Impact of maternal hepatitis B carrier status on congenital abnormalities: a systematic review and meta-analysis

Shiyao Huang, Jing Wang, Yiquan Xiong, Chunrong Liu, Yana Qi, Kang Zou, Jing Tan, Xin Sun

ABSTRACT

Objectives This study aims to explore whether maternal hepatitis B carrier status is associated with an increased risk of congenital abnormalities.

Design A systematic review and meta-analysis of observational studies.

Data sources PubMed, Embase (Ovid), Scopus, the China National Knowledge Infrastructure (CNKI) and the Wanfang databases.

Study selection Five databases were searched systematically from inception to 7 September 2021. Cohort and case–control studies that investigated the association between maternal hepatitis B virus (HBV) infection and congenital abnormalities were included. This study was conducted according to MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.

Data extraction and synthesis Two reviewers independently collected data, as well as assessed risk of bias using Newcastle–Ottawa Scale. We pooled crude relative risk (cRR) and adjusted OR (aOR) by DerSimonian–Laird random-effects model. Heterogeneity was explored by I² statistics, Cochran’s Q test. Several subgroup analyses and sensitivity analyses were performed.

Results In total, 14 studies involving 16 205 pregnant women exposed to HBV were included. The pooled cRR of 1.15 (95% CI: 0.92 to 1.45; 14 studies included) showed a marginal but not significant association between maternal HBV-carrier status and congenital abnormalities. However, the pooled aOR of 1.40 (95% CI: 1.01 to 1.93; 8 studies included) indicated that pregnant women with HBV infection might be associated with a higher risk of congenital abnormalities. Subgroup analyses of adjusted data showed a higher pooling cRR or aOR on high prevalence HBV infection populations, as well as studies from Asia and Oceania.

Conclusions Maternal hepatitis B carrier status might be at potential risk for congenital abnormalities. The existing evidence was not sufficient to draw a firm conclusion. Additional studies may be warranted to confirm the association.

PROSPERO registration number CRD42020205459.

INTRODUCTION

Hepatitis B virus (HBV) carrier status was defined as the hepatitis B surface antigen (HBsAg) seropositive on serological testing, which is a major public health problem around the world. It has a high risk of death from hepatic diseases, such as cirrhosis and hepatocellular cancer. In 1991, the World Health Assembly proposed integrating hepatitis B vaccination into the national immunisation programme and it became the principal strategy for controlling the spread of the HBV infection. Despite these measures, HBV infection still leads to a huge disease burden. According to a WHO report in 2019, there are 296 million people worldwide suffering from chronic HBV infection, which results in 820 000 deaths.

Maternal carriage of the HBV during pregnancy is deemed to be an important gestational comorbidity. The maternal HBV carrier status prevalence varied from regions. It has been reported that 5.5–15.5% of pregnant women are infected with HBV in Asia and Africa, and 1.6–2.6% in the USA and Europe. Prior evidence demonstrates that HBV infection during pregnancy contributes to an increased risk of adverse obstetrical and neonatal outcomes, including preterm birth (relative risk (RR)=1.24, 95% CI: 1.19 to 1.33), miscarriage (adjusted OR (aOR)=1.71,
95% CI: 1.23 to 2.38),\(^9\) macrosomia (aOR=1.68, 95% CI: 1.19 to 2.37)\(^10\) and low birth weight (RR=1.26, 95% CI: 1.05 to 1.51).\(^11\) Congenital abnormalities, as the critical outcome susceptible to viral infection during pregnancy, are similarly possible to be affected.

Congenital abnormalities are defined as structural or functional anomalies occurring during intrauterine life. Congenital abnormalities are major causes of the global burden of disease.\(^12\) The prevalence of congenital abnormalities has been estimated to be about 6% worldwide.\(^12\) Such disease results in millions of associated deaths and also exerts long-term adverse impacts on disability and health conditions. Several types of viral infections during pregnancy have been clarified to contribute the higher risks of congenital abnormalities, such as zika virus,\(^13\) syphilis\(^14\) and rubella.\(^15\)

HBV has been found to be detectable in placental tissue, which suggests a potential impact on embryonic development.\(^16\) However, the association between maternal HBV infection and congenital abnormalities is controversial. Tan and colleagues\(^17\) conducted a multicentre retrospective cohort study and reported a significant association between maternal HBV infection and congenital abnormalities. Several studies showed a higher frequency of congenital abnormalities among the HBV infection group too, but with no significant differences.\(^18\)\(^19\) Moreover, several other studies observed that the HBV infection in pregnancy had no impact on congenital abnormalities.\(^20\)\(^21\) Therefore, we conducted this systematic review and meta-analysis to explore whether maternal HBV infection was associated with a higher risk of congenital abnormalities.

