

## Complication on Premature Rupture of Membrane in Intrapartum Mother Infected with COVID-19: Meta-Analysis

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### ABSTRACT

**Background:** Pregnant women and fetuses are populations that are at high risk of being infected with the virus. COVID-19 in pregnant women is considered a risk factor for causing complications in pregnancy such as premature rupture of membranes. This study aims to analyze complications of premature rupture of membranes in mothers infected with COVID-19.

**Subjects and Method:** This was a systematic review and meta-analysis. Article searches were conducted using electronic databases such as Google Scholar, PubMed and Science Direct. The articles used are articles published from 2020-2022. Keywords to search for articles were: "COVID-19" OR "2019-nCoV" OR "novel coronavirus" OR "SARS-CoV-2" OR "coronavirus 2" AND "premature rupture of membrane" OR "prelabour rupture of membrane" AND "pregnancy." The inclusion criteria used were full text articles in English with a cohort study design, multivariate analysis with Adjusted Odds Ratios (aOR), research subjects were pregnant women, intervention was COVID-19 infection, comparison was not infected with COVID-19, the outcome of the study was premature rupture of membranes. The results of the search for articles were included in the PRISMA diagram and analyzed using the Review Manager 5.3 application.

**Results:** A total of 9 cohort study articles from the United States, Bangladesh, China, India, Mexico, Romania, and Spain were selected for systematic review and meta-analysis. The results showed that pregnant women infected with COVID-19 had a risk of complications of premature rupture of membranes as much as 2.26 times compared to pregnant women who were not infected with COVID-19 and the results were statistically significant (aOR = 2.26; 95% CI = 1.33 to 3.82; p = 0.002).

**Conclusion:** Pregnant women infected with COVID-19 increase the risk of premature rupture of membranes.

**Keywords:** COVID-19, pregnancy, premature rupture of membranes, meta-analysis

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### BACKGROUND

In December 2019 in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found which causes acute respiratory tract disorders called corona-virus disease 2019 (Dashraath et al.,

2020). COVID-19 has infected most of the vulnerable populations around the world with a high rate of transmission, causing a global health crisis (Lopez et al., 2021). As of 7 February 2022, a total of 16,282,334 confirmed cases with 77,031 deaths globally

were documented by involving at least 25 countries (WHO, 2022).

The spread of COVID-19 has raised concerns about intrauterine transmission from mother to fetus in pregnant women (WHO, 2020). Pregnant women and their fetuses are among the population at high risk of being infected with COVID-19 (Amorita and Syahriarti, 2021). In pregnant women, there are physiological changes in the body and the mother's immunity which causes an increase in susceptibility to infectious diseases. Changes in cell-mediated immunity contribute to the increased susceptibility of pregnant women to infection by intracellular organisms such as viruses (Zaigham and Andersson, 2020). Experts report that pregnant women are susceptible to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which can increase the risk of harm to pregnant women (Xu et al., 2020).

Pregnant women infected with COVID-19 have a 15.8% greater chance of experiencing complications of premature rupture of membranes compared to pregnant women who are not infected with COVID-19 (Pérez et al., 2021). COVID-19 infection in pregnancy causes an increased risk of pregnancy complications such as premature rupture of membranes (PROM) by 8% (Akhtar et al., 2020).

The results showed that the risk of premature rupture of membranes in pregnant women during the COVID-19 pandemic was higher than before the COVID-19 pandemic (Du et al., 2021). Many studies have shown that pregnant women who test positive for COVID-19 are more at risk of developing pregnancy complications such as premature rupture of membranes (Kasuga et al., 2020).

During pregnancy there are physiological changes that result in a partial decrease (Budiarti et al., 2021). Physiolo-

gical and immunological changes that occur as a normal component of pregnancy can have systemic effects that increase the risk of obstetric complications from respiratory infections in pregnant women (Nawsherman et al., 2020).

Premature rupture of membranes (PROM) or often called premature rupture of membranes (PROM) is defined as the rupture of the membranes before delivery (Purwaningtyas and Prameswari, 2017). Premature rupture of membranes is an important problem in obstetrics which can also cause infection in mothers and babies and can increase morbidity and mortality in mothers and babies (Legawati and Riyanti, 2018).

