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Meta Analysis
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Meta-Analysis the Effect of Pregnancy with Hepatitis B on Preterm Birth and Gestational Diabetes Mellitus

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ABSTRACT

Background: HBsAg positive pregnant women are responsible for around 50% of the global disease burden. Hepatitis B is caused by inflammation or infection of liver cells caused by the HBV virus. Pregnant women with hepatitis B can experience increased levels of cytokines which then cause pregnancy disorders. This study aims to examine the effect of pregnancy with hepatitis B on the incidence of preterm birth and Gestational Diabetes Mellitus (GDM).
Subjects and Method: This study is a meta-analysis study and a systematic review. The articles used were obtained from several electronic databases including PubMed, Science Direct, Research Gate, and Google Scholar. The articles used in this study were articles that have been published from 2012-2022. The keywords to search for articles are as follows Pregnancy AND ("Hepatitis B" OR HBV OR HBsAg) AND ("pregnancy outcome" OR "fetal outcome") AND ("preterm birth" OR "preterm delivery" OR premature) AND ("gestational diabetes mellitus" OR GDM). The researched article is a complete text with an observational study design. Articles were collected using the PRISMA diagram, and analyzed using the Review Manager 5.4 application.
Results: A total of 14 prospective and retrospective cohort studies were analyzed. Articles were originated from China, Hong Kong, France and Botswana. Hepatitis B in pregnancy increased the risk of preterm birth (aOR=1.20; CI 95%=1.09 to 1.33; p<0.001) and gestational diabetes mellitus (aOR= 1.20; CI 95%= 1.12 to 1.28; p<0.001).
Conclusion: Hepatitis B in pregnancy increases the risk of preterm birth and GDM significantly.

Keywords: Hepatitis B, pregnancy;, preterm birth, gestational diabetes mellitus

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BACKGROUND

Hepatitis B virus (HBV) infection has become a global public health problem. Hepatitis B is caused by inflammation or infection of liver cells caused by the HBV virus (World Health Organization, 2021). Hepatitis B attacks all ages, gender and races worldwide and can cause acute or chronic inflammation of the liver which can develop into cirrhosis and liver cancer.

The prevalence of hepatitis B in pregnant women worldwide is 1.5-2.5% (Mishra, 2017). According to data from the Hepatitis and Gastrointestinal Infection Information System (SIHEPI) 2018-2019, Indonesia is one of the countries with a large number of pregnant women infected with HBV, namely 30,965 people. Pregnant women with hepatitis B can experience increased levels of cytokines which are the main mediators of the body's response to inflammation and infection. Cytokines that increased included interleukin-6 (IL-6) and Tumor Necrotic Factor (TNF-α).

Increased levels of IL-6 are closely related to increased matrix-metalloproteinase (MMP-9) which is the main enzyme in preterm labor (has the ability to reconstruct and lyse collagen tissue, especially in the amnion membrane) secreted by most of the cytokines produced which increase due to the absence of good micronutrient regulation. Interleukin-6 increases most of the secretion of matrix metalloproteinases and is associated with the formation of prostaglandins induced by the cyclooxygenase enzyme. IL-6 induces the production of prostaglandins from the placental tissue which results in contractions. Increased TNF-α in serum also activates its release in the amniotic membranes. Increased levels of MMP-9 lead to degradation of type IV collagen which is the main strength of the amnion and chorion. The process of collagen degradation is followed by apoptosis (programmed cell death during the process of tissue development) of amniotic epithelial cells which then causes membrane stretching and rupture.

Pregnant women who suffer from hepatitis B can be at risk of experiencing cell damage to cirrhosis of the liver. The condition of the liver that has cirrhosis also increases the production of TNF-α thereby interfering with the performance of insulin in glucose absorption which ultimately causes insulin resistance. Increased levels of TNF-α which is a pro-inflammatory cytokine and the occurrence of cirrhosis of the liver simultaneously makes insulin unable to work properly and disrupts the absorption of glucose into cells, so that glucose levels in the blood increase and cause GDM.

Previous studies have shown that the hepatitis B virus during pregnancy can increase the incidence of preterm birth and the risk of GDM (Lao, 2020). The risk of preterm birth increases significantly by 21% in HBsAg positive or HBeAg positive pregnant women compared to uninfected pregnant women (Ma, 2018).

