more than 1000 vs. less than 1000) and sensitivity analyses (e.g. omit NOS scores less than 7) will be conducted, and publication bias will be assessed through funnel plots, Begg's and Egger's tests using STATA 18.0.

Ethics and Dissemination: This systematic review and meta-analysis do not require ethics approval and the results will be published in peer-reviewed journals. The findings of this systematic review will provide evidence on the impact of maternal HBV infection on PPH, which will contribute to better prevention and management of PPH in clinical practice and a better understanding of the disease burden of HBV infection.

PROSPERO registration number: CRD42023442626

Keywords: adverse pregnancy outcome, HBsAg, maternal HBV infection, pregnancy, postpartum hemorrhage

Introduction

Hepatitis B virus (HBV) infection is a major global public health challenge. In 2019, the global seroprevalence of the hepatitis B surface antigen (HBsAg) is estimated to be 3.5%, affecting approximately 296 million people worldwide[1]. Notably, the Pacific and African regions report the highest infection rates, with 116 million and 81 million cases, respectively, contrasting with lower infection rates in the Americas[1,2]. Despite advances in vaccines and antiviral therapies, HBV infection continues to be a significant health concern in recent decades.

Maternal HBV infection, a common comorbidity in pregnancy, is prevalent worldwide[3]. In Africa and China, maternal HBV infection rates are reported at 6.8%[4] and 6.6%[5], respectively. Previous studies have indicated an association between maternal HBV and an increased risk of adverse obstetric and perinatal outcomes, such as preterm birth [adjusted odd ratio (aOR) = 1.21, 95% CI: 1.05–1.39][6] and gestational diabetes mellitus (aOR = 1.47, 95% CI: 1.22–1.76)[7]. Furthermore, HBV infection may impact postpartum hemorrhage (PPH), a major pregnancy complication[8,9].

PPH is defined as more than 500 ml of blood loss after vaginal delivery or more than 1000 ml after cesarean, is a significant

HIGHLIGHTS

- This systematic review and meta-analysis will provide evidence on the impact of maternal hepatitis B virus infection on postpartum hemorrhage.
- The results of this study will contribute to better prevention and management of postpartum hemorrhage in clinical practice.

[a]Institute of Integrated Traditional Chinese and Western Medicine, Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, [b]NMPA Key Laboratory for Real World Data Research and Evaluation in Hainan, [c]Sichuan Center of Technology Innovation for Real World Data, Chengdu and [d]Acupuncture and Tuina, College of Chinese Medicine, Chongqing Medical University, Chongqing, People's Republic of China

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*Corresponding author. Address: Institute of Integrated Traditional Chinese and Western Medicine, Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, People's Republic of China. Tel./fax: +862 885 423 040. E-mail: xiongyq@scu.edu.cn (Y. Xiong).

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cause of maternal morbidity and mortality globally, responsible for a large proportion of pregnancy-related deaths[10,11]. There have been controversial results in studies of the association between maternal HBV infection and PPH. For instance, a multicenter retrospective cohort study involving 22 374 participants found a significant increase in the risk of PPH associated with maternal HBV (aOR = 1.44, 95% CI: 1.13–1.83)[12]. However, other studies did not report a significant association[13,14]. Therefore, to address this clinical question, we will conduct this systematic review and meta-analysis to investigate whether maternal HBV infection is associated with an increased risk of PPH.

Methods

Study protocol and registration

This systematic review protocol was registered on PROSPERO (registration number CRD42023442626) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[15].

Eligibility criteria

Cohort studies and case–control studies that evaluated the association between maternal HBV infection and PPH will be eligible for inclusion. Cohort studies without a comparison group, reviews, comments, case reports, letters, editorials, nonhuman studies, and duplicate publications will be excluded. If data from the same study were reported in multiple reports, we will select the information with the largest sample size.

Exposure and outcome definitions

In this study, maternal HBV infection is considered to be chronic HBV, which is defined as HBsAg seropositivity during pregnancy. The primary definition of PPH is more than 500 ml of blood loss after vaginal delivery or more than 1000 ml after cesarean delivery[10]. At the same time, as the definition of PPH has changed in recent years, those who meet the criteria of the American College of Obstetricians and Gynecologists (ACOG), which defines PPH as a cumulative blood loss of 1000 ml or more or blood loss associated with signs or symptoms of hypovolemia within 24 h of delivery, regardless of mode of delivery, will also be considered as PPH[16].

Search strategy

The following eight databases were initially searched from their inception to 26th June 2023, including five English databases (PubMed, Embase, Scopus, Cochrane Library, and Wed of Science) and three Chinese databases (China National Knowledge Infrastructure, Wanfang Databases, and Weipu Databases). Searches in Chinese databases were limited to those journals included in the Peking University Core Periodical Catalog, which represents excellent Chinese journals. All searches were not restricted by language. In addition, reference lists of included studies and published related reviews will be manually retrieved for additional potentially relevant studies.

