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Meta-Analysis

Risk of Premature Birth in Pregnant Women Infected with COVID-19: A Meta Analysis

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ABSTRACT

Background: Pregnancy is a state of great susceptibility to infectious diseases, and it is not surprising that viral infections can affect pregnancy outcomes. COVID-19 infection during pregnancy is considered a risk factor for adverse outcomes such as, preterm delivery. This study aimed to analyze the risk of preterm delivery in pregnant women with COVID-19.
Subjects and Method: This study was conducted using a systematic review and meta-analysis. Article searches were conducted using electronic databases such as Google Scholar, PubMed, and Scopus. The articles used are articles published from 2020-2021. The keywords used to retrieve the articles were: [(COVID-19 OR 2019-nCoV OR "novel coronavirus" OR SARS-CoV-2 OR "coronavirus 2") AND ("preterm birth" OR preterm OR "preterm delivery")] . The inclusion criteria used were full paper with observational studies (retrospective or prospective cohorts), multivariate analysis with Adjusted Odd Ratios (aOR), study subjects were pregnant women who were confirmed to be infected with COVID-19, comparison were pregnant women who were negative for COVID-19, outcome study was preterm birth (<37 weeks). The article search results are listed in the PRISMA diagram and analyzed using the Review Manager 5.3 . application.
Results: A total of 10 articles from Iran, France, Bangladesh, Spain, the United States, Romania, the United Kingdom and China showed that the heterogeneity of the primary studies in the meta-analysis was low (I^2= 4%; p= 0.40), therefore this study used a fixed effect model. The results showed that the risk of premature birth in pregnant women infected with COVID-19 was 2.18 times that of pregnant women not infected with COVID-19 (aOR=2.18; 95% CI=2.00 to 2.37) and statistically significant (p<0.001).
Conclusion: Higher risk of preterm birth in pregnant women with COVID-19.

Keywords: premature birth, pregnancy, COVID-19.

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BACKGROUND

In December 2019, there was an outbreak of Corona Virus 2 (SARS-CoV-2) which is the pathogen that causes Corona Virus Disease 2019 (COVID-19), in Wuhan, Hubei Province, China (Liu et al., 2020). The novel coronavirus disease (COVID-19) has spread rapidly throughout the world since it was first identified in Wuhan (China) and declared a pandemic by WHO (Chen et al., 2020). Data on the development of COVID-19 in Indonesia to date on August 17, 2021, are 3,892,479 positive cases and 3,414,109

recovered cases and 120,013 deaths. (Directorate General of P2P Ministry of Health RI, 2020)

The global pandemic that has occurred since late 2019 has raised significant concerns about the infection of vulnerable populations such as pregnant women and newborns. WHO identified pregnant women as a vulnerable group based on initial reports of an increased risk of stillbirth, preterm delivery, and fetal growth restriction (FGR) and from accumulated knowledge about previous outbreaks of respiratory viruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and respiratory syndrome. Middle East (MERS) (Wong et al., 2004).

Many studies have confirmed that most pregnant women infected with SARS-CoV-2 are asymptomatic. In June 2020, the Centers for Disease Control and Prevention (CDC) actually reported that among those with COVID-19, 31.5% of pregnant women had to be hospitalized compared to 5.8% of women who were not pregnant. Exposure to COVID-19 in pregnancy, compared to unexposed, will increase infection-related obstetric morbidity including preterm delivery and premature rupture of membranes which in turn will increase the number of neonates requiring intensive care units (Zambrono et al., 2020).

Every year in the world there are about 15 million babies born prematurely (before 37 weeks of gestation), this number continues to increase and premature birth also has long-term consequences of delayed child development (WHO, 2018). Preterm delivery was initially reported as the most adverse pregnancy outcome in affected patients and is associated with acute/chronic inflammation and vascular malperfusion (Wong et al., 2021).