Based on the high incidence of hepatitis B in pregnancy and because of the inconsistent results of previous studies, pregnancy with hepatitis B which is responsible for 50% of global health becomes very important to study by knowing how pregnancy accompanied by hepatitis B affects the incidence of preterm birth and GDM. The author is interested in studying the effect of pregnancy with hepatitis B on preterm birth and GDM. The data obtained were analyzed using a systematic review and meta-analysis. Systematic review is a review that is carried out systematically to synthesize findings from previous primary studies. Meanwhile, meta-analysis is an epidemiological research design that is carried out to systematically assess previous studies and integrate the findings to obtain quantitative conclusions. Systematic review and meta-analysis were carried out as an effort to obtain comprehensive results by synthesizing the results of primary studies involving preterm birth and GDM with hepatitis B pregnancies.

SUBJECTS AND METHOD

1. Study Design

This study is a systematic review and meta-analysis involving several primary articles using a cohort study design. Primary studies

come from databases of e-journals: PubMed, Science Direct, Research Gate, and Google Scholar. The keywords used in the article search process are: The keywords used in the database search are: Pregnancy AND ("Hepatitis B" OR HBV OR HBsAg) AND ("pregnancy outcome" OR "fetal outcome") AND ("preterm birth" OR "preterm delivery" OR premature) AND ("gestational diabetes mellitus" OR GDM).

2. Steps of Meta-Analysis

1) Formulate research questions in the PICO format (Population, Intervention, Comparison, Outcome).
2) Search primary study articles from databases such as PubMed, Science Direct, Research Gate, and Google Scholar.
3) Perform screening by determining inclusion and exclusion criteria and conducting critical assessments.
4) Perform data extraction and analysis using RevMan 5.3 Software
5) Interpret the results and draw conclusions.

3. Inclusion Criteria

The primary articles involved in the analysis were primary studies with a cohort study design, full English text available, published between 2012-2022, reporting the results of adjusted odds ratio (aOR) calculations, research subjects were pregnant women, exposure in the form of hepatitis B, including Preterm Birth and GDM outcomes.

4. Exclusion Criteria

Articles published before 2012. The study was conducted using RCT, case control, quasi experiment, protocol study and pilot study. Articles published in languages other than English.

5. Operational Definition of Variable

The subjects of the study were pregnant women suffering from hepatitis B both carriers, acute and chronic, the categorization of babies born before reaching 37 weeks of gestation is called premature birth and symptoms of diabetes mellitus that occur in pregnant women who experience impaired glucose tolerance and are only found during pregnancy.

6. Instrument

Primary studies that have been screened are subject to critical appraisal or study reviews to determine eligibility. The assessment instrument uses the Critical Appraisal from Master's Program of Public Health Universitas Sebelas Maret, Surakarta (Murti, 2023),

7. Data Analysis

Article search results are collected with the help of the PRISMA diagram. Primary articles that match the determination of inclusion criteria and CASP assessment were analyzed using the Review Manager (RevMan) 5.4 application. The magnitude of the effect size and confidence interval (CI 95%) is obtained from calculating the aggregate aOR value. The calculation of the estimated amount of heterogeneity (I^2) was carried out by choosing a random effect model approach because the estimated amount of heterogeneity was > 50%.

RESULTS

1. Characteristic of the study

Search results on the electronic database obtained 2,632 articles. Duplication removal was performed on 670 articles. After the initial screening, 1,678 articles were issued. Full text article reviews were conducted on 284 primary articles. A total of 270 articles were re-issued for certain reasons. The final results obtained were 14 cohort articles that were synthesized by meta-analysis (Figure 1). The search review process can be seen in the PRISMA Flowchart in Figure 1 while the distribution of the research areas (Figure 2).

2. The Effect of Hepatitis B in pregnancy on Preterm Birth

There were nine cohort study articles included in the meta-analysis of the effect of Hepatitis B in pregnancy on Preterm Birth.

Figure 2 summarizes the distribution of the cohort primary articles included in the meta-analysis. Table 1 and Table 2 show that the results of critical appraisal for the cohort study. Table 3 and Table 5 show that the Summary of PICO cohort articles on the effect of hepatitis B in pregnancy on the incidence of Preterm Birth and GDM from primary study sources. Table 4 and Table 6 show that the data of aOR from the primary study.

