American Journal of Pediatrics
2025, Vol. 11, No. 2, pp. 49-54
https://doi.org/10.11648/j.ajp.20251102.13

Research Article

The Impact of COVID-19 Infection on the Incident of Preterm Birth

I Made Rian Amerta Dananjaya*, I Made Kardana

Pediatric Medical Faculty, Udayana University, Pediatric Departement Ngoerah Hospital, Denpasar, Indonesia

Abstract

Corona virus disease (COVID-19) has been a global pandemic since 2019, impacting various aspects of life, including maternal and neonatal health. Pregnant women diagnosed with COVID-19 are at a higher risk of obstetric complications, such as preterm birth. This study aims to analyze the relationship between COVID-19 infection in pregnant women and the incidence of preterm birth. This study employed a cross-sectional design using medical record data from the Neonatology division at Ngoerah Hospital Denpasar since February 2021 until Desember 2022. Samples were collected using consecutive sampling, including 167 subjects: 67 babies born to mothers with infection of COVID-19 and 100 babies born to mothers without COVID-19. Bivariate analysis was performed using the Chi-Square test, while multivariate analysis employed logistic regression to control for confounding variables. For the result, preterm birth was observed in 29.9% of babies born to COVID-19-positive mothers, compared to 13% of those born to COVID-19-negative mothers, with a significant association (p = 0.008; PR = 2.27; 95% CI 1.301-6.233). Multivariate analysis showed that mothers with COVID-19 had a 2.78 times higher risk of delivering preterm (p = 0.014; 95% CI 1.232-6.301) COVID-19 infection in pregnant women has a significant association with the incidence of preterm birth.

Keywords

COVID-19, Pregnancy, Preterm Birth

1. Introduction

Corona Virus Disease 19 (COVID-19) is a disease that has caused a global pandemic. Cases of pneumonia associated with COVID-19 have been occurring since 2019. COVID-19 has posed significant challenges for all groups, affecting nearly every aspect of life. One example is the high risk of complications during childbirth for mothers infected with COVID-19.

The number of COVID-19 cases continues to rise, including cases among pregnant women. According to data from the Centers for Disease Control and Prevention (CDC) in the United States, out of a total of 326,335 women of reproductive age who tested positive for SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus 2), 91,412 (28%) were women with infections, and among them, 8,207 (9%) were pregnant women [1]. In Indonesia, as of January 2023, there have been 6,728,676 confirmed COVID-19 cases, but data on pregnant women affected by COVID-19 remains limited [2]. According to a report from the Indonesian Society of Obstetrics and Gynecology collected from April 2020 to April 2021, there were 536 confirmed cases of COVID-19 in pregnant

*Corresponding author: rianamerta@gmail.com (I Made Rian Amerta Dananjaya)

Received: 13 March 2025; **Accepted:** 24 March 2025; **Published:** 10 April 2025

women. Among these cases, 51.9% were asymptomatic, 72% occurred at a gestational age of over 37 weeks, 4.5% required intensive care in the ICU, and 3% resulted in death. Between April 2020 and July 2021, Ngoerah Hospital in Denpasar treated 225 COVID-19 patients who were pregnant women. Additionally, in Buleleng Regency, 53 pregnant women were hospitalized due to COVID-19 from January to June 2020.

Pregnant women are more susceptible to COVID-19 due to changes in their immune system compared to non-pregnant women. COVID-19 in pregnant women has been associated with various obstetric complications, such as fetal distress, cesarean section (C-section) delivery, and preterm birth. The mechanisms behind these complications remain under debate, with vertical transmission through the uterus (transplacental route) being proposed as a possible pathway, leading to increased decidual arteriopathy and vascular perfusion disorders [3].

The causes of preterm birth can be categorized into maternal, fetal, and placental factors. Maternal factors include preeclampsia, maternal infections such as toxoplasmosis, rubella, cytomegalovirus, and herpes simplex (TORCH), as well as COVID-19 infection. Other maternal conditions such as severe anemia, diabetes, a history of preterm birth in previous pregnancies, multiple pregnancies, psychosocial factors (stress, depression, lack of social support), unhealthy lifestyle habits (smoking, alcohol consumption, or drug use), extreme maternal age (<20 years or >35 years), and low socioeconomic status leading to inadequate maternal nutrition can also contribute to preterm birth [4].