Preterm birth rates of up to 30% were reported in the initial cohort of COVID-19 patients, preterm births accounted for 75% of perinatal deaths and more than half of long-term morbidity (Mendoza et al., 2020). Premature birth can have a negative impact on both mother and baby and is the second leading cause of under-five mortality and is the leading cause of neonatal death with a mortality percentage of almost 35%.

To date, studies that directly evaluate the effect of COVID-19 infection on preterm birth are limited (Adhikari et al., 2020; Perez et al., 2021). Large population-based studies are urgently needed to evaluate whether COVID-19 infection during pregnancy may affect preterm birth. This study aimed to analyze the risk of preterm delivery in pregnant women with COVID-19.

RESULTS

1. Study Design

This was a systematic review and meta-analysis. Article searches were conducted using electronic databases such as Google Scholar, PubMed, and Scopus. The articles used are articles published from 2020-2021. The keywords used to retrieve the articles were: [(COVID-19 OR 2019-nCoV OR "novel coronavirus" OR SARS-CoV-2 OR "coronavirus 2") AND ("preterm birth" OR preterm OR "preterm delivery")] . The article search results are listed in the PRISMA diagram and analyzed using the Review Manager 5.3 application.

2. Inclusion Criteria

Full paper article with observational studies (retrospective or prospective cohorts), multivariate analysis with Adjusted Odd Ratios (aOR) to measure the estimated effect, study subjects are pregnant women who are confirmed to be infected with COVID-19, comparison are pregnant women who are negative for COVID-19 , the outcome of the study was premature birth (<37 weeks).

3. Exclusion Criteria

The main articles are those published from the meta-analysis, articles published in

languages other than English, and articles before 2020.

4. Operational Definition of Variable

In formulating research problems PICO is used. The population is pregnant women. The intervention was positive for COVID-19 and the comparison was negative for COVID-19, the final result was premature birth.

Positive confirmation of COVID-19 is being declared positive for being infected with the COVID-19 virus as evidenced by an RT-PCR (swab) laboratory examination. Premature birth is the birth of a baby before 37 weeks of gestation.

5. Study Instrument

Quality assessment in this study used the Cohort Study Checklist published by CASP (Critical Appraisal Skills Program).

6. Data Analysis

Articles were collected using PRISMA diagrams and analyzed using the Review Manager 5.3 application by calculating effect sizes and heterogeneity to determine the combined research model and form the final results of the meta-analysis.

RESULTS

Research from a primary study related to the risk of premature birth in pregnant women with COVID-19 consisted of 9 articles from 5 studies from the European continent (France, Spain, Romania, England), 3 studies from Asia (Iran, Bangladesh, and China), and 1 study from the United States.