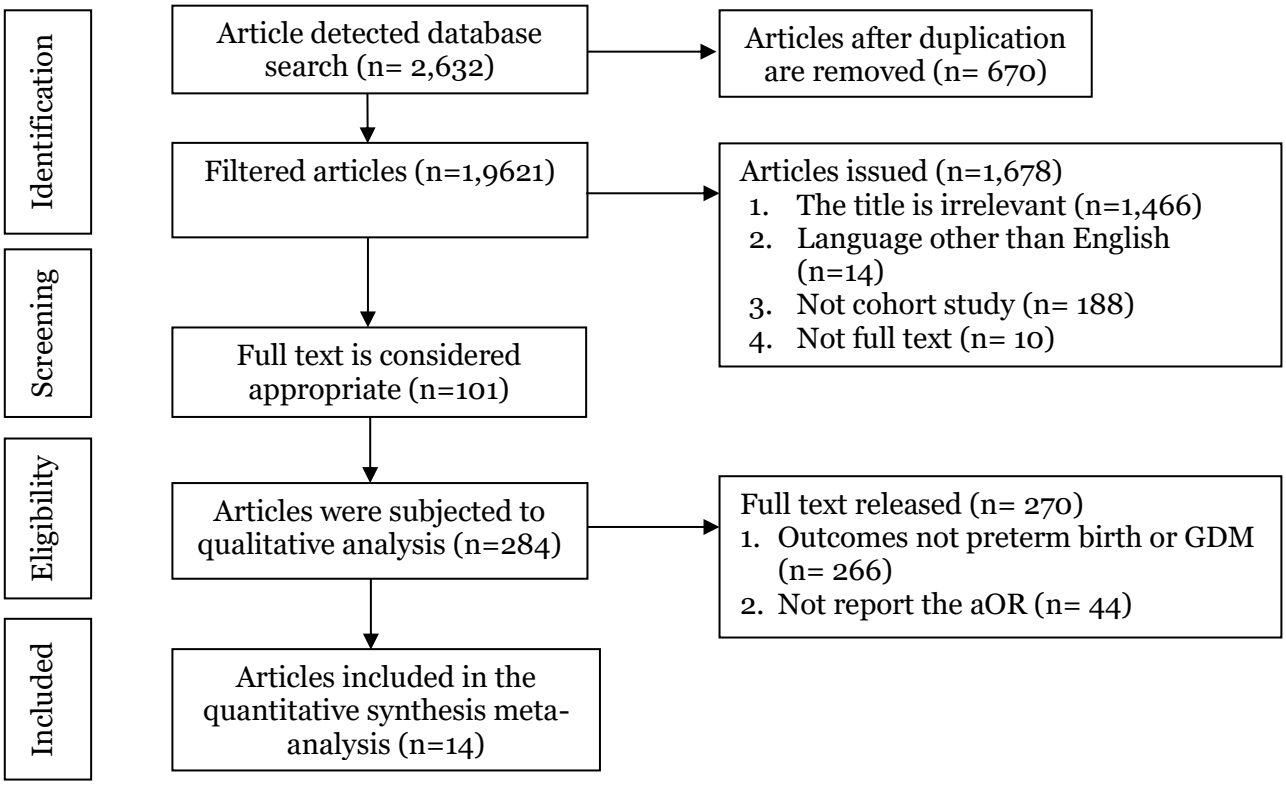

Figure 1. PRISMA Flow Diagram Results

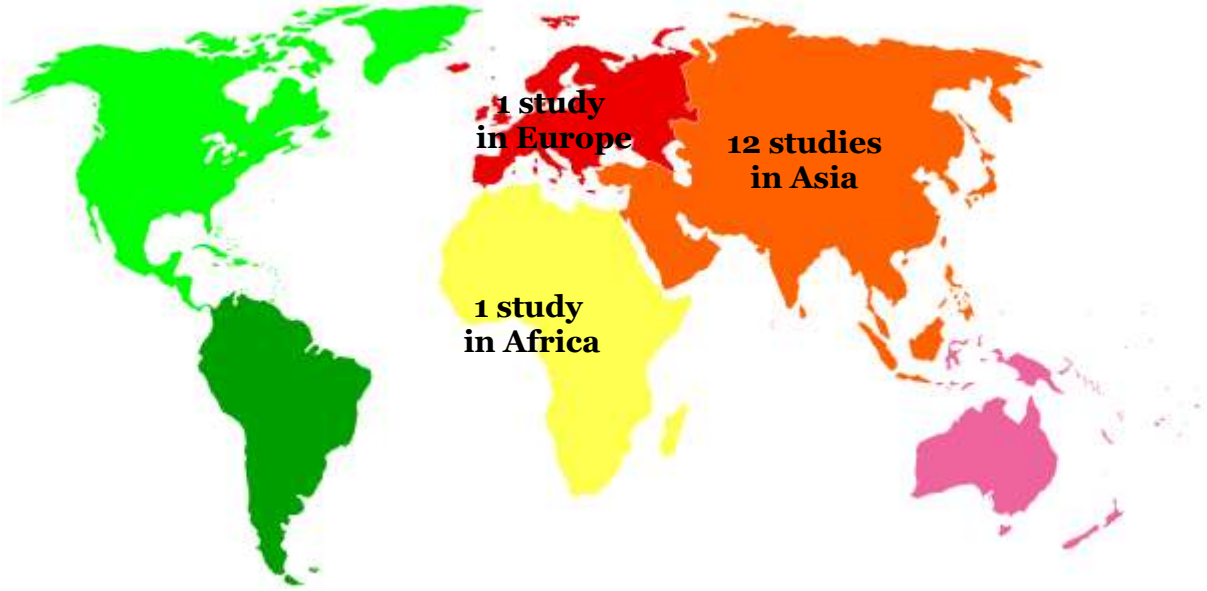

Figure 2. Research area of studies toward the effect of hepatitis B in pregnancy on preterm birth and GDMAnd GDM

Table 1. The results of the quality assessment study of the effect of hepatitis B in pregnancy on preterm birth

Author (year)	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5	6a	6b	7	Total
Benhammou(2018)	2	2	0	2	2	0	2	2	2	2	2	2	2	2	24
Cai (2019)	2	2	2	2	1	2	2	2	2	2	2	2	2	2	27
Chen (2015)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Li (2020)	2	2	2	2	1	2	1	2	2	2	2	2	2	2	26
Mbangiwa (2019)	2	2	2	2	1	2	2	2	2	2	2	2	2	2	27
Tan Jing (2017)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Wu (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Xiong (2021)	2	2	2	2	1	2	1	2	1	1	2	2	2	2	24
Zheng (2021)	2	2	2	2	0	2	2	2	2	2	2	2	2	2	26

Table 2. Results of the quality assessment study of the effect of hepatitis B in pregnancy on GDM

Author (year)	1a	1b	1c	1d	2a	2b	3a	3b	4a	4b	5	6a	6b	7	Total
Benhammou (2018)	2	2	0	2	2	0	2	2	2	2	2	2	2	2	24
Cai (2019)	2	2	2	2	1	2	2	2	2	2	2	2	2	2	27
Lao (2016)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Peng (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Tan, J (2016)	2	2	2	2	1	2	2	2	2	2	1	2	2	2	26
Wu (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Xiong (2021)	2	2	2	2	1	2	2	2	1	1	2	2	2	2	24
Yin (2021)	2	2	2	2	1	2	2	2	2	2	2	2	2	2	27
Zhao (2020)	2	2	2	2	2	2	2	2	1	1	2	2	2	2	26

Description:

1. Formulation of research questions in the acronym PICO

a. Is the population in the primary study the same as the population in the PICO meta-analysis?

b. Is the operational definition of intervention, namely the exposed status in the primary study, the same as the definition intended in the meta-analysis?

c. Is the comparison, namely the unexposed status used by the primary study, the same as the definition intended in the meta-analysis?