METHODS
This study was conducted according to Meta-analysis of Observational Studies in Epidemiology (MOOSE),\(^22\) and it was registered at PROSPERO. Since this study is an analysis based on the results from published articles, no ethical approval was required.

Patient and public involvement
None.

Literature search
We searched PubMed, Embase (Ovid), Scopus, the China National Knowledge Infrastructure (CNKI) and the Wanfang databases. No limitation was applied on languages and regions in two English databases. Chinese articles were restricted to being published in the Chinese core journals. The search was conducted on 7 September 2021. Medical Subject Headings terms and free-text were used to generate the search strategy, which comprised the terms ‘hepatitis B’, ‘HBV’, ‘pregnancy’, ‘gestation’, ‘congenital abnormalities’, ‘cohort’ and ‘case–control study’. The details of our search strategy are listed in online supplemental appendix A. Paired reviewers (SH and JW) screened titles and abstracts independently to identify relevant studies. Potentially eligible articles were reviewed and assessed subsequently for full-text. For studies published other than English and Chinese, we extracted information based on the abstract and we would not evaluate the quality of the study. Discrepancies were addressed through discussion or, if necessary, judged by a third reviewer (JT). In addition, we searched the reference lists of included studies manually for additional relevant studies.

Eligibility criteria
We included cohort and case–control studies that investigated association between maternal HBV infection and congenital abnormalities. We excluded pregnant women who were infected with other viruses (eg, syphilis, rubella or zika virus). Reviews, guidelines, comments, case reports, letters, editorials and news were excluded. There was no restriction with respect to sample size or drug usage. If several reports were spawned from the same study, the findings from the study of the largest sample size were used.

Exposure and outcome definitions
HBV carrier status was defined as the HBsAg seropositive on serological testing. The outcome of interest was congenital abnormalities, which were defined as structural or functional anomalies occurring during intrauterine life\(^12\) and diagnosed by clinicians. Congenital abnormalities are usually classified according to the International Classification of Diseases (ICD-10: Q00–Q99), which include cleft lip and cleft palate, microcephalus, congenital heart disease and so on.

Data extraction
According to a standardised and pilot-tested form, two reviewers (SH and JW) extracted specific information independently from each eligible study: study characteristics (eg, first author name, publication year, study conducted area, study design and sample size); HBV infection characteristics (eg, diagnostic criteria of HBV infection, prevalence of HBV infection); criteria of outcome (eg, definition of congenital abnormalities, category of congenital abnormalities, such as overall congenital abnormalities, cleft lip and cleft palate, microcephalus, congenital heart disease and so on); specific characteristics of the exposed and non-exposed groups (eg, the number of events and pregnancies in each group, as well as the adjusted data and confounders for adjusting, if available). The criteria of outcome were identified as overall congenital abnormalities if authors did not point out the specific categories of congenital abnormality in their study. Discussions were carried out with a third reviewer (JT) if consensus could not be reached.

Quality assessment
We used the Newcastle–Ottawa Scale (NOS) for the risk assessment of cohort or case–control studies.\(^23\) The NOS involves three perspectives and eight items. Each item was awarded one star if it was of high quality (except for the
item ‘comparability’ that could receive a maximum of two stars) and there were nine stars in total. The risk of bias was assessed independently by SH and JW. A discrepancy of the risk assessment was discussed or adjudicated by a third reviewer (JT). More stars indicated that the given study was of low risk of bias.

**Statistical analyses**

We pooled the crude RR (cRR) and adjusted OR with the corresponding 95% CI, respectively, by DerSimonian-Laird random-effects models. Given the low incidence of congenital abnormalities, aOR has a good approximation to adjusted RR, and therefore we combined them together noting as aOR. We evaluated heterogeneity among studies by their clinical characteristics, as well as I² and Cochran’s Q test. Subgroup analyses and sensitivity analyses were conducted based on adjusted data. Subgroup analyses were as follows: (1) sample size (>1000 vs. ≤1000), (2) study conducted area (Asia and Oceania vs. the USA and Europe) and (3) the prevalence of HBV infection (high vs. low). The high prevalence of HBV infection was defined as >3.61% according to a report by Schweitzer and colleagues. We applied an interaction test to estimate the difference between subgroups. Sensitivity analyses were carried out by omitting studies: (1) that with NOS<7 stars; (2) that published in non-English language; (3) that did not report the definition of outcome. Moreover, we used funnel-plot analysis, Begg’s test and Egger’s test to measure the publication bias. The interaction test for subgroups were undertaken by Review Manager V.5.3, while the other data analyses were undertaken by Stata V.12.0.