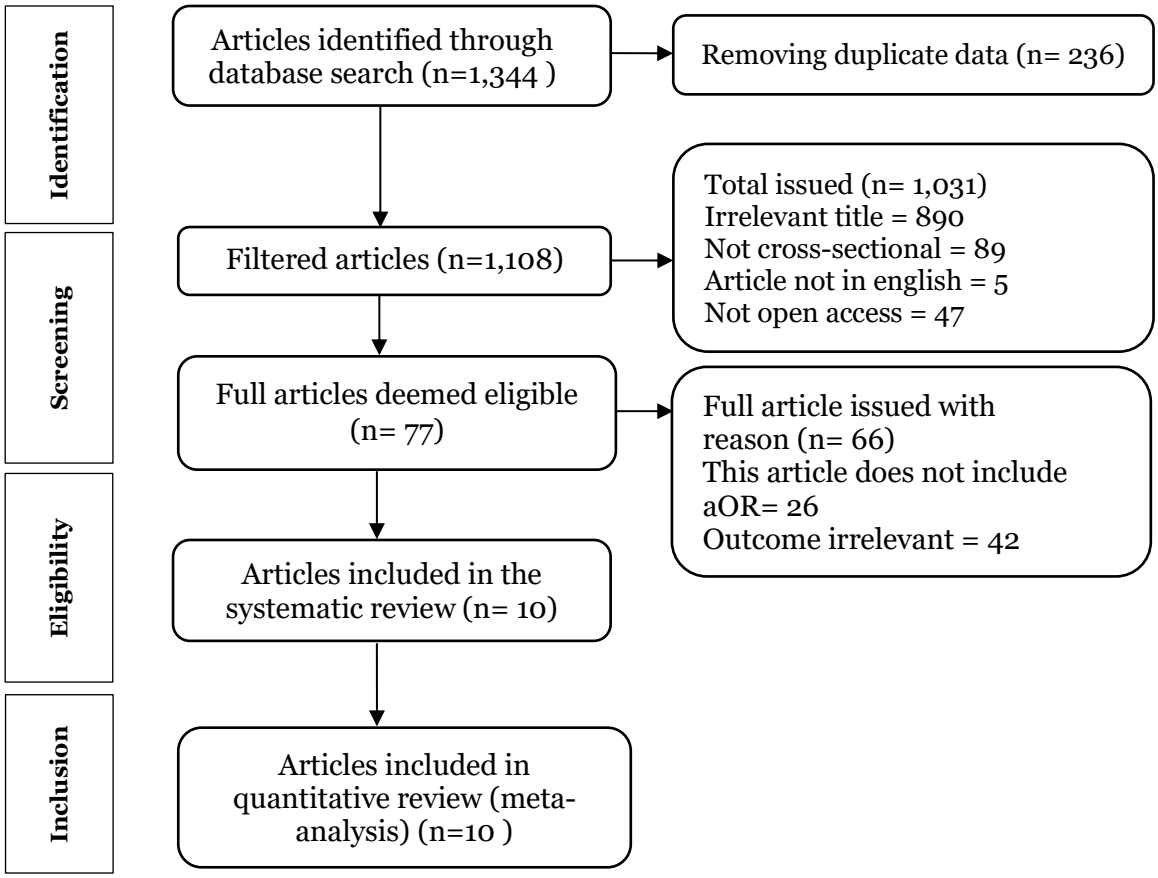

Figure 1. PRISMA Flowchart

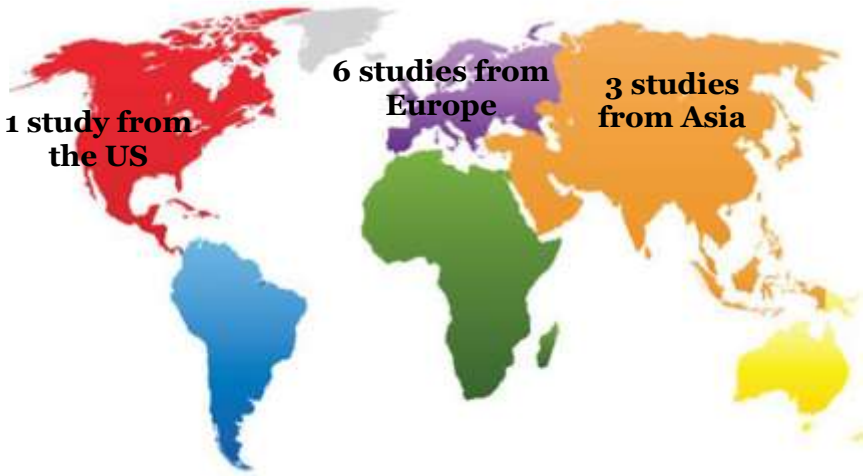

Figure 2. Research Map

A total of 1,344 articles were identified through the electronic database. After removing duplication, 1,108 articles were screened. Of these, 77 articles were assessed for eligibility. The following reasons are given for full-text articles that meet the exclusion criteria:

1. The article only reports (OR) resulting from bivariate analysis.
2. The effect size used is aRR/aHR, not aOR.
3. Articles reporting outcomes other than preterm delivery in pregnant women with COVID-19.