d. Are the outcome variables examined in the primary studies the same as the definitions intended in the meta-analysis?

2. Methods for selecting research subjects

a. Did the target population and accessible population not experience the outcomes studied at the start of the study?

b. Was there a distinction between the exposed group and the unexposed group at the start of the study?

3. Methods for measuring exposure (intervention) and outcome variables (outcome)

a. Are the exposure and outcome variables measured with the same instruments (measuring tools) in all primary studies?

b. If the variable is measured on a categorical scale, are the cutoffs or categories used the same across primary studies?

4. Design-related bias

a. Is there no possibility of "Loss-to Follow-up Bias" in primary studies?

b. Whether primary study researchers have made efforts to prevent or overcome such bias (for example, selecting highly motivated subjects, subjects who are easy to track, or providing incentives to subjects so they do not drop out)

5. Methods for controlling confusion
Whether the primary study researcher has made efforts to control the influence of confounding (for example, conducting a multivariate analysis to control the influence of a number of confounding factors, or performing matching)
6. Statistical analysis methods
a. Did the researcher analyze the data in this primary study with a multivariate analysis model (e.g., multiple linear regression analysis, multiple logistic regression analysis, Cox regression analysis)
b. Does the primary study report effect sizes or relationships resulting from multivariate analysis (e.g., adjusted OR, adjusted regression coefficient)
7. Conflict of interest Is there no possibility of a conflict of interest with the research sponsor, which could cause bias in concluding the research results?