Large population-based studies are needed to estimate the risk of complications of premature rupture of membranes in pregnant women infected with COVID-19. On this basis, researchers are interested in conducting research using a systematic review and meta-analysis approach to investigate relevant epidemiological studies to assess the risk of complications of premature rupture of membranes in pregnant women with COVID-19.

## SUBJECTS AND METHOD

### 1. Study Design

This study was conducted using a systematic review and meta-analysis. Article searches were conducted using electronic databases such as Google Scholar, PubMed and Science Direct. The articles used are articles published from 2020-2022. The keywords to search for articles were: "COVID-19" OR "2019-nCoV" OR "novel coronavirus" OR "SARS-CoV-2" OR "coronavirus 2" AND "premature rupture of membrane" OR "prelabour rupture of membrane" AND "pregnancy." The search results for articles are listed in the PRISMA

diagram and analyzed using the Review Manager 5.3 application.

## 2. Inclusion Criteria

Full paper article with a cohort study, multivariate analysis with adjusted Odd Ratio (aOR) to measure the estimated effect, research subjects are pregnant women, comparisons are pregnant women who are not infected with COVID-19, the outcome of the study is premature rupture of membranes.

## 3. Exclusion Criteria

Articles published in languages other than English, statistical results reported in the form of bivariate analysis, articles before 2020.

## 4. Operational Definition of Variables

In formulating research problems PICO is used. Population= pregnant women. Intervention= COVID-19 infection. Comparison= not infected with COVID-19. The end result= premature rupture of membranes.

**SARS-CoV-2 or COVID-19** is a virus that attacks the respiratory system which can cause mild disorders of the respiratory system, severe lung infections and even death. Corona virus is a new type of corona virus that is transmitted to humans.

**Pregnancy** is the fertilization of spermatozoa and ovum followed by nidation or implantation. Fertilization until the birth of a baby in a normal pregnancy is 40 weeks.

**Premature Rupture of Membrane (PROM)** is the premature rupture of the membranes without any signs of labor and after 1 hour, the delivery process is still not followed properly.

## 5. Study Instruments

Quality assessment in this study uses the Cohort Study Checklist published by the Critical Appraisal Skills Program (CASP, 2018).

## 6. Data Analysis

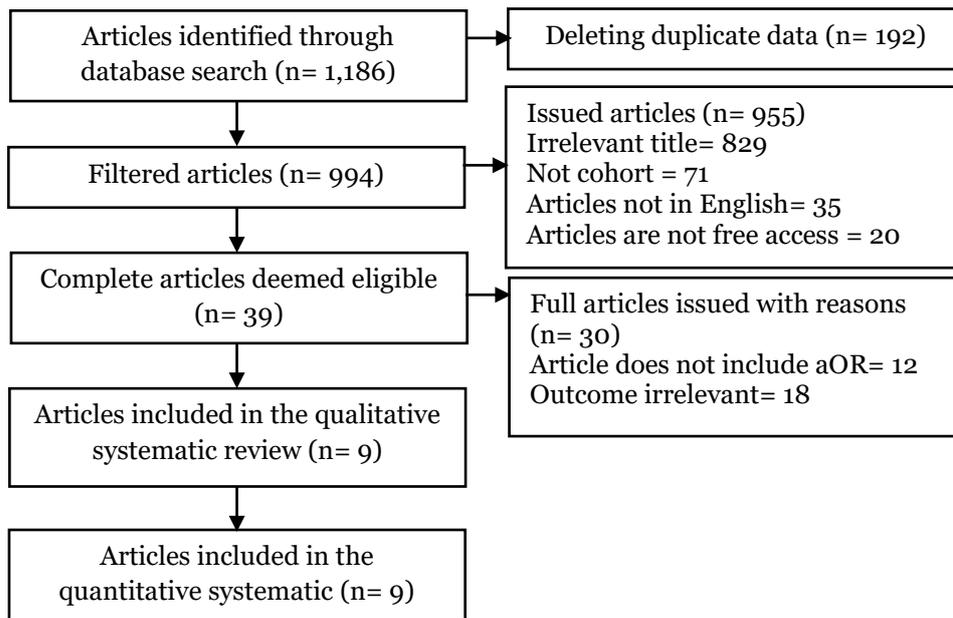
Data analysis was carried out with the help of computer software, namely the review manager application (RevMan 5.3). Forest plots and Funnel plots will be used to determine the size of the effect of the effect of night shift work on hypertension and sleep patterns in factory workers and also to determine the heterogeneity of the data. Fixed effect model is used for homogeneous data, while random effect is used for heterogeneous data across sectors.