**RESULTS**

A total of 16358 articles were retrieved in the initial search, of which 10618 remained after deduplication. We excluded 9768 publications by screening the title and abstract, and 850 full-text articles were assessed for eligibility. No additional articles were identified by manual searching. Ultimately, 14 studies were included. The flow chart of literature was described in figure 1.

**Characteristics of studies and pregnant women**

The characteristics of included studies are shown in table 1. Fourteen studies involving 16205 participants exposed to the HBV infection were included. The sample size ranged from 100 to 1 670 133, of which nine studies enrolled >1000 pregnant women. All studies were cohort studies (eight retrospective...
### Table 1  Characteristics of included studies and baseline characteristics of included pregnant women

<table>
<thead>
<tr>
<th>Study</th>
<th>Study location</th>
<th>Publication language</th>
<th>Study design</th>
<th>No. of participants</th>
<th>Period of data collection</th>
<th>Exposure group</th>
<th>No. in exposure group</th>
<th>Control group</th>
<th>No. in control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bierhoff et al</td>
<td>Myanmar–Thailand border</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>9928</td>
<td>16 Aug 2012 to 31 Dec 2016</td>
<td>HBsAg (+) or HBeAg (+)</td>
<td>606</td>
<td>HBsAg (−) and HBeAg (−)</td>
<td>9322</td>
</tr>
<tr>
<td>Li et al</td>
<td>China</td>
<td>Chinese</td>
<td>Prospective cohort</td>
<td>6347</td>
<td>Feb 2010 to Dec 2011</td>
<td>HBsAg (+)</td>
<td>277</td>
<td>HBsAg (−)</td>
<td>6070</td>
</tr>
<tr>
<td>Stokkeland et al</td>
<td>Sweden</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>1090349</td>
<td>2001 to 2011</td>
<td>HBV</td>
<td>2967</td>
<td>non-HBV</td>
<td>1087382</td>
</tr>
<tr>
<td>Tan et al</td>
<td>China</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>21947</td>
<td>1 Jan 2009 to 31 Dec 2010</td>
<td>HBsAg (+)</td>
<td>923</td>
<td>HBsAg (−)</td>
<td>21024</td>
</tr>
<tr>
<td>Chen et al</td>
<td>China</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>808</td>
<td>2002 to 2004</td>
<td>HBsAg (+)</td>
<td>380</td>
<td>HBsAg (−)</td>
<td>428</td>
</tr>
<tr>
<td>Hu et al</td>
<td>China</td>
<td>English</td>
<td>Prospective cohort</td>
<td>100</td>
<td>Jan 2011 to Feb 2013</td>
<td>HBsAg (+)</td>
<td>50</td>
<td>HBsAg (−)</td>
<td>50</td>
</tr>
<tr>
<td>Lao et al</td>
<td>China</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>86572</td>
<td>Jan 1995 to Dec 2009</td>
<td>HBsAg (+)</td>
<td>8636</td>
<td>HBsAg (−)</td>
<td>77936</td>
</tr>
<tr>
<td>Connell et al</td>
<td>USA</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>1670133</td>
<td>1998 to 2007</td>
<td>HBV</td>
<td>1222</td>
<td>non-HBV</td>
<td>1668911</td>
</tr>
<tr>
<td>Lobstein et al</td>
<td>Germany</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>8193</td>
<td>Jan 1 2001 to 31 Dec 2006</td>
<td>HBsAg (+)</td>
<td>39</td>
<td>HBsAg (−)</td>
<td>8154</td>
</tr>
<tr>
<td>Tse et al</td>
<td>China</td>
<td>English</td>
<td>Retrospective cohort</td>
<td>506</td>
<td>Jan 2000 to 2002</td>
<td>HBsAg (+)</td>
<td>253</td>
<td>HBsAg (−)</td>
<td>253</td>
</tr>
<tr>
<td>Xue et al</td>
<td>China</td>
<td>Chinese</td>
<td>Prospective cohort</td>
<td>520</td>
<td>Jan 1999 to Dec 2002</td>
<td>HBsAg (+) or HBeAg (+)</td>
<td>260</td>
<td>HBsAg (−) and HBeAg (−)</td>
<td>260</td>
</tr>
<tr>
<td>Yue et al</td>
<td>China</td>
<td>Chinese</td>
<td>Prospective cohort</td>
<td>1576</td>
<td>Jan 1990 to Oct 1992</td>
<td>HBsAg (+)</td>
<td>94</td>
<td>HBsAg (−)</td>
<td>1482</td>
</tr>
<tr>
<td>Hak et al</td>
<td>Korea</td>
<td>English</td>
<td>Prospective cohort</td>
<td>117</td>
<td>1982 to 1984</td>
<td>HBsAg (+)</td>
<td>50</td>
<td>HBsAg (−)</td>
<td>67</td>
</tr>
<tr>
<td>Ryoo et al</td>
<td>Korea</td>
<td>English</td>
<td>Prospective cohort</td>
<td>5284</td>
<td>1 Apr 1985 to 30 June 1987</td>
<td>HBsAg (+)</td>
<td>448</td>
<td>HBsAg (−)</td>
<td>4836</td>
</tr>
</tbody>
</table>

HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
cohort studies\textsuperscript{17–18, 20–21, 29–32} and six prospective cohort studies\textsuperscript{18, 28, 33–36} even though the authors of one study proclaimed it to be a case–control study.\textsuperscript{18} These studies were conducted in China (n=8),\textsuperscript{17–19, 21, 28, 30, 33–34} Korea (n=2),\textsuperscript{35, 36} Sweden (n=1),\textsuperscript{29} the USA (n=1),\textsuperscript{31} Germany (n=1)\textsuperscript{32} and Myanmar–Thailand border (n=1).\textsuperscript{20} Eleven

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic criteria of HBV infection</th>
<th>Diagnostic criteria of congenital abnormalities</th>
<th>Prevalence of HBV positivity</th>
<th>Incidence of congenital abnormalities</th>
<th>Multivariable analysis of congenital abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bierhoff et al\textsuperscript{20}</td>
<td>HBsAg (+) or HBeAg (+)</td>
<td>Not reported</td>
<td>6.23%</td>
<td>2.03%</td>
<td>No</td>
</tr>
<tr>
<td>Li et al\textsuperscript{28}</td>
<td>HBsAg (+)</td>
<td>Not reported</td>
<td>4.36%</td>
<td>2.87%</td>
<td>Yes*</td>
</tr>
<tr>
<td>Stokkeland et al\textsuperscript{29}</td>
<td>ICD-10 (B18.0; B18.1)</td>
<td>ICD-10 (Q00–Q99)</td>
<td>0.27%</td>
<td>3.53%</td>
<td>Yes†</td>
</tr>
<tr>
<td>Tan et al\textsuperscript{17}</td>
<td>HBsAg (+)</td>
<td>Prenatal malformation diagnosed by systematic ultrasound examination during pregnancy. Neonatal malformation was defined as any visible malformation diagnosed by clinicians after birth</td>
<td>4.21%</td>
<td>0.95%</td>
<td>Yes‡</td>
</tr>
<tr>
<td>Chen et al\textsuperscript{21}</td>
<td>HBsAg (+)</td>
<td>Not reported</td>
<td>6.55%</td>
<td>1.11%</td>
<td>Yes§</td>
</tr>
<tr>
<td>Hu et al\textsuperscript{19}</td>
<td>HBsAg (+)</td>
<td>Birth defects were defined as dysplasia and physical abnormalities of the fetuses that already existed in the womb before birth; these include two types: deformity and dysfunction</td>
<td>— —</td>
<td>1.00%</td>
<td>No</td>
</tr>
<tr>
<td>Lao et al\textsuperscript{30}</td>
<td>HBsAg (+)</td>
<td>According to the ICD coding.</td>
<td>9.98%</td>
<td>0.39%</td>
<td>No</td>
</tr>
<tr>
<td>Connell et al\textsuperscript{31}</td>
<td>ICD-9-CM (070.20–23; 070.30–33)</td>
<td>The congenital anomaly variable is a composite of all congenital anomalies identified in the database.</td>
<td>0.09%</td>
<td>3.37%</td>
<td>Yes¶</td>
</tr>
<tr>
<td>Lobstein et al\textsuperscript{32}</td>
<td>HBsAg (+)</td>
<td>Not reported</td>
<td>0.48%</td>
<td>3.89%</td>
<td>No</td>
</tr>
<tr>
<td>Tse et al\textsuperscript{18}</td>
<td>HBsAg (+)</td>
<td>Not reported</td>
<td>7.56%</td>
<td>7.11%</td>
<td>Matching**</td>
</tr>
<tr>
<td>Xue et al\textsuperscript{33}</td>
<td>HBsAg (+) or HBeAg (+)</td>
<td>Not reported</td>
<td>— —</td>
<td>2.69%</td>
<td>Matching††</td>
</tr>
<tr>
<td>Yue et al\textsuperscript{34}</td>
<td>HBsAg (+)</td>
<td>WHO (1964) criteria</td>
<td>5.96%</td>
<td>1.97%</td>
<td>Yes‡‡</td>
</tr>
<tr>
<td>Hak et al\textsuperscript{35}</td>
<td>HBsAg (+)</td>
<td>Not reported</td>
<td>6.12%</td>
<td>0.49%</td>
<td>No</td>
</tr>
<tr>
<td>Ryoo et al\textsuperscript{36}</td>
<td>HBsAg (+)</td>
<td>Not reported</td>
<td>8.48%</td>
<td>1.05%</td>
<td>No</td>
</tr>
</tbody>
</table>