A total of 10 articles that met the quality assessment were included in the quantitative synthesis using the Meta-Analysis.

Research Quality Assessment

Quality assessment in this study used the Cohort Study Checklist published by CASP (Critical Appraisal Skills Program).

This assessment criteria consists of twelve criteria, with each measure given a score of 2= if you answered yes, 1 = if you answered you don't know, and 0 = if you answered no. The following are the assessment criteria from the Cohort Study Checklist published by CASP (Critical Appraisal Skills Program), including:

1. Does the cohort study clearly address the research problem?
2. Does the cohort study clearly address the research problem?
3. Is exposure to COVID-19 accurately measure to minimize bias?
4. Are results measured accurately to minimize bias?
5. Did the researcher identify all the important confounding factors? Did the researcher take confounding factors into account in the design and/or analysis?
6. Was the follow-up of the subject sufficiently complete? Was the follow-up of the subject long enough?
7. Is this study reported in aOR ?
8. How precise are the results?
9. Are the results reliable?
10. Are the results applicable to the local population?
11. Do the research results match the available evidence?
12. Are the results applicable in practice/ community?

The next step is to calculate the overall effect of combining the data. Data analysis was performed using Review Manager (RevMan) 5.3 software released by the Cochrane Collaboration.

Table 1. Shows the assessment of study quality using the Study Cohort Checklist published by CASP (Critical Appraisal Skills Program) as follows:

Table 1. Assessment of study quality published by the Critical Appraisal Skills Program (CASP)

No	Questions Checklist	Publication (Author and Year)									
		Alpour et al., 2021	Epelboin et al., 2021	Melguizo et al., 2021	Masud et al., 2021	Peres et al., 2021		Torres et al., 2021	Timircan et al., 2021	Urganci et al., 2021	Vousden et al., 2021	Yang et al., 2020
1.	Does the cohort study clearly address the research problem?	2	2	2	2	2	2	2		2	2	2
2.	Was the group recruited in an acceptable way?	2	2	2	2	2	2	2		2	2	2
3.	Is exposure to COVID-19 accurately measured to minimize bias?	2	2	2	2	2	2	2		2	2	2
4.	Are results measured accurately to minimize bias?	2	2	2	2	2	2	2		2	2	2
5.	Did the researcher identify all confounding factors? Did the researcher take confounding factors into account in the design and/or analysis?	2	2	2	2	2	2	2		2	2	2
6.	Was the follow-up of the subject sufficiently complete and long?	2	2	2	2	2	2	2		2	2	2
7.	Is this study reported in aOR ?	2	2	2	2	2	2	2		2	2	2
8.	How precise are the results?	2	2	2	2	2	2	2		2	2	2
9.	Are the results reliable?	2	2	2	2	2	2	2		2	2	2
10.	Are the results applicable to the local population?	2	2	2	2	2	2	2		2	2	2
11.	Do the research results match the available evidence?	2	2	2	2	2	2	2		2	2	2
12.	Are the results applicable in practice/community?	2	2	2	2	2	2	2		2	2	2
	Total	24	24	24	24	24	24	24		24	24	24

Note: 2: Yes; 1: Don't know; 0: No

Table 2. Description of the main studies included in the primary study of the meta-analysis

No	Author (Year)	Country	Study Design	Sample Size		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR (CI 95%)
				Total	Positive COVID-19					
1.	Alipour et al., 2021	Iran	Retrospective cohort	198	133	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 3.01 (1.4 to 6.54)
2.	Epelboin et al., 2021	France	Prospective cohort	244,645	874	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 2.52 (2.09 to 3.05)
3.	Masud et al., 2021	Bangladesh	Cohort	210	70	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 2.15 (1.06 to 4.37)
4.	Melguizo et al, 2021	Spain	Prospective Cohort	2,954	1,347	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 2.00 (1.53 to 2.62)
5.	Perez et al., 2021	Spain	Prospective cohort	1.009	246	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 2.12 (1.32 to 3.36)
6.	Torres et al., 2021	The US	Retrospective cohort	209	106	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 2.73 (1.19 to 6.3)
7.	Timircan et al., 2021	Romania	prospective cohort	938	101	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 1.61 (1.19 to 2.04)
8.	Urganci et al., 2021	The UK	Cohort	342,080	3,527	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 2.17 (1.92 to 2.42)
9.	Vousden et al., 2021	The UK	Prospective cohort	364,830	1,148	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 1.87 (1.23 to 2.85)
10.	Yang et al., 2020	China	Retrospective cohort	11,078	65	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature Birth	AOR= 3.34 (1.60 to 7.00)