Assessment guide:
1. Total number of questions = 13 questions. Answer "Yes" to each question gives a score of "2". The answer "Undecided" gives a score of "1". The answer "No" gives a score of "0".
2. Maximum total score= 14 questions x 2= 28.
3. Minimum total score = 14 questions x 0= 0. So the range of total scores for a primary study is between 0 and 28.
4. If the total score of a primary study is >= 24, then the study can be included in the meta-analysis. If the total score of a primary study was <24, then the study was excluded from the meta-analysis.

Table 3. Summary table of PICO cohort articles on the effect of hepatitis B in pregnancy on the incidence of Preterm Birth from primary study sources (n=84.886)

Author (Year)	Country	Sample	Population	Intervention	Comparison	Outcome
Benhammou et al. (2018)	France	4236	Pregnant mother	Hepatitis B	Non-hepatitis B	Preterm Birth
Cai et al. (2019)	China	3329	Pregnant mother ≥35 years	Hepatitis B	Non-hepatitis B	Preterm Birth
Chen et al. (2015)	China	808	Pregnant mother 20-42 years	Hepatitis B	Non-hepatitis B	Preterm Birth
Li et al. (2020)	China	13198	Pregnant mother 24-35 years	Hepatitis B	Non-hepatitis B	Preterm Birth
Mbangiwa et al. (2019)	Bostwana	752	Pregnant mother	Hepatitis B	Non-hepatitis B	Preterm Birth
Tan et al. (2017)	China	21937	Pregnant mother ≥35 years	Hepatitis B	Non-hepatitis B	Preterm Birth
Wu et al. (2020)	China	19500	Pregnant mother of average age 32 years	Hepatitis B	Non-hepatitis B	Preterm Birth
Xiong et al. (2021)	China	7011	Pregnant mother	Hepatitis B	Non-hepatitis B	Preterm Birth
Zheng et al. (2021)	China	14115	Pregnant mother of average age 30 years	Hepatitis B	Non-hepatitis B	Preterm Birth

Table 4. Data on adjusted odds ratio (aOR) and 95% confidence interval (CI 95%) effect of hepatitis B in pregnancy on the incidence of Preterm Birth

Author	aOR	Lower limit	Upper limit
Benhammou et al. (2018)	1.09	0.75	1.57
Cai et al. (2019)	1.07	0.76	1.51
Chen et al. (2015)	0.98	0.39	2.47
Li et al. (2020)	0.82	0.38	1.77
Mbangiwa et al. (2019)	1.06	0.48	2.37
Tan et al. (2017)	1.20	0.95	1.51
Wu et al. (2020)	1.42	1.17	1.72
Xiong et al. (2021)	1.20	0.97	1.48
Zheng et al. (2021)	1.06	0.79	1.41