*Maternal age, educational level, job status and parity.
†Maternal age, year of birth, smoking, lives with the father of the child, body mass index, parity, diabetes mellitus, alcohol or are diagnosed with other dependencies.
‡Sociodemographic variables, gestational characteristics, medical interventions and significant medical conditions.
§Maternal age, parity, educational level and history of abnormal pregnancies.
¶Sociodemographic variables, parity, obstetrical complications and risk factors.
**Matching for maternal age and parity.
††Matching for birth period, maternal age, parity and number of birth.
‡‡History of toxic exposures, anti-HBs, anti-HBc, drug use during pregnancy, medical history and radiation exposure.
CM, Clinical Modification; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICD, International Classification of Diseases.
of these studies were published in English17–21 29–32 35 36 and the others were in Chinese.28 33 34

Most studies (n=10) defined HBV infection as involving positivity to the HBsAg only.17–19 21 28 30 32 34–36 Two studies defined HBV infection as involving positivity to HBsAg or hepatitis B e antigen (HBeAg).20 33 Additional two studies identified HBV infection according to ICD coding.29 31

Nine studies reported that the prevalence of HBV infection was higher than 3.61%,17 18 20 21 28 30 34–36 Three studies reported that it was lower,29 31 32  and the remainders did not report the rate explicitly.19 33

Among 14 studies, all articles provided the information on overall congenital abnormalities. Eight of them did not report the specific diagnostic criteria for congenital abnormalities.18 20 21 28 30 32 35 36 In the remaining six studies, two provided detailed definition,17 19 three defined the outcomes according to ICD,29–31 and one adopted a description from the WHO34 (tables 1 and 2).

Eight studies examined the impact of potential confounders, of which six evaluated it by multivariable analyses17 21 28 30 31 34 and two by matching.18 33 Nearly all of these studies adjusted for maternal age and parity. Other confounders, such as sociodemographic variables (eg, educational level, job status, body mass index), gestational or obstetrical variables (eg, gestational diabetes mellitus, number of fetuses, history of abnormal pregnancies) and variables of health behaviours (eg, smoking, alcohol consumption, medical history and radiation exposure) were considered by dissimilar studies.

### Risk of bias in cohort studies

We used the NOS to assess risk of bias in observational studies, of which the results are shown in table 3. Overall, the median NOS was 7 stars and ranged from 5 to 8 stars. Among them, there were eight (57.14%) studies being awarded with 7 stars and over, indicating a relatively low risk of bias. We also showed the information of each NOS item. Ten studies that were not awarded with stars on representativeness for their data was from a single hospital.18–21 28 30 35–36 The comparability between the exposure group and control group in 10 studies was limited (three studies showed significant differences in confounding factors other than age between the two groups,17 28 31 whereas seven differed significantly in all confounding factors between the two groups19 20 29 34–36). Six studies clarified the specific definition of the outcome.17 19 29–31 34 With respect to the remaining items, all studies were identified as being of high quality.