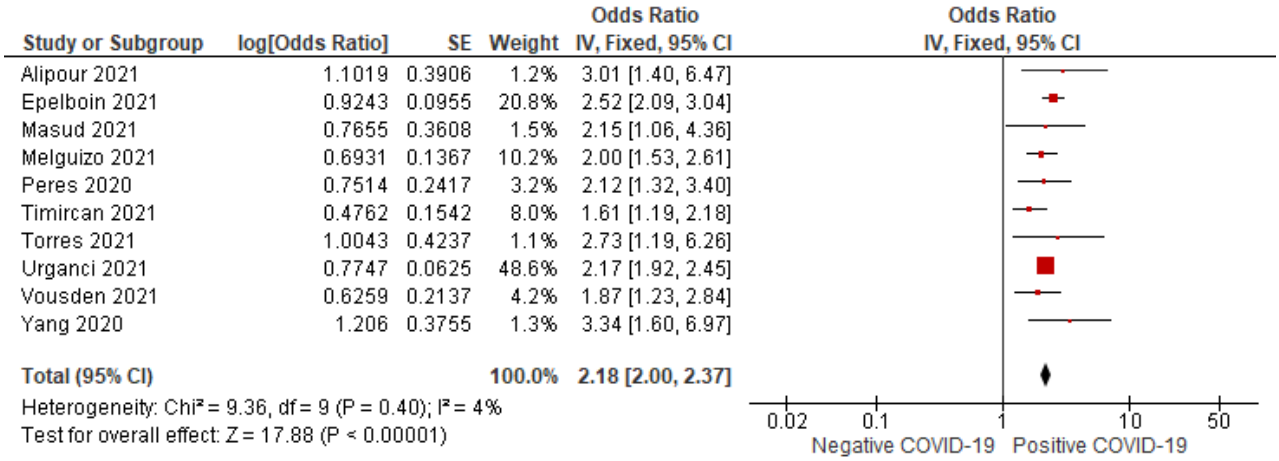

Figure 2. Forest Plot of the Risk of Premature Birth in Pregnant Women with COVID-19