Fetal factors contributing to preterm birth include umbilical cord entanglement, congenital malformations (such as anencephaly or gastroschisis), intrauterine growth restriction (IUGR), fetal infections (cytomegalovirus (CMV), toxoplasmosis, or rubella), polyhydramnios, and oligohydramnios. Umbilical cord factors include implantation abnormalities, umbilical cord blood flow disturbances, infections and inflammation of the umbilical cord, and structural abnormalities such as a short, long, or atrophic umbilical cord [5].

Preterm birth has a significant impact on a baby's growth and development. Premature infants often have low birth weights and immature organ functions, making them vulnerable to various complications that can affect their development and have long-term consequences into adulthood [6]. Among the many factors causing preterm birth, maternal infections—particularly COVID-19—have gained special attention. Therefore, this study aims to investigate the relationship between preterm birth and COVID-19 infection in pregnant women.

2. Materials and Methods

This study was a cross-sectional design, which is a non-experimental epidemiological study aimed at identifying the relationship between independent and dependent variables without intervention at a single point in time, using medical record data registered in the Neonatology division.

The sample for this study was selected using a consecutive sampling technique, where samples were collected sequentially until the required sample size was met, from February 2021 to December 2022. The sample size was determined using the prevalence estimation with minimum required sample size of 96 subjects meeting the inclusion and exclusion criteria. The inclusion criteria for this study were neonates born to mothers infected with COVID-19 at Ngoerah Hospital, Denpasar, Bali, and neonates born within the expected gestational period. The exclusion criteria included missing or unregistered medical records, multiple pregnancies, mothers with preeclampsia, and mothers with antepartum bleeding. Multiple pregnancy is a condition in which a mother carries two or more fetuses in a single pregnancy. Preeclampsia is a hypertensive disorder during pregnancy characterized by elevated blood pressure and proteinuria or signs of organ dysfunction occurring after 20 weeks of gestation in women with previously normal blood pressure. Antepartum bleeding refers to bleeding from the genital tract occurring after 20 weeks of gestation until before the onset of labor.

The independent variable in this study was maternal COVID-19 infection, defined as pregnant women who tested positive for SARS-CoV-2 via PCR testing. The dependent variable was preterm birth, defined as birth occurring at a gestational age of <37 weeks. The confounding variables included: Maternal age defined as the age of the mother during pregnancy. Parity defined as the number of previous pregnancies resulting in live births, categorized into parity 1 (primipara) and parity >1 (multipara). History of premature rupture of membranes (PROM) defined as the rupture of fetal membranes with amniotic fluid leakage through the vagina in the absence of labor contractions, as determined by the attending obstetrician.

The data were analyzed using computer software to describe the characteristics of the study variables. The variables were presented in numerical values (n) and percentages (%). The Chi-square test was used for bivariate analysis between categorical independent and dependent variables. Multivariate analysis using logistic regression was performed to control for confounding variables if they were significantly associated with the dependent variable. The significance level (α) was set at a p-value < 0.05.

This study was submitted to the Research and Development Unit of the Faculty of Medicine, Udayana University/ Ngoerah Hospital and has obtained ethical approval (No: 0735/UN14.2.2.VII.14/LT/2024) and research permission (No: DP.04.03/D.XVII.2.2.216779/ 2025) from Ngoerah Hospital.

3. Results

The study initially included a total of 193 subjects; however, 26 subjects were excluded for not meeting the inclusion cri-

teria (2 cases of multiple pregnancies, 20 cases of preeclampsia, and 4 cases of antepartum bleeding). As a result, the final sample consisted of 167 subjects who met the inclusion criteria.

Among the 167 eligible subjects, 97 were male (55.1%) and 70 were female (39.8%). The maternal age ranged from 20 to 45 years, with a mean age of 30.1 ± 4.4 years. Regarding parity, 55 subjects (33.3%) were primiparous (parity 1), while 112 subjects (66.7%) were multiparous (parity >1). A comprehensive summary of the general characteristics is presented in Table 1.