### Association between maternal HBV infection and congenital abnormalities

Among 14 studies evaluating the relationship between maternal HBV infection and congenital abnormalities, 8 studies reported adjusted results.17 18 21 28 30 31 33 34 The pooled results of unadjusted data showed a marginal but not significant association between maternal HBV infection and overall congenital abnormalities with cRR of 1.15 (95% CI: 0.92 to 1.45, I² =48.5%; 14 studies included) (figure 2). However, pooled results of adjusted data...
suggested that maternal HBV infection was associated with a higher risk of overall congenital abnormalities with aOR of 1.40 (95% CI: 1.01 to 1.93, $I^2=62.7\%$; 8 studies included) (figure 3).

**Subgroup analyses**

Among the 14 studies that reported cRR, our prespecified subgroup analyses revealed no differential effects between studies by sample size (test for interaction: $p=0.97$; sample size $>1000$ vs sample size $\leq 1000$: cRR=1.16, 95% CI 0.89 to 1.52, $I^2=61.6\%$ vs cRR=1.00, 95% CI 0.68 to 2.01, $I^2=3.5\%$), study conducted area (test for interaction: $p=0.60$; Asia and Oceania vs the USA and Europe: cRR=1.16, 95% CI 0.80 to 1.69, $I^2=54.7\%$ vs cRR=1.04, 95% CI 0.86 to 1.26, $I^2=14.1\%$) and prevalence of HBV infection (test for interaction: $p=0.83$; high vs low: cRR=1.10, 95% CI: 0.73 to 1.66, $I^2=62.2\%$ vs cRR=1.04, 95% CI: 0.86 to 1.26, $I^2=14.1\%$). Among the eight studies that reported aOR, we did not find difference between studies by sample size (test for interaction: $p=0.89$; sample size $>1000$ vs sample size $\leq 1000$: aOR=1.43, 95% CI: 0.95 to 2.17, $I^2=77.8\%$ vs aOR=1.37, 95% CI: 0.79 to 2.36, $I^2=0.0\%$). However, we found a difference of effect estimates in study conducted area (test for interaction: $p<0.001$; Asia and Oceania vs the USA and Europe: aOR=1.89, 95% CI 1.35 to 2.64, $I^2=9.0\%$ vs aOR=0.99, 95% CI 0.83 to 1.18, $I^2=0.0\%$), and prevalence of HBV infection (test for interaction: $p=0.006$; $I^2=62.7\%$).

![Figure 2](http://bmjopen.bmj.com/)

**Figure 2** Meta-analysis by pooling unadjusted ORs for risk of congenital abnormalities in pregnant women with hepatitis B virus infection. cRR, crude relative risk.

![Figure 3](http://bmjopen.bmj.com/)

**Figure 3** Meta-analysis by pooling adjusted ORs (aORs) for risk of congenital abnormalities in pregnant women with hepatitis B virus infection.
high vs low: aOR=1.86, 95% CI 1.24 to 2.81, I²=27.1% vs aOR=0.99, 95% CI 0.83 to 1.18, I²=0.0%) (table 4).

Sensitivity analyses
In the sensitivity analyses, the results were consistent with the pooled unadjusted effect values. Among studies excluding articles with NOS <7 stars, the pooled cRR was 1.20 (95% CI: 0.89 to 1.61; I²=64.5%) while the pooled aOR was 1.32 (95% CI: 0.92 to 1.88; I²=67.5%). Among the studies excluding articles published in non-English language, the pooled cRR was 1.02 (95% CI: 0.89 to 1.16; I²=55.6%) while the pooled aOR was 1.29 (95% CI: 0.88 to 1.88; I²=72.7%). Among the studies excluding articles that did not report the definition of outcome, the pooled cRR was 1.03 (95% CI: 0.89 to 1.19; I²=70.6%) while the pooled aOR was 1.44 (95% CI: 0.88 to 2.35; I²=82.5%) (online supplemental appendix B).

Publication bias
Publication bias was not observed across any measure both in unadjusted and adjusted data pooled analyses. The funnel-plot analysis appeared as a symmetric funnel plot. Begg’s test and Egger’s test did not yield significant results (cRR: P for Begg’s test=0.827, P for Egger’s test=0.620; aOR: Begg’s test, p=0.386, Egger’s test, p=0.104) (online supplemental appendix C).

