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Effect of Covid-19 on Premature Birth : A Systematic Review and Meta-Analysis

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ABSTRACT

COVID-19 is growing very rapidly and spreading across the globe. Pregnant women are group at risk of being infected by COVID-19. Premature birth is as a major contributor to death in early life. The purpose of this study was to determine the relationship between pregnant women infected with COVID-19 with the incidence of premature birth.This study used the PRISMA checklist. The PECOS framework was used as a search strategy tool. Search literature was using 3 databases consisting of Pubmed, Spinger, and Proquest. The quality of the articles screened was assessed by using The Joanna Briggs Institute Critical Appraisal tools was applyed in JBI Systematic Reviews in 2017. The results of the study show that there is a significant relationship between COVID-19 and Premature labor with p value < 0.00001. Pregnant women with COVID-19 have a 1.48 times risk of experiencing Premature birth compared to those who are not infected with COVID-19 (OR 1.48 (95% CI 1.16 - 1.90)).

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INTRODUCTION

The first case of COVID-19 was reported on December 31, 2019 in Wuhan, Hubei Province, China. The number of cases of COVID-19 is growing very rapidly and is spreading between countries (Galang et al., 2020). WHO declared the COVID-19 outbreak a pandemic on March 11, 2020. Previous outbreaks, Middle East Respiratory Syndrome (MERS) in 2012 and Severe Acute Respiratory Syndrome (SARS) in 2002 were reported to have symptoms similar to COVID-19 including cough, fever, and shortness of breath. MERS-CoV and SARS-CoV have case fatality rates (CFRs) of 10% and 37% respectively and over 10,000 deaths globally (Tekbali et al., 2020). In addition, Pregnancy with MERS-CoV and SARS-CoV is associated with a higher incidence of spontaneous preterm birth, intrauterine growth restriction (IUGR), premature rupture of membranes, miscarriage, preeclampsia, and perinatal mortality (Karami et al., 2020).

Pregnancy during the COVID-19 pandemic is a challenge for pregnant women. Physiological and immunological changes during pregnancy will make pregnant women more susceptible to

infection (Mertz et al., 2013). Given that SARS-CoV and MERS-CoV have similarities to COVID-19, it's a concern, it is feared that COVID-19 poses a dangerous risk during pregnancy. Research reports that pregnant women with COVID-19 had an increased risk of adverse birth outcomes including preterm birth and cesarean section delivery compared to pregnant women without COVID-19 (Ademuyiwa et al., 2020).

Premature birth is the leading cause of death in early life. Premature birth is birth before 37 weeks of gestation (Vogel et al., 2018). The rate of premature birth in the world is about 10% worldwide. Preterm birth is associated with an increased risk of several long-term health problems, growth and development delays, and risks of morbidity and mortality. Therefore, premature babies can contribute to a major public health problem (Chawanpaiboon et al., 2019)

The results show that a high rate of preterm birth has been reported in women with COVID-19 infection (Delahoy et al., 2020). Based on research reports that 30% of babies are born prematurely because of transplacental transmission (Kirtsman et al., 2020). In addition, the results of the study reported that the fear of COVID-19 infection as a new deadly epidemic and economic problems was associated with increased maternal morbidity and premature birth (Ramanathan et al., 2020). Until now, information about the effect of COVID-19 infection on preterm birth is still limited. So we are interested in conducting a systematic review and meta-analysis to know the effect of COVID-19 in pregnant women with the incidence of premature birth.

RESEARCH METHOD

We conducted an article search on 1-10 December 2021 and identified 859 articles from three databases. After eliminating duplication, there were 707 articles to filter titles and abstracts. After eliminating irrelevant articles, we found 19 articles for in-depth review and left 7 for analysis. The article search process can be seen in the PRISMA flow diagram in figure 1. Based on the study quality assessment using the Joanna Briggs Institute Critical Appraisal tools in 2017 for cohort and cross-sectional study designs. A total of 7 articles that were included in the quantitative synthesis of the meta-analysis were articles that were categorized as good. Research related to the relationship of COVID-19 to preterm birth consists of 7 articles. The studies come from different countries in table 1