## RESULTS

The article search process is carried out by searching electronic databases through Google Scholar, PubMed and Science Direct. Article search results are listed in the PRISMA diagram in Figure 1.

A total of 1,186 articles were identified after removing duplications, 994 articles were screened. Of these, 39 articles were assessed for eligibility. The following reasons are given for full-text articles that meet the exclusion criteria: Articles report only (ORs) resulting from bivariate analysis. The article reports on outcomes other than premature rupture of membranes, the effect size used is aRR/aHR, not aOR.

A total of 9 articles that met the quality assessment were included in the quantitative synthesis using a meta-analysis. Research from primary studies related to complications of premature rupture of membranes in mothers infected with COVID-19 can be seen in Figure 2 consisting of 9 articles from 3 studies from the Asian continent (Bangladesh, China, and India), 4 European continents (Romania and Spain) and 2 studies from the Americas (United States and Mexico).



**Figure 1. PRISMA Flowchart**



**Figure 2. Map of study area**

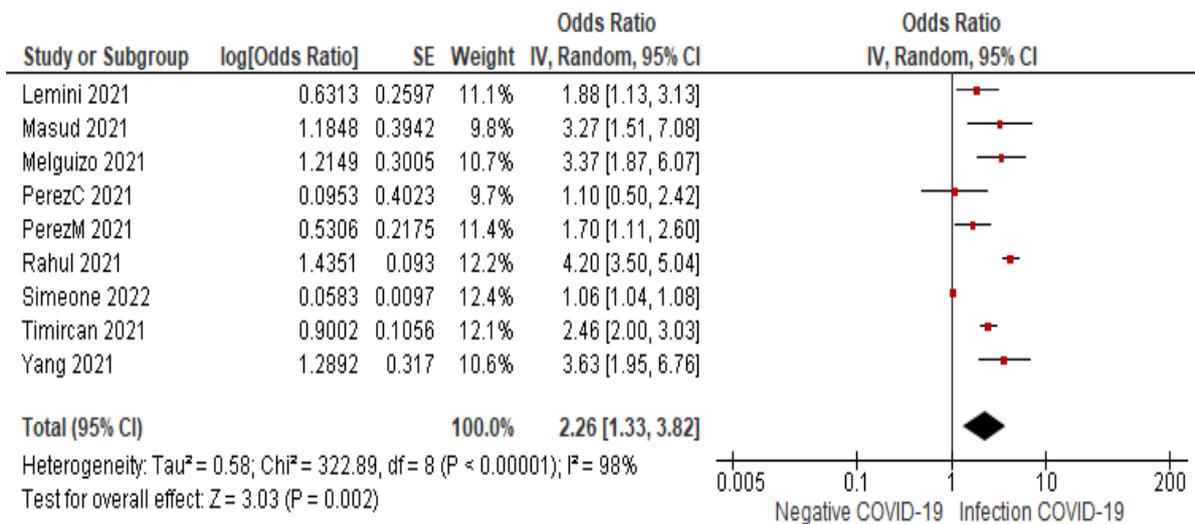
**Table 1. Quality Assessment of Cohort Studies**

No	Checklist of Questions	Publication (Author and Year)								
		Lemini <i>et al.</i> (2021)	Masud <i>et al.</i> (2021)	Melguiz o <i>et al.</i> (2021)	Perez <i>et</i> <i>al.</i> (2021)	Perez <i>et</i> <i>al.</i> (2021)	Rahul <i>et al.</i> (2021)	Simeon e <i>et al.</i> (2022)	Timirca n <i>et al.</i> (2021)	Yang <i>et</i> <i>al.</i> (2020)
1.	Does the cohort study clearly address the research problem?	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
3.	Is exposure to COVID-19 accurately measured to prevent or minimize bias?	2	2	2	2	2	2	2	2	2
4.	Is the outcome (premature rupture of membranes) measured accurately to minimize bias?	2	2	2	2	2	2	2	2	2
5.	Did the researcher identify all confounding factors? Did the researcher account for confounding factors in the design and/or analysis?	2	2	2	2	2	2	2	2	2
6.	Was the follow-up to the subject sufficiently complete and complete?	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
8.	How precise are the results?	2	2	2	2	2	2	2	2	2
9.	Are the results reliable?	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
11.	Do the research results match the available evidence?	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
<b>Total</b>		<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>	<b>24</b>