DISCUSSION
Based on the most comprehensive evidence, the pooling of unadjusted data in this study did not show significant association between maternal HBV infection and overall congenital abnormalities (cRR=1.15). However, the pooling of adjusted data suggested that pregnant women with HBV infection might be associated with a higher risk of overall congenital abnormalities (aOR=1.40). There were nearly half of the studies that did not adjust for confounders, which may be related to the low incidence of congenital abnormalities.

A previous meta-analysis that was published in 2015 reported no significant association between maternal HBV infection and overall congenital abnormalities (cOR=1.10, 95% CI: 0.85 to 1.43; three studies included). The result in the prior study should be interpreted with caution. First, the sample size was so small that only three studies involving 1514 cases were included. The statistical power may be insufficient to detect the potential association, particularly with respect to rare events. On the other hand, the study only provided the pooled result of unadjusted data. As for an observational study, the risk of bias is always present because the allocation is non-randomised, and estimates from unadjusted data were likely to deviate from the underlying true effect. We suggest providing the pooled result of both unadjusted and adjusted data for an observational study.

Our subgroup analyses yielded a higher pooling cRR or aOR on high prevalence HBV infection populations, as well as studies from Asia and Oceania (table 4). The difference was significant among subgroups of adjusted data. These variabilities may be due to, at least in part, the differences in the degree of active viral replication across populations. For example, HBeAg-positivity (as a marker of active replication of HBV) has been reported to prevail among Asian women. HBeAg has been shown in studies to cause more severe neonatal outcomes by causing more damage to organ function than inactive HBV (ie, only HBsAg-seropositivity). We did not examine the association between HBeAg-positivity and congenital abnormalities because only two studies reported the HBeAg-positivity information, and both did not report adjusted results. Further studies are warranted to assess comprehensively the influence of HBeAg serostatus (or more precisely, the HBV DNA load) on congenital malformations.

The pathogenesis and aetiology of congenital abnormalities induced by maternal HBV infection is poorly understood. A growing body of evidence suggests that...
HBV infection could increase tumour necrosis factor (TNF-α) production, which is similar to zika virus and syphilis. Pan and colleagues recently pointed out that a higher serum level TNF-α would increase the risk of congenital heart disease. Furthermore, McDougall and colleagues recently observed that HBV infection caused mitotic spindle misorientation. This anomaly may contribute, ultimately, to microcephaly. In addition, HBV can be detected in non-liver tissues (eg, lymph nodes, spleen, ovaries, placenta) and, notably, the HBV can be transferred through the placental barrier, which may intensify subtle disorders on the fetus. Thus, more studies are encouraged to the casual effect of HBV infection on congenital abnormalities. Specifically, the type of congenital abnormalities susceptible to HBV infection deserve increased attention.

Our study has several strengths. First, this meta-analysis investigates the association between maternal HBV infection and congenital abnormalities based on a comprehensive literature search and rigorous methodological processes. Second, our findings have implications for clinical work. It may emphasise the importance of screening for congenital abnormalities among mothers with HBV infection. Moreover, hepatitis B immunisation programme should be enhanced to reduce the probability of pregnant women being infected. Third, we propose some directions for future research. We call for more high-quality large-sample original studies, especially those from the maternal HBV infection epidemic region. We also encourage researchers to adopt more detailed information about exposure and outcome, such as HBeAg-positivity, viral load and specific categories of congenital abnormalities, to clarify the effect of maternal HBV infection on congenital abnormalities further.

This paper has the following shortcomings. First, most studies did not record the diagnostic criteria of congenital abnormalities, which would weaken the precision of our results. Second, there was significant heterogeneity among the included studies in several pooling analyses. Although we performed subgroup analyses, the results did not identify the precise reason for heterogeneity. Third, all the articles included in our study only provide the information on overall congenital abnormalities, thus we were unable to conduct a deeper exploration for specific anomalies.

CONCLUSIONS
Maternal hepatitis B carrier status might be at a potential risk for congenital abnormalities. However, the existing evidence was not sufficient to draw a firm conclusion. We call for more high-quality large-sample original studies to confirm the association. We also encourage researchers to adopt more detailed information of exposure and outcome, such as HBeAg-positivity, viral load and specific categories of congenital abnormalities, to clarify the effect of maternal HBV infection on congenital abnormalities further.
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