Both Medical Subject Headings (MeSH) and free text terms will be combined to identify relevant articles, such as 'Hepatitis B', 'HBV', 'Postpartum Hemorrhage', 'Pregnancy Outcome', 'Cohort Studies', and 'Case-Control Studies'. The specific search strategy for PubMed is shown in (Table 1), which includes all search terms. Similar strategies will be adapted for other electronic databases. The search strategy will be updated in accordance with the reviewers' comments on study protocol and will be up to date.

Search selection

All retrieved studies will be imported into an Endnote library (version X9), and duplicates will be removed. Two researchers (K.Z. and J.G.) will independently screen the titles and abstracts and review the full text according to the predefined criteria to select the final eligible studies. Disagreements between the researchers will be resolved by negotiation through discussion or arbitration by the third party (Y.Q.). The flowchart of the selection process will be presented in the PRISMA flowchart (Fig. 1).

Data extraction and management

Using a standardized and predesigned form, two researchers (K.Z. and W.Q.) will independently perform data extraction from the eligible studies: study characteristics (e.g. first author, publication year, publication language, study location, study design, time of data collection, and sample size); included participant characteristics (e.g. maternal age); HBV infection characteristics (e.g. diagnostic criteria of HBV infection, the prevalence of HBV infection); PPH characteristics (e.g. diagnostic criteria of PPH, the incidence of PPH); exposed and unexposed characteristics (e.g.

Table 1

PubMed search strategy.

No.	Search term
#1	(((((((("Hepatitis B"[Mesh]) OR "Hepatitis B virus"[Mesh]) OR "Hepatitis B Surface Antigens"[Mesh]) OR "Hepatitis B e Antigens"[Mesh]) OR (Hepatitis B Virus Infection[Title/Abstract])) OR (Hepatitis B[Title/Abstract])) OR (HBV[Title/Abstract])) OR (HBsAg[Title/Abstract])) OR (HBeAg[Title/Abstract])
#2	((((((((("Postpartum Hemorrhage"[Mesh]) OR "Pregnancy Outcome"[Mesh]) OR "Pregnancy Complications"[Mesh]) OR (PPH[Title/Abstract])) OR (Pregnancy Outcomes[Title/Abstract])) OR (adverse pregnancy outcomes[Title/Abstract])) OR (Pregnancy Complication[Title/Abstract])) OR (Maternal[Title/Abstract])) OR (Pregnan*[Title/Abstract])) OR (Mother*[Title/Abstract])) OR (Gestation*[Title/Abstract])
#3	((((((((((((((((((((("Cohort Studies"[Mesh]) OR "Case-Control Studies"[Mesh]) OR "Prospective Studies"[Mesh]) OR "Longitudinal Studies"[Mesh]) OR "Retrospective Studies"[Mesh]) OR "Registries"[Mesh]) OR (Cohort[Title/Abstract])) OR (Case control[Title/Abstract])) OR (Prospective study[Title/Abstract])) OR (Longitudinal study[Title/Abstract])) OR (Retrospective study[Title/Abstract])) OR (Population based[Title/Abstract])) OR (Population research[Title/Abstract])) OR (Registr*[Title/Abstract])) OR (Electronic medical record [Title/Abstract])) OR (EMR[Title/Abstract])) OR (EHR[Title/Abstract])) OR (Database[Title/Abstract])) OR (RWS[Title/Abstract])) OR (RWD[Title/Abstract])) OR (Real-world[Title/Abstract])) OR (Real world[Title/Abstract])
#4	#1 AND #2 AND #3

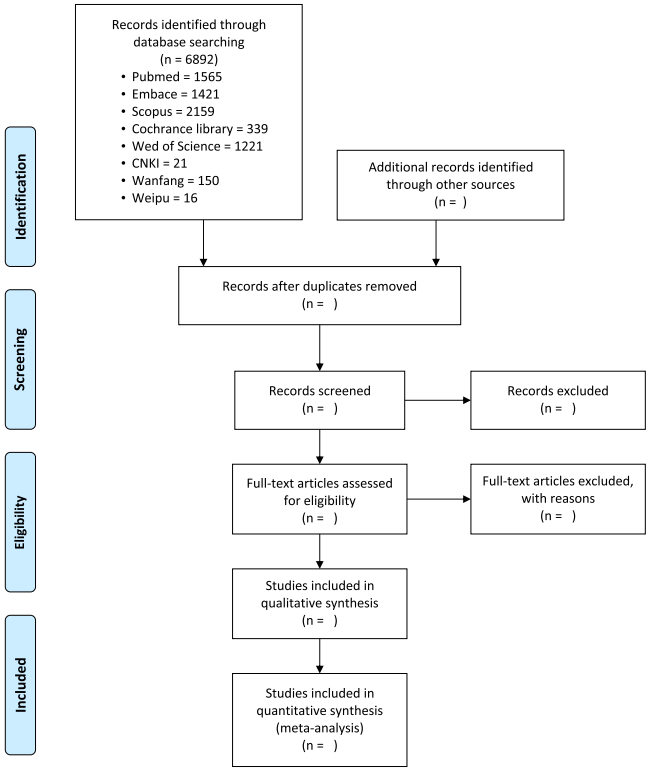

Figure 1. The PRISMA flowchart of the studies selection process.

number of events and pregnancies in each group); and outcome measures and effect estimates (e.g. adjusted OR, adjusted RR, and corresponding 95% CI, and confounders in multivariable analysis, if available). If there is disagreement, it will be resolved by discussion.