a. Forest plot

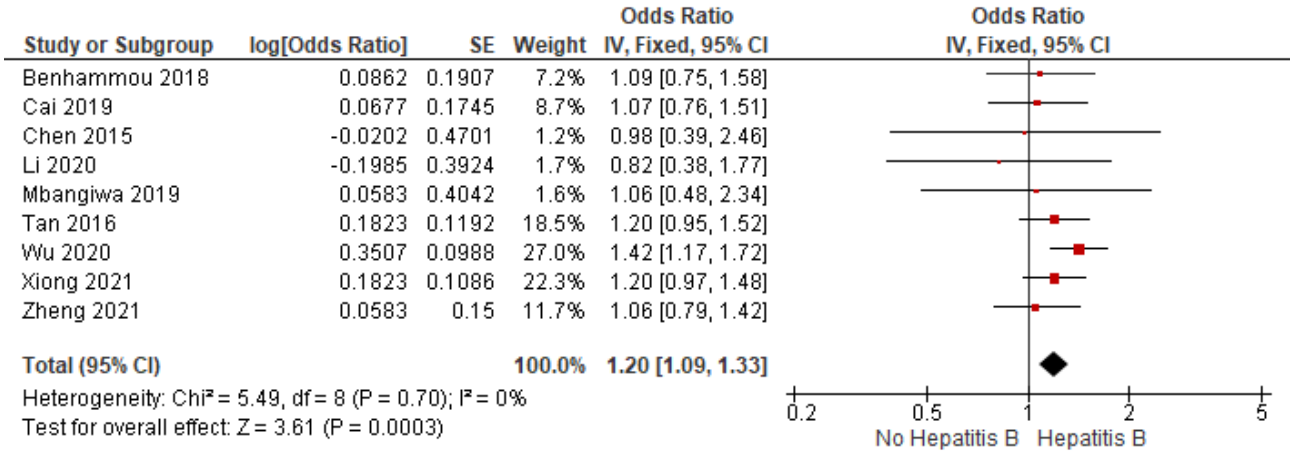

Figure 3. Forest plot of the effect of hepatitis B in pregnancy on Preterm Birth

The forest plot in Figure 3 shows that there was an effect of hepatitis B infection on the risk of preterm labor. HBV-infected pregnant women had 1.2 times higher risk of delivering preterm babies compared to non-HBV-infected women, and the effect was statistically significant (aOR= 1.20; 95% CI= 1.09 to 1.33; p<0.001).

The forest plot also showed that the effect estimates between studies have low variation or heterogeneity (I^2= 0%; p= 0.700). Thus the calculation of the average effect estimate was carried out using the fixed effect model approach.

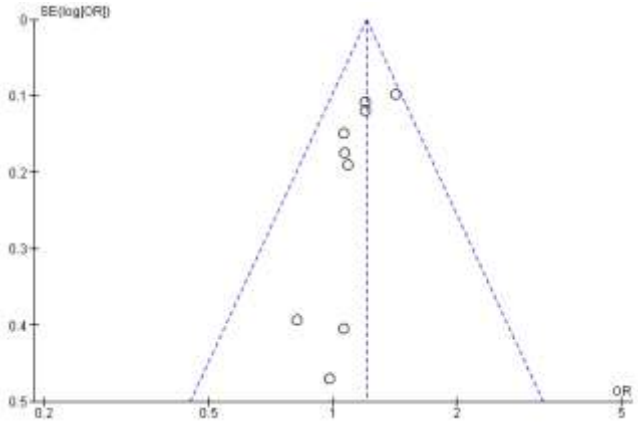

Figure 4. Funnel plot of the effect of hepatitis B in pregnancy on Preterm Birth

b. Funnel plot

The funnel plot in Figure 4 shows that the distribution of effect estimates between studies lies more to the left of the estimated average vertical line than to the right, thus indicating publication bias. Because the distribution of the estimated effect on the funnel plot was located to the left of the mean vertical line as opposed to the location of the diamond shape which was located to the right of the vertical line of hypothesis 0 in the forest plot image, this publication bias tends to reduce the true effect (under-estimate).

Table 5. Summary table of PICO cohort articles on the effect of hepatitis B in pregnancy on the incidence of GDM from primary study sources (n=131872)

Author (Year)	Country	Sample	Population	Inter-vention	Compa-rison	Outcome
Benhammou et al. (2018)	France	4236	Pregnant mother	Hepatitis B	Non-hepatitis B	GDM
Cai et al. (2019)	China	3329	Pregnant mother ≥35 years	Hepatitis B	Non-hepatitis B	GDM
Lao et al. (2016)	Hongkong	418	Pregnant mother of average age 32 years	Hepatitis B	Non-hepatitis B	GDM
Peng et al. (2019)	China	2028	Pregnant mother of average age 29 years	Hepatitis B	Non-hepatitis B	GDM
Tan et al. (2016)	China	22374	Pregnant mother ≥35 years	Hepatitis B	Non-hepatitis B	GDM
Wu et al. (2020)	China	19500	Pregnant mother of average of 32 years	Hepatitis B	Non-hepatitis B	GDM
Xiong et al. (2021)	China	7011	Pregnant mother	Hepatitis B	Non-hepatitis B	GDM
Yin et al. (2021)	China	39539	Pregnant mother of average age 30 years	Hepatitis B	Non-hepatitis B	GDM
Zhao et al. (2020)	China	33437	Pregnant mother 25-40 years	Hepatitis B	Non-hepatitis B	GDM

Table 6. Adjusted odds ratio (aOR) data and 95% confidence interval (95% CI) influence of hepatitis B in pregnancy on the incidence of GDM