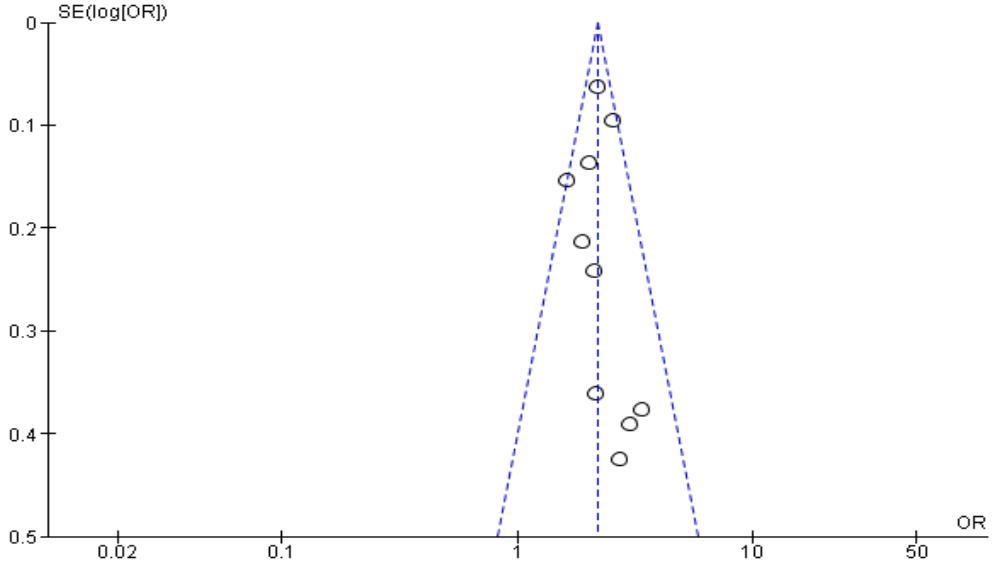

Figure 3. Funnel Plot of the Risk of Premature Birth in Pregnant Women with COVID-19

The forest plot in Figure 2 shows that the risk of preterm birth in pregnant women infected with COVID-19 is 2.18 times higher than pregnant women negative/not infected with COVID-19 (aOR=2.18; 95% CI= 2.00 to 2.37) and statistically significant p<0.001. Statistical heterogeneity among studies was I^2= 4% indicating a homogeneous data distribution (fixed effect model).

A funnel plot is a plot that depicts the approximate size of the effect of each study on its estimated accuracy, which is usually the standard error. The following funnel plot shows the risk of publication bias among the included studies.

In Figure 3 the funnel plot shows the existence of publication bias. The distribution of the plots is not symmetrical and there is an imbalance in the distance between the studies on the right and left sides of the funnel plot. The plot on the left of the graph appears to have a standard error of 0 to 0.40, while the plot on the right appears to have a standard error of 0 to 0.50.

DISCUSSION

The coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, is highly contagious and is currently spreading rapidly around the world. It has caused thousands of morbidity and mortality worldwide since it first appeared in Wuhan, Hubei Province, China in December 2019 (Wang et al, 2020). Many studies have focused on infected patients from the general population; however, details of COVID-19-related pregnancy outcomes are scarce. Chen et al. (2020) reported on maternal-neonatal outcomes and the potential for vertical transmission of COVID-19 pneumonia in pregnant women. There are very limited data currently on maternal outcomes in COVID-19 infection in pregnancy. However, as per data from other viral diseases such as influenza, SARS and MERS, pregnant women are more likely to develop viral pneumonitis, with higher morbidity and mortality (Yu et al, 2020).

Preliminary studies suggest that physiological and immunological changes during pregnancy can increase the risk of pregnant women being infected with respiratory viruses such as influenza (Wang et al, 2020). It has been reported that pregnant women are more susceptible to infection, develop more severe disease complications, and have a higher mortality rate compared to the non-pregnant population (Yu et al, 2020). More than 100 million pregnant women worldwide are at high risk of contracting COVID-19 due to various physiological conditions, such as elevation of the diaphragm, decreased residual lung functional capacity, increased oxygen consumption, edema of the mucous membranes of the respiratory tract, and immune modulation during pregnancy. In addition, reports indicate that with respiratory viral infections, pregnant women have a higher risk of obstetric and perinatal complications due to changes in their immune response (Wong et al, 2004).

This meta-analysis study investigated the risk of preterm delivery in pregnant women with COVID-19. The independent variable is pregnant women who are positive for COVID-19 and the dependent variable is preterm labor. The intervention is a COVID-19 infection. This research is important because COVID-19 infection in pregnant women will affect pregnancy. Research that discusses premature birth is considered important because premature birth is a problem in increasing infant mortality, both in developing and developed countries. In this meta-analysis the sample size was more than 968,151 individuals from nine cohort studies conducted in Iran, India, Spain, France, Bangladesh, Romania, United Kingdom, United States, and China. studies were identified from 2020 to 2021, each article having an aOR statistical outcome. This study explains that the risk of premature birth in pregnant women infected with COVID-19 is 2.18 times that of pregnant women who are negative/not infected with COVID-19 (aOR=2.18; 95% CI=2.00 to 2.37) and statistically significant $p<0.001$. This meta-analysis study provides evidence that pregnant women infected with COVID-19 are more at risk for preterm labor. In this study, there is a tendency for publication bias which is indicated by the funnel plot with an asymmetric distribution of plots.

The results of this study are similar to those conducted by Blitz et al. (2021) who explained that there was a relationship between COVID-19 infection in pregnant women and the incidence of preterm birth. Patients with COVID-19 symptoms at delivery were more likely to give birth prematurely (19.0%; aOR= 2.76; 95% CI= 1.92 to 3.88). Research by Mullins et al. (2021) described that 16.1% (100/622) of women with confirmed infection gave birth prematurely.

Allotey et al. (2020) also explained that compared to pregnant and newly pregnant women without the disease, pregnant women with COVID-19 had a higher risk of giving birth prematurely (aOR = 1.47; 95% CI = 1.14 to 1.91) from 18 studies and 8,549 women). In a population-based study of women giving birth to singleton babies in the UK in 2020–2021 reported that women with a record of laboratory-confirmed COVID-19 infection at birth were more than twice as likely as women without COVID-19 infection to have fetal death or preterm delivery (Urganci, 2021).

Anton et al. (2020) reported 36.8% of preterm births in pregnant women who tested positive for COVID-19 in the UK. Ayed et al. (2020) revealed that 26.6% of pregnant women were positive for COVID-19. Another similar study explained that among pregnant women who were positive for SARS-CoV-2, 27% of neonates had a preterm birth (Knight et al, 2020). A systematic review of 33 studies described a 15.2% preterm birth rate in pregnant women infected with COVID-19 (Elshafeey et al. 2020). Previous studies have also shown that SARS and Middle East respiratory syndrome (Mers) infections are associated with preterm delivery, intensive care treatment for newborns, and even perinatal mortality (Schwartz et al, 2020). There are several studies that suggest otherwise, such as the study by Zeng et al., (2020), showing that women with COVID-19 who give birth prematurely have other medical indications for preterm birth besides COVID-19.

Similar to SARS-CoV, COVID-19 or SARS-COV-2 virus uses Angiotensin-converting enzyme 2 (ACE 2) as its functional receptor to infect human cells. Research shows ACE 2 is mainly excreted in the respiratory, cardiovascular and digestive systems. Any changes in pregnant women will affect the growth and development of the fetus. Physiological conditions, the cardiopulmonary load on pregnant women has increased significantly in the second and third trimesters. If a viral infection causes lung injury in pregnant women, it will accelerate the occurrence of respiratory problems. After experiencing respiratory distress, pregnant women will experience hyposemia which causes inadequate blood and oxygen supply to the placenta, which causes fetal distress and premature birth.

The first reports of obstetric outcomes of pregnant women with COVID-19 revealed a significant increase in preterm delivery (Knight et al., 2020). As a result, newborns have short, medium, and long-term health risks. In the neonatal period and the first months of life, the main complications of premature infants are respiratory disorders, retinopathy of prematurity, bronchopulmonary dysplasia, metabolic disorders, sepsis, intraventricular hemorrhage. Premature birth can cause long-term complications, including cerebral palsy, impaired lung function, learning disorders, vision and hearing disorders, dental abnormalities, behavioral and psychological problems, growth disorders, and chronic adult diseases, namely insulin resistance, chronic kidney disease (CKD), and hypertension (Halimi et al., 2017; Reddy et al., 2015).

The limitations of this study are that there is a language bias because it only uses English articles, a publication bias shown in the funnel plot results, and a search bias because it only uses three databases.

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This study is self-funded.

AUTHORS CONTRIBUTION

Ratih Hermas Purnasari as the main researcher who chose the topic, conducted a search for data collection in this study. Yulia Lanti Retno Dewi and Bhisma Murti

conducted data analysis and reviewed research documents.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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