Table 1. *General characteristics.*

	Neonates born to mothers infected with COVID-19 (N=67 (%))	**Neonate born to a mother who is not infected with COVID-19 (N=100 (%))**
Gender		
Male	43 (44.3)	54 (55.7)
Female	24 (34.3)	46 (65.7)
Age of mother (years)		
< 20 and > 35	10 (35.7)	18 (64.3)
20-35	57 (41)	82 (59)
Parity		
Parity I	27 (49.1)	28 (50.9)
Parity > 1	40 (35.7)	72 (64.3)
Gestational age		
< 37 weeks	20 (60.6)	13 (39.4)
> 37 weeks	47 (35.1)	87 (35.3)
Premature rupture of membrrane	22 (64.7)	12 (35.3)

The relationship between neonates born to mothers infected with COVID-19 and premature birth can be seen in Table 2.

Table 2. *The relationship between neonates born to mothers infected with COVID-19 and premature birth.*

	Neonates born to mothers infected with COVID-19 (N=67 (%))	**Neonate born to a mother who is not infected with COVID-19 (N=100 (%))**	**P**	**PR**	**CI 95%**
Neonates born to mothers infected with COVID-19	20	47	0.008	2.27	1.301-6.233
Neonate born to a mother who is not infected with COVID-19	13	87			

Multivariate analysis was conducted using an etiological framework with logistic regression analysis. All independent variables were included in the multivariate analysis. The results of the multivariate analysis can be seen in Table 3.

Table 3. Multivariate analysis of factors influencing preterm birth.

Research variables	Adjusted OR (exp B)	P	95% CI	
			minimum	maximum
Neonates born to mothers infected with COVID-19	2.786	0.014	1.232	6.301
Mother's age	1.985	0.203	0.691	5.707
Parity	1.776	0.193	0.748	4.215
History of PROM	0.962	0.936	0.371	2.489

4. Discussion

The COVID-19 pandemic has posed significant challenges to global health, including its impact on pregnancy and childbirth. In pregnant women, COVID-19 infection has been associated with an increased risk of obstetric complications such as preterm birth, low birth weight (LBW), and the need for medical interventions, including cesarean delivery [7].

Several mechanisms have been proposed to explain these risks. COVID-19 infection in pregnant women can cause systemic inflammation, contributing to changes in the intrauterine environment, such as placental insufficiency and fetal hypoxia. Additionally, maternal stress due to illness may trigger stress hormone activity, such as cortisol, which has been shown to have negative effects on fetal growth [8].

In this study, the majority of infants born to mothers with COVID-19 were male. This phenomenon has also been reported in several other studies. One hypothesis suggests that male fetuses may be more vulnerable to intrauterine stress caused by maternal infection. Research indicates that male fetuses exhibit a weaker immune response to inflammation, making them more susceptible to changes in the uterine environment [8]. However, further analysis is required to confirm the validity of these findings.

Maternal age is an important factor influencing pregnancy outcomes. In the general population, maternal age below 20 years and above 34 years is often associated with an increased risk of preterm birth. In younger mothers, this is often due to an immature endometrium and the body's limited ability to adapt to pregnancy [9]. On the other hand, older mothers face higher risks of complications such as preeclampsia, gestational diabetes, and placental insufficiency, all of which directly impact fetal birth weight [10]. However, in this study, no significant association was found between maternal age and preterm birth. This discrepancy may be due to several factors. First, previous pregnancy history and the quality of antenatal care may help mitigate age-related risks. Second, differences in research methods and study populations may also influence findings. For example, a study conducted at Dr. Soekardjo Tasikmalaya Hospital by Elsa Nur et al. (2021) also found no significant relationship between maternal age and LBW, suggesting that socioeconomic factors, nutrition, and antenatal care quality may be more dominant factors in certain populations [11].

Parity, the number of previous pregnancies, also affects pregnancy outcomes. Studies indicate that primiparity (first pregnancy) is associated with an increased risk of preterm birth due to complications such as preeclampsia and prolonged labor. Additionally, grand multiparity (≥5 pregnancies) carries a higher risk of preterm birth, primarily due to placental insufficiency and the maternal depletion of nutritional reserves from repeated pregnancies [10]. However, in this study, parity did not show a significant association with preterm birth. This may be explained by the control of other risk factors, such as antepartum hemorrhage and preeclampsia, which were excluded from the study. Good antenatal care may also reduce the negative impact of parity on pregnancy outcomes.