Author	aOR	95% CI	
		Lower limit	Upper limit
Benhammou et al. (2018)	0.96	0.55	1.66
Cai et al. (2019)	1.00	0.55	1.81
Lao et al. (2016)	1.77	1.01	3.11
Peng et al. (2019)	1.47	1.06	2.03
Tan et al. (2016)	1.41	1.15	1.74
Wu et al. (2020)	1.24	1.07	1.43
Xiong et al. (2021)	1.13	0.95	1.34
Yin et al. (2021)	1.42	1.01	2.00
Zhao et al. (2020)	1.13	1.03	1.23

a. Forest plot

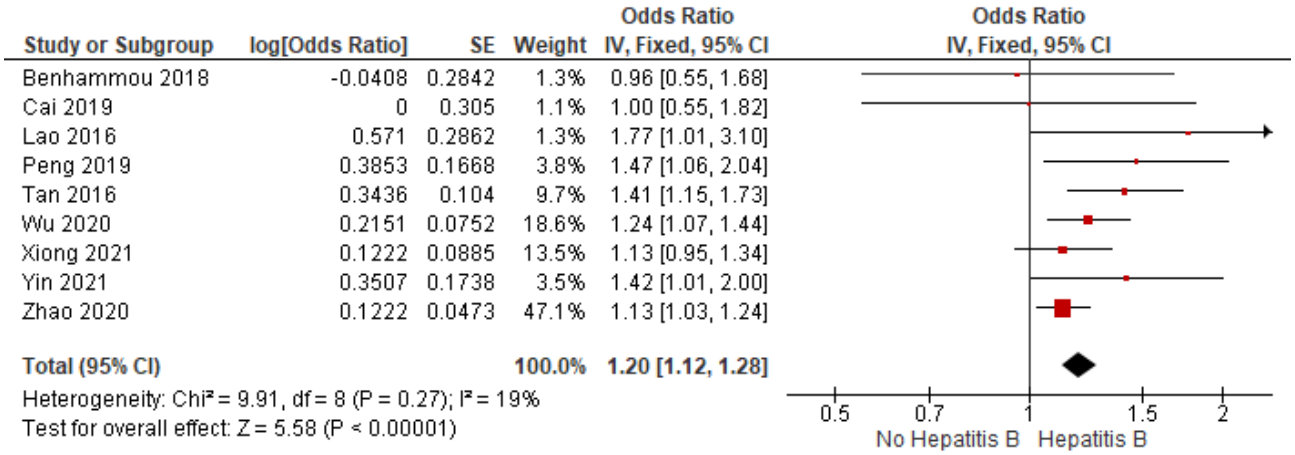

Figure 5. Forest plot of the effect of hepatitis B in pregnancy on GDM

The forest plot in Figure 5 shows that there was an effect of hepatitis B infection on the risk of GDM. HBV-infected pregnant women had 1.2 times higher risk of developing GDM compared to non-HBV-infected women, and the effect was statistically significant (aOR= 1.20; 95% CI= 1.12 to 1.28; p<0.001).

The forest plot also shows that the effect estimates between studies have low variation or heterogeneity (I^2=19%; p= 0.270). Thus the calculation of the average effect estimate was carried out using the fixed effect model approach.

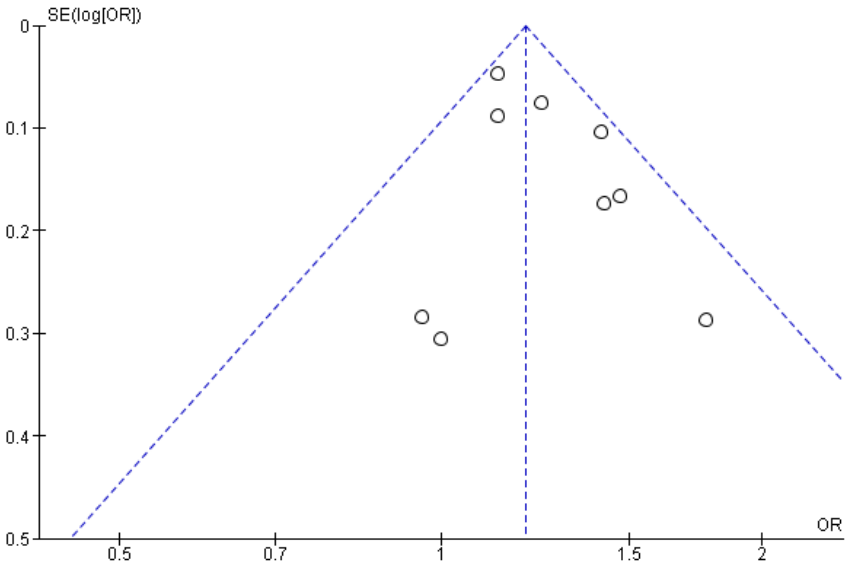

Figure 6. Funnel plot of the effect of hepatitis B in pregnancy on GDM

b. Funnel plot

The funnel plot in Figure 4.7 shows the distribution of effects from small sample primary studies more or less evenly to the right and left of the mean vertical line, so it did not indicate publication bias.