Quality evaluation on methodology

A Newcastle–Ottawa Scale (NOS) will be used to assess the quality of cohort or case–control studies[17]. There are three parameters in NOS: (1) selection, (2) comparability, and (3) outcome or exposure (depending on whether the study is cohort or case–control). The NOS assigns a total value of 9 scores to the eight assessment items, with the item comparability of cases and controls receiving a value of 2 scores. Our analysis defines low-quality, medium-quality, and high-quality studies with NOS scores of 1–3, 4–6, and 7–9, respectively.

Statistical analysis

The pooled RR or OR with 95% CI between HBV infection and PPH will be used to estimate the effect size. The I^2 statistic and Cochran's Q test will be used to test heterogeneity between studies[18]. The fixed effect model (Inverse-Variance) will be used if $I^2 \leq 50\%$; otherwise, the random effect model (DerSimonian–Laird) will be used if $I^2 > 50\%$. Given the existing literature suggesting that the adverse effects of HBV infection on pregnant women may vary by sample size, region, and areas with different prevalence of HBV[6,7,19], we will conduct the following three subgroup analyses: (1) sample size (more than 1000 vs. less than 1000), which will assess the robustness and consistency of findings across study populations of different sizes; (2) study region (Asia vs. non-Asia), which will explore the geographical differences between maternal HBV infection and PPH; and (3) prevalence of HBV infection (higher vs. lower), which will examine how varying HBV infection rates affect the risk of PPH. According to a study based on 1800 HBsAg prevalence reports from 161 countries, the high-prevalence of HBV infection was defined as $>3.61\%$[20]. The interaction test will be applied to estimate the difference between the two subgroups[21]. To test the robustness of the results, we will conduct three sensitivity analyses by omitting studies: (1) that with NOS scores less than 7, (2) that were published in non-English language, and (3) that did not report the definition of PPH. Publication bias will be assessed using funnel plots, Begg's, and Egger's tests. $P < 0.05$ will be considered statistically significant when testing for publication bias. If there is a significant publication bias, trim and fill method will be used to analyze the impact of the publication bias on the pooled results[22]. All statistical analyses will be performed with Stata 18.0 (StataCorp LLC, aCollege Station).

Discussion

HBV infection is a significant global health issue, with notable variations in prevalence across different regions, and poses considerable challenges to maternal health. Maternal HBV infection can complicate pregnancy and may increase the risk of several adverse outcomes, such as preterm birth[23,24], gestational diabetes mellitus[12,25], intrahepatic cholestasis of pregnancy[13,14], and probably PPH[12,26]. For PPH, previous studies reported that HBV infection can lead to coagulation dysfunction[27], which could be the potentially underlying mechanism for the increased risk of PPH. Given the extensive adverse effects of maternal HBV infection, effective vaccination and screening are critical in the management of HBV infection during pregnancy. Particularly in high-prevalence regions, there is a need to implement integrated healthcare approaches that combine routine HBV screening with maternal healthcare services[28].

Clarifying the relationship between maternal HBV infection and PPH will have multidisciplinary implications for obstetric care practice and public health. Beyond obstetric practice, our findings will provide the latest evidence to better understand the impact of HBV infection in specific populations, not just the general population. In addition, our findings will encourage public health practitioners to advocate for and implement HBV vaccination and screening programs in women of childbearing age, particularly in regions with high-prevalence of HBV infection. Additionally, multidisciplinary collaboration will be necessary for the effective management of HBV infection in pregnancy and the prevention of PPH.

Our study has several strengths, First, to the best of our knowledge, this study is the first systematic review to comprehensively evaluate the association between maternal HBV infection and PPH. Second, our search system searches both Chinese and English databases. As China has the highest burden of HBV infection in the world, the inclusion of Chinese databases made the literature included in the study more comprehensive. Third, our analysis will use multiple subgroup and sensitivity analyses to validate the results' reliability further. On the other hand, this study may have two limitations. First, this study only searches English and Chinese databases, which may lead to study selection bias. However, we will not restrict the language in the search process, which will reduce the

correlation bias. Second, the inclusion criteria and the representativeness of the participants in the included original studies will also introduce bias to this study. Following this study, prospective, multicenter studies with large sample sizes may be needed to further confirm the association between maternal HBV infection and PPH.

Ethical approval

Ethical approval is not be required as the data in this study will be derived from published research.

Consent

Patients and/or volunteers were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Author contribution

The original idea of this study was conceived by Y.Q.X.; K.Z. and J.W.C.: designed the protocol and drafted the manuscript; J.G., W.Q.W., and M.Y.L.: participated in developing the eligibility criteria, search strategy, and data extraction methods; J.W.C. and Q.X.C.: registered the protocol in the International Prospective Register for Systematic Reviews and Meta-analysis. All authors contributed to the article and approved the submitted version.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

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Guarantor

Yiquan Xiong.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. All data used in the current study are provided in the article.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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