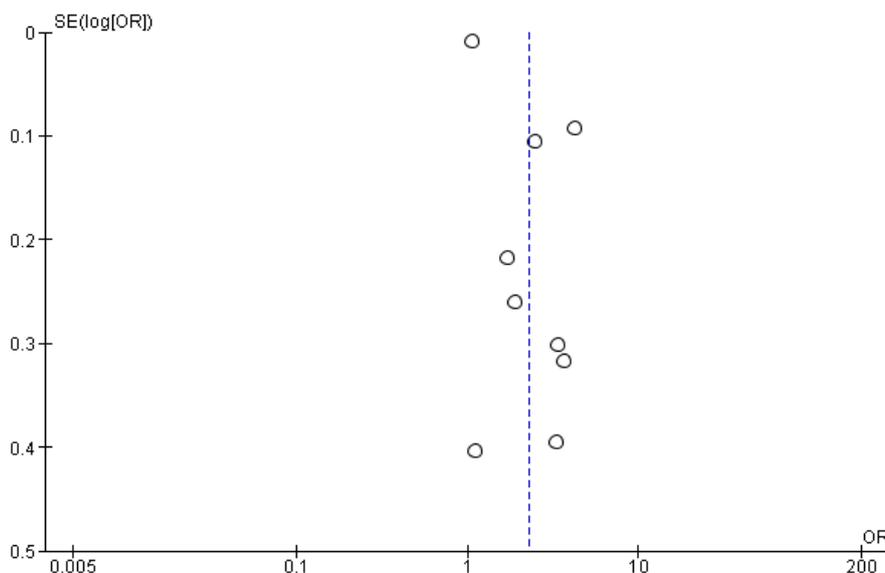
**Note:****2: Yes; 1: Can't tell; 0: No**

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

Author (Year)	Country	Study Design	Sample Size		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR (CI 95%)
			Total	Sample					
Lemini et al. (2021)	Spanish	Prospective Cohort	604	174	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	1.88 (1.13 to 3.11)
Masud et al. (2021)	Bangladesh	Cohort	210	70	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	3.27 (1.51 to 7.07)
Melguizo et al. (2021)	Spanish	Prospective Cohort	2,954	1,347	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	3.37 (1.87 to 6.05)
Perez et al. (2021)	Mexico	Retrospective Cohort	240	70	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	1.10 (0.50 to 3.10)
Perez et al. (2021)	Spanish	Prospective Cohort	1009	246	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	1.70 (1.11 to 2.57)
Rahul et al (2021)	India	Prospective Cohort	4293	3213	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	4.20 (3.50 to 4.90)
Simeone et al. (2022)	United States of America	Cohort	604,193	15,083	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	1.06 (1.04 to 1.08)
Timircan et al. (2021)	romania	Prospective Cohort	1039	101	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	2.46 (2.00 to 3.19)
Yang et al. (2020)	China	Retrospective Cohort	11,078	65	Pregnant mother	Positive for COVID-19	Negative COVID-19	Premature rupture of membranes	3.63 (1.95 to 6.76)



**Figure 3. Forest Plot Complications of Premature Rupture of Amniotic Mothers Infected with COVID-19**



**Figure 4. Funnel plot of premature rupture of membranes in pregnant women infected with COVID-19**

Table 1. shows the assessment of study quality using the study cohort checklist published by CASP (Critical Appraisal Skills Program). Table 2 shows a description of the primary studies included in the meta-analysis. Based on the Forest plot in Figure 3, it shows that pregnant women infected with COVID-19 have a risk of complications of premature rupture of membranes as much as 2.26 times com-

pared to pregnant women who are not infected with COVID-19 and the results are statistically significant (aOR= 2.26; 95% CI= 1.33 to 3.82; p=0.002). The heterogeneity of the research data showed I<sup>2</sup>= 98% so that the distribution of the data was declared heterogeneous and the synthesis of the average effect estimate from all studies was carried out using the Random Effect Model (REM) approach.

Based on Figure 4, the Funnel plot shows that there is no publication bias which is indicated by symmetrical results between the right and left plots.