DISCUSSION

1. Hepatitis B in pregnancy on preterm birth

Study characteristics in the hepatitis B study on preterm birth consisted of 8 retrospective cohort studies and one of them was a

prospective cohort with a sample size of 84,886. The data sources used include PubMed, Science Direct, Research Gate, and Google Scholar.

The results of the forest plot show that there is an effect of hepatitis B infection on the risk of preterm labor. HBV-infected pregnant women have 1.2 times higher risk of delivering premature babies compared to those who are not infected with HBV, and the effect was statistically significant (aOR=1.20; 95% CI =1.09 to 1.33; p<0.001).

When infected with hepatitis B, cytokine levels in the body increase as an inflammatory response. Interleukin 6 (IL-6) and TNF-α are cytokines that will increase in hepatitis B sufferers, especially in the acute and chronic phases as the main mediators of the body's response to inflammation and infection. These cytokines induce the production of prostaglandins from the placental tissue which can result in contractions. IL-6 increases causing Matrix-Metalloprotenase (MMP9) to also increase. Increased MMP9 causes degradation of the extracellular matrix followed by the process of apoptosis of amniotic epithelial cells (programmed cell death during the process of tissue development) then causes membrane stretching and rupture.

TNF-α activates the release of MMP9 in the amniotic membranes and triggers amniotic membrane apoptosis then causes degradation of type IV collagen. The increase in IL-6 and TNF-α levels above can cause premature rupture of membranes which is one of the triggers for preterm birth.

Previous research conducted by Xu et al. (2021) found that chronic active hepatitis had a more significant impact on overall preterm birth, spontaneous preterm birth and iatrogenic preterm birth compared to women who screened negatively for HBsAg.

There are substantial immunological changes that occur during pregnancy and in the postpartum period that may influence the natural history and clinical manifestations of chronic hepatitis B infection. The increased risk of spontaneous preterm birth associated with chronic HBV infection may be associated with HBV-mediated inflammation.

2. Hepatitis B in pregnancy on GDM

The results of the RevMan 5.4 analysis in this meta-analysis stated that there was an effect of hepatitis B infection on the risk of GDM. HBV-infected pregnant women had 1.2 times the risk of developing GDM compared to non-HBV-infected women, and the effect was statistically significant (aOR=1.20; 95% CI=1.12 to 1.28; p<0.001).

Forest plots show that the effect estimates between studies have low variation or heterogeneity (I^2=19%; p=0.270). Thus, the calculation of the average effect estimate is carried out using the fixed effect model approach. The funnel plot shows the distribution of effects from small sample primary studies more or less evenly to the right and left of the vertical mean line, thus not indicating publication bias.

When infected with the hepatitis B virus, apart from increasing levels of interleukin-6, another cytokine that also experienced an increase was TNF-α. When TNF-α rises, iron levels in the body also increase, causing insulin resistance where there is impaired absorption of glucose in the muscles and increased glucose production by the liver so that the body can no longer respond to insulin action so that glucose cannot enter the body's cells and remains in the bloodstream, this is what triggers GDM. In addition, serum ferritinin levels also play an important role in the relationship between HBV infection and GDM.

Research conducted by Tan et al. (2018) stated that positive HbsAg during pregnancy had an effect on increasing the risk of GDM (aOR 1.47; 95% CI= 1.22 to 1.76;

I^2 = 62.0%). Pregnant women with positive HbsAg had a statistically higher risk of GDM (more than 47%).

The findings of our study differ from those of previous meta-analyses which discussed the same matter. Kong et al. (2014) showed that chronic hepatitis B infection during pregnancy does not represent a significant general risk for the development of GDM compared with chronic non-hepatitis B in infected controls (aOR 1.11; 95% CI= 0.96 to 1.28).

AUTHOR CONTRIBUTION

Alfi Zamilul Haniah as the main researcher chose the theme, conducted a primary article search, processed the results and compiled interim results. Uki Retno Budihastuti and Eti Poncorini Pamungkasari provided a review of the results of the analysis, selected articles, gave directions in preparing the results of the analysis and discussion.

FUNDING AND SPONSHORSHIP

This study used personal funds.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

ACKNOWLEDGMENT

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