Premature rupture of membranes (PROM), particularly at gestational age <37 weeks (preterm premature rupture of membranes/PPROM), is one of the leading causes of preterm birth. Studies indicate that up to 40% of preterm births are caused by PPROM [12]. Premature rupture of membranes (PROM) increases the risk of preterm birth because labor is usually induced or occurs spontaneously within 24–48 hours to prevent intrauterine infections such as chorioamnionitis. Premature rupture of membranes (PROM) is also associated with preterm birth due to intrauterine infections, which can affect fetal growth. Infections such as chorioamnionitis trigger the release of pro-inflammatory cytokines, which can damage the placenta and impair fetal growth. However, the findings of this study should consider other variables such as the duration of PROM and maternal infection status, which may influence the results.

COVID-19 infection in pregnant women triggers the release of pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, creating a systemic inflammatory environment. This inflammation directly impacts placental function and the intrauterine environment. The release of pro-inflammatory cytokines can

disrupt uteroplacental blood flow, leading to placental insufficiency, which affects the supply of nutrients and oxygen to the fetus. A study by Schoenmakers et al. (2021) found that placentas from mothers with COVID-19 exhibited signs of inflammation and thrombosis [13]. Maternal hypoxia due to COVID-19 infection, particularly in severe cases, can lead to fetal hypoxia, which may accelerate early labor as a compensatory response to protect the fetus from further damage [8].

Increased uterine activity leading to early labor in mothers with COVID-19 is primarily driven by local inflammatory responses, medical complications, and medical interventions. Regarding local inflammatory responses, cytokines such as IL-6 stimulate prostaglandin production in the uterus, which accelerates labor. Complications such as preeclampsia or acute respiratory distress syndrome (ARDS) in mothers often necessitate early delivery to protect both mother and fetus. A study by Knight et al. (2020) found that 60% of preterm births in mothers with COVID-19 resulted from medical decisions aimed at reducing the risk of complications [7].

A study by Juan et al. (2020) found that infants born to mothers with COVID-19 had a higher risk of low birth weight (LBW), with a prevalence of 15–20%. This study highlighted that intrauterine growth restriction (IUGR) due to placental insufficiency caused by COVID-19 reduces optimal nutrient supply for fetal growth. Fetuses exposed to long-term intrauterine hypoxia tend to have lower birth weights due to growth impairment [14].

Consistent with the findings of Juan et al. (2020), this study also found a significant association between maternal COVID-19 infection and preterm birth. This strengthens the evidence that COVID-19 significantly impacts pregnancy outcomes, whether through inflammatory mechanisms, hypoxia, or other medical complications [15]. The findings of this study are consistent with global literature indicating a significant relationship between COVID-19 and preterm birth. This provides further support for understanding the impact of COVID-19 on pregnancy across different populations.

5. Study Limitations

This study has several limitations. Certain confounding factors were not analyzed, such as previous pregnancy history, history of antenatal care visits, socioeconomic status, and umbilical cord factors, including implantation abnormalities, umbilical cord attachment disorders, umbilical cord blood flow disturbances, infections and inflammation of the umbilical cord, and structural abnormalities such as a short, long, or atrophic umbilical cord. These factors were not included in the analysis and may have influenced the results. Additionally, there was no data on the severity of COVID-19 in pregnant women, which might have impacted the study findings. Furthermore, as this study was conducted in a single hospital, there is a potential for selection bias.

6. Conclusions

COVID-19 infection in pregnant women is significantly associated with the incidence of preterm birth.

Abbreviations

COVID-19	Corona Virus Disease
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus 2
TORCH	Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes Simplex
IUGR	Intrauterine Growth Restriction
CMV	Cytomegalovirus
PCR	Polymerase Chain Reaction Test
LBW	Low Birth Weight
PPROM	Preterm Premature Rupture of Membranes

Acknowledgments

We thank Departement of Pediatrics medical school of Udayana University, Ngoerah Hospital.

Author Contributions

I Made Kardana: Conceptualization, Resources, Methodology, Validation, supervision, writing-review & editing

I Made Rian Amerta Dananjaya: Data curation, Formal Analysis, Investigation, software, visualization, writing-original draft

Funding

This work is not supported by any external funding.

Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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