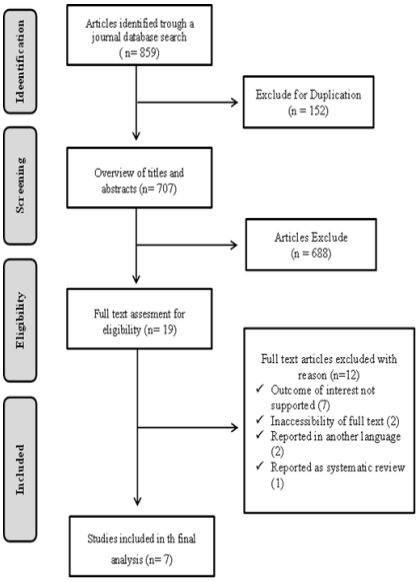

Figure 1. Article selection process with PRISMA

RESULT AND DISCUSSION

Table 1. Data Extraction for included studies

No.	Author	Country	Lenght of study	Method	Population	Main results	Relationship strength
1	(Yang *et al.*, 2021)	Wuhan, China	3 months	Retrospective cohort	11,078	Women with COVID-19 who confirmed to have a preterm birth rate which was significantly higher (p= 0.01)	3.34, (95% CI 1.60–7.00)
2	(Du *et al.*, 2021)	Beijing, China	6 months	Retrospective Cohort	7699	There was no significant difference in the prevalence of preterm birth during the COVID-19 pandemic and before the pandemic (p = 0.184)	0.86 (95% CI 0.69-1.08)
3.	(Arnaez *et al.*, 2021)	European	4 months	Cross sectional	2,139	Slightly significant improvement among very premature births (p = 0.042)	2.09 (95% CI 1.02–4.28
4.	(Martinez-Perez *et al.*, 2021)	Spain	3 months	Prospective study	1009	Woman with confirmed COVID-19 has a preterm birth rate which is much higher (p = 0.002)	2.12 (95% CI 1.32–3.36)
5.	(Pirjani *et al.*, 2020)	Iran	7 months	Prospective cohort	199 .	Pregnant women with COVID-19 had a preterm birth (PB) that was almost the same as without infection (p= 0.064)	1.16 (95% CI: 0.54, 2.48)
6	(Blitz *et al.*, 2021)	New York	4 months	Retrospective cohort	33 629	Pregnant women with COVID-19 symptoms are significantly more likely to give birth premature compared to patients without infection (p < 0.001)	1.53 (95% CI 1.24–1.87)
7	(Karasek *et al.*, 2021)	California	7 months	Retrospective cohort study	240,157	Pregnant women with COVID-19 increase the risk of birth premature birth, especially among people with medical comorbidities	1.4 (95% CI 1.3-1.4)

The association between pregnant women and COVID-19 status increases the risk of adverse birth outcomes. The results showed that there was a significant relationship between COVID-19 and the incidence of preterm birth (Arnaez et al., 2021; Blitz et al., 2021; Martinez-Perez et al., 2021; Yang et al., 2021). Of the four studies that had the highest influence, namely 3.34 (95% CI 1.60-7.00) and the lowest effect was 1.53 (95% CI 1.24–1.87) (Yang et al., 2021). On the other hand, the results showed that there was no significant relationship between COVID-19 and the incidence of preterm birth (Du et al., 2021; Karasek et al., 2021; Pirjani et al., 2020)

Premature rupture of membranes and fetal distress during the COVID-19 pandemic have increased compared to pre-COVID-19. Before the COVID-19 pandemic they were 11% (95% CI, 1.04-1.18; p<0.01) and 14% (95% CI, 1.01-1.29; p<0, 05). Whereas during the COVID-19 pandemic the premature rupture of membranes was 9.91 (95% CI, 3.84, 15.25), and in fetal distress it was 12.28 (95% CI, 0.99 to 22.48) (Du et al., 2021). Similarly, study results Martinez-Perez *et al* (2021) The risk of premature rupture of membranes (PROM) and preterm (PPROM) was significantly associated in the infected group (p = 0.009 and p = 0.031, respectively). Increased incidence with OR 2.12 (95% CI 1.32-3.36) compared to uninfected patients.

In the study there were 1,009 patients who reported no maternal death but had intrauterine fetal death, with a much higher proportion of the positive group than the negative group. Mothers infected with SARS-CoV-2 had significantly more babies who were admitted to the NICU than

mothers who were not infected (p < 0.001, OR = 4.62, 95% CI: 2.43-8.94). Premature birth and respiratory distress are the leading causes of NICU care (Blitz et al., 2021)

Research suggests associations between pre-existing comorbidities may magnify the effect of SARS-CoV-2 infection on adverse outcomes. Association for COVID-19-infected individuals diagnosed with comorbidities to increase the risk of very preterm delivery compared to those without a comorbid diagnosis (aOR 2.6, 95% CI [2.1, 3.1]), preterm delivery (aOR 2.0, 95% CI [1.8) , 2.2), and term delivery (aRR 1.3, 95% CI [1.2, 1.4]) (Du et al., 2021; Karasek et al., 2021).

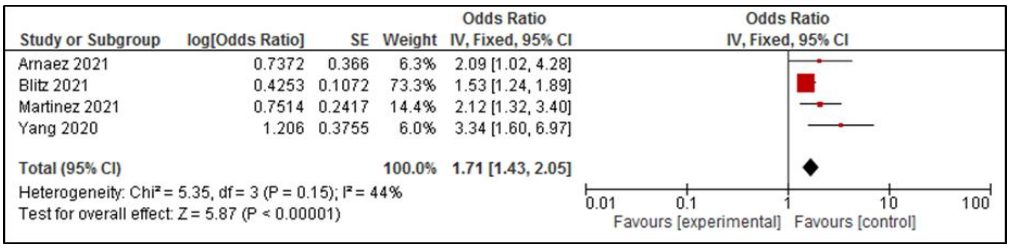

Figure 2. Forest plot of the relationship between coronavirus disease 2019 (COVID-19) and premature birth

The interpretation of the results in figure 2 shows that there is a significant relationship between COVID-19 and preterm labor with p value < 0.00001. The pooled odds ratio value is 1.48 (95% CI 1.16 - 1.90) so increase the risk of very preterm delivery compared to those without a comorbid diagnosis (aOR 2.6, 95% CI [2.1, 3.1]), preterm delivery (aOR 2.0, 95% CI [1.8) , 2.2), and term delivery (aRR 1.3, 95% CI [1.2, 1.4]) (Du et al., 2021; Karasek et al., 2021).

The interpretation of the funnel plots in Figure 3 shows that it has a small publication bias marked by the asymmetry of the right and left plots where there are 3 plots on the right, and 1 plot on the left. Detection of publication bias could be affected because few articles were combined in estimating the effect of the association of COVID-19 with preterm birth.

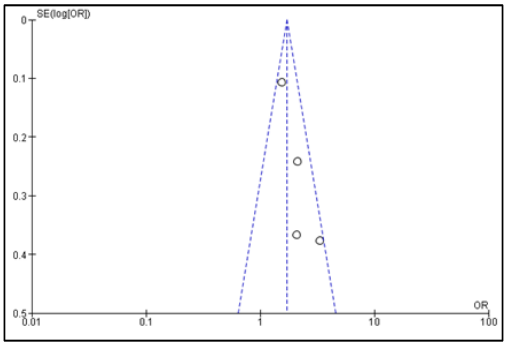

Figure 3. Forest plot of the relationship between coronavirus disease 2019 (COVID-19) and premature birth

Premature birth is a major contributor to death in early life. Preterm birth was defined as birth before 37 weeks' gestation (Vogel *et al.*, 2018). The exact cause of premature birth in pregnant women with confirmed COVID-19 is not known. The results of the study by Martinez-Perez et al (2021) that in 189 (76.8%) cases of SARS-CoV-2 infection, PCR analysis was performed on samples of the nasopharynx and/or oropharynx of newborns; 147 were performed during the first 12 hours of life, three of which were positive, and another 42 were performed for up to 48 hours of life, all of which resulted in negative. Of the 3 newborns who had an initial positive result, they were retested at 48 hours, with a final negative result. The results of the analysis of samples of amniotic fluid, umbilical cord blood, neonatal throat swabs, and breast milk were taken from six of the nine

patients who tested negative for COVID-19. Thus, preterm birth is not caused by vertical maternal-fetal transmission of SARS-CoV-2. Infection in neonates can occur through close contact after delivery. During this period, direct breastfeeding is not recommended. An option that allows a woman to pump her breast milk, which is given to her baby by a nurse or healthy caregiver. Several studies have shown otherwise that SARS-CoV-2 infection may occur due to vertical maternal-fetal transmission (Patberg *et al.*, 2021). SARS-CoV-2 causes an exaggerated systemic inflammatory response that interferes with the optimal status of the placenta for fetal growth and development. The presence of vascular malperfusion from the placental unit to the fetus can be a contributing factor to the development of adverse pregnancy outcomes including the occurrence of preterm delivery (Tasca *et al.*, 2021).

On the other hand, the results of studies in Beijing and Iran showed that the prevalence of premature birth was not significantly different during the COVID-19 pandemic compared to the pre-pandemic period (p = 0.184) and (p = 0.064) and has a very weak influence on the incidence of premature birth (Pirjani *et al.*, 2020; Du *et al.*, 2021). This may be related to the implementation of a policy in Beijing, China that limits two children since 2016. The restriction on having 2 children certainly has a positive impact on women's reproductive health. Pregnancy >3 (multipara) is associated with a decrease in the function of the reproductive organs so that it can cause complications in pregnancy and childbirth (Manuaba, 2010). In Iran, with the emphasis on social distancing, restrictions on human activities, such as movement between countries and reduction of factory operations, air quality improvement is maximized due to reduced air pollution (Seo *et al.*, 2020). Exposure to air pollution during pregnancy has been associated with the risk of premature birth (Bekkar *et al.*, 2020). Breathing polluted air increases toxic chemicals in the blood and suppresses the immune system. Changes during the COVID-19 pandemic have a positive influence on the health of pregnant women, especially the incidence of preterm birth. We found that the proportion of pregnancies was greater in Beijing, China in women aged ≥35 years in the COVID-19 infected cohort. This will certainly increase the risk of premature birth even though this study has a small effect. In addition, it was found that the prevalence of cesarean section and premature rupture of membranes was higher during the COVID-19 pandemic compared to women before the pandemic (48.16% vs. 45.80%, p=0.040 for cesarean section, and 33.59% vs. 30.72). %; p=0.008 for premature rupture of membranes). The safe gestational age is the age of 20-34 years. At the age of more than 35 years, the function of the reproductive organs has decreased, the quality of egg cells has decreased, and various diseases have begun to appear that reduce the mother's ability so that there is a possibility of complications in pregnancy and childbirth (Prawirohardjo, 2010).

Premature birth can be influenced by multifactorial. According to Du *et al* (2021) that The COVID-19 pandemic has an impact on the mental health of pregnant women including stress, worry, and anxiety during pregnancy frequently. mental health disorders associated with intrauterine growth restriction and/or preterm delivery (Hobel, Goldstein and Barrett, 2008; Kirchengast and Hartmann, 2021). Anxiety in pregnant women during the covid pandemic caused by, First, pregnant women feel worried about the lack of accessibility to health services. In addition, pregnant women are worried about the possible risk of contracting COVID-19 in the hospital environment, so some cancel routine check-up visits at the hospital (Mertz *et al.*, 2019)(Ding *et al.*, 2021). Second, pregnant women have increased anxiety about the health status of their family members during the pandemic than ever before (Corbett *et al.*, 2020). Third, COVID-19 has an impact on increasing the risk of unemployment, low-income status, and family conflicts (Sholihah *et al.*, 2022). Fourth, social response due to panic when listening to information from online media (Kusumawati, 2019) (Nasrullah *et al.*, 2021). Stress during pregnancy is associated with various complications such as premature birth, miscarriage, low birth weight, and impaired fetal growth and development. This is due to the activation of the HPA axis due to stressors experienced by the mother during pregnancy. The fetus may be "stressed" by increased concentrations of CRH in fetal plasma, amniotic fluid, and maternal plasma compared to levels in

normal pregnancy (Novitasari, 2013) Increased production of CRH by the placenta plays a role in increasing the production of fetal cortisol to produce positive feedback so that the placenta produces more CRH. CRH stimulates the fetal adrenal glands to make steroids. CRH directly or indirectly will increase androgen secretion, namely dehydroepiandrosterone sulfate (DHEAS) through the release of pituitary adrenocorticotropin (ACTH). Androgens are converted to estrogens in the placenta. Increased estrogen production will change the ratio of estrogen to progesterone and stimulate uterine contractions. This causes rupture of membranes and premature birth and low birth weight (Cunningham., 2014). As well as, The results Martinez-Perez *et al* (2021) also stated that patients infected with COVID 19 experienced 2.12 times premature rupture of membranes compared to those who were not infected (OR 2.12 (95% CI 1.32-3.36)).

Research suggests the association between pre-existing comorbidities may magnify the effect of SARS-CoV-2 infection on adverse outcomes (Du *et al.*, 2021; Karasek *et al.*, 2021). Association for COVID-19-infected individuals diagnosed with comorbidities compared with those without a comorbid diagnosis of having very preterm delivery (aOR 2.6, 95% CI [2.1, 3.1]), preterm delivery (aOR 2.0, 95% CI [1.8, 2.2]). The results of research Stubblefield *et al*. (2021) reported that pregnant women with SARS-CoV-2 infection had a higher prevalence of preeclampsia than pregnant women who were not infected (7.7% vs 4.3%; OR=1.84; 95% CI 1.004-3, 36). There is an increase in mothers diagnosed with COVID-19 with preeclampsia between 33 and 37 weeks of gestation, especially in nulliparas (Papageorghiou *et al.*, 2021). ACE2 receptors on villous cytotrophoblasts in the placenta may be associated with an increased risk of preeclampsia (Coronado-Arroyo JC, Concepcio´n-Zavaleta MJ, Zavaleta-Gutie´ rrez FE, 2020). ACE2 plays an important role in the regulation of arterial pressure and expresses itself in excess in placental tissues, including the syncytiotrophoblast, cytotrophoblast, endothelium, and villous vascular smooth muscle (Stubblefield *et al.*, 2021). Intrauterine infection caused by COVID-19 can alter ACE2 expression, triggering a state of preeclampsia (Coronado-Arroyo JC, Concepcio´n-Zavaleta MJ, Zavaleta-Gutie´ rrez FE, 2020; Shanes *et al.*, 2020). Therefore, infection with SARS-CoV-2 is suspected as one of the causes of severe preeclampsia, thereby increasing the risk of preterm birth (Cosma *et al.*, 2021). Preeclampsia causes decreased placental blood flow to the fetus. As a result, the supply of nutrients and oxygen for the needs of the fetus is hampered, so the fetus grows slowly in birth and eventually gives birth prematurely (Wei *et al.*, 2021). In contrast, the results of the study of Bloise *et al.* (2021) reported that ACE2 did not change so it did not cause complications of preeclampsia. Thus, the results do not indicate that pregnancies complicated by preeclampsia have an increased risk of SARS-CoV-2. Identification of the prevalence of preeclampsia in pregnant women with SARS-CoV-2 infection is very important to provide appropriate obstetric management and provide critical interventions needed by pregnant women during the COVID-19 pandemic (Karimi-Zarchi *et al.*, 2021)

CONCLUSION

Pregnant women infected with SARS-CoV-2 have an increased risk of preterm delivery compared to pregnant women who are not infected with COVID-19. However, the cause of this is not known. The importance of improving pregnancy management during the COVID-19 pandemic to reduce the negative impact on both pregnant women and their babies. The provision of services during the pandemic is urgently needed in monitoring the risk of pregnancy outcomes during the COVID-19 pandemic and vaccination

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