## DISCUSSION

Coronavirus (COVID-19) caused by the SARS-CoV-2 virus, is highly contagious and is currently spreading rapidly throughout the world, causing worldwide morbidity and mortality since its first appearance in Wuhan, China in December 2019 (Wang et al., 2020). Many studies have focused on patients infected with COVID-19 but details of outcomes regarding COVID-19 infected pregnancies are scarce. The results of maternal-neonatal data and the potential for vertical transmission of COVID-19 in pregnant women are still very limited (Chen et al., 2020). According to data from other viral diseases such as influenza, SARS and MERS, pregnant women are more susceptible to viral infections than the general population (Yu et al., 2020).

Preliminary studies show that physiological and immunological changes during pregnancy may increase the risk of pregnant women being infected with respiratory viruses such as influenza (Wang et al., 2020). Pregnant women are more susceptible to infection, cause more severe complications and have a higher mortality rate compared to the non-pregnant population (Yu et al., 2020).

This meta-analysis study investigated the risk of complications of premature rupture of membranes in pregnant women infected with COVID-19. The independent variable is COVID-19 infection and the dependent variable is premature rupture of membranes. The subjects in this study were pregnant women. The intervention is COVID-19 infection with a comparison not infected with COVID-19. This research is important to investigate because COVID-19

infection in pregnant women will affect pregnancy. Research that discusses premature rupture of membranes is considered important because premature rupture of membranes is a problem that increases infant mortality, both in developing and developed countries. This meta-analysis involved 625,620 pregnant women from nine cohort studies conducted in the United States, Bangladesh, China, India, Mexico, Romania and Spain. This study was identified from 2020 to 2022 with each aOR statistical outcome. This study showed that pregnant women infected with COVID-19 had a risk of complications of premature rupture of membranes as much as 2.26 times compared to pregnant women who were not infected with COVID-19 and the results were statistically significant (aOR= 2.26; 95% CI=1.33 to 3.82; p =0.002). This meta-analysis study provides evidence that pregnant women infected with COVID-19 are at greater risk of premature rupture of membranes. In this study, there was no publication bias indicated by the Funnel plot with a symmetrical distribution of the plot.

The results of this study are similar to the results that reported 36.8% premature rupture of membranes in pregnant women who were positive for COVID-19 from a high COVID-19 prevalence area in the UK (Antoun et al., 2020). A systematic review consisting of 33 studies described a 15.2% incidence rate of premature rupture of membranes in pregnant women infected with COVID-19 (Elshafeey et al. 2020). Previous studies have also shown that the SARS respiratory syndrome and Middle East (Mers) infection are associated with the incidence of premature amniosis, intensive care treatment for newborns, and even perinatal mortality (Schwartz et al, 2020).

Ruptured membranes in labor are generally caused by uterine contractions

and repeated stretching. The amniotic membrane ruptures because in certain areas there are biochemical changes that cause the inferior amniotic membrane to be fragile (Panjaitan and Tarigan, 2018). There is a balance between synthesis and degradation of the extracellular matrix. Changes in the structure, number of cells, and collagen catabolism cause the activity of collagen to change and cause the membranes to rupture. Risk factors for premature rupture of membranes are reduced ascorbic acid as a component of collagen as well as copper and ascorbic acid deficiency which results in the growth of abnormal structures (Alexander et al., 2021). Collagen degradation is mediated by matrix metalloproteinases (MMPs) which are inhibited by tissue-specific inhibitors and protease inhibitors (TIMP-1). Approaching the time of delivery, the balance between MMP and TIMP-1 leads to proteolytic degradation of the extracellular matrix and fetal membranes. The activity of this proteolytic degradation increases before delivery. In periodontitis where there is an increase in MMP, premature rupture of membranes tends to occur (Supriyatno, 2020).

The rupture of the amniotic membrane is related to the biochemical processes that occur in the amnion extracellular matrix collagen, cotion and apoptosis of fetal membranes (Pradana and Surya, 2020). The fetal membranes and decidua react to stimuli such as infection and stretching of the amniotic membrane by producing mediators such as prostaglandins, cytokinins, and protein hormones that stimulate matrix degrading enzyme activity.

The amniotic membrane is very strong in early pregnancy. In the third trimester, the membranes break easily. Weakening of the strength of the amniotic membranes has to do with uterine enlarge-

ment, uterine contractions and fetal movement. In the last trimester, there are biochemical changes in the amniotic membrane (Deviana et al., 2021). Rupture of membranes at term pregnancy is a physiological thing. In addition, the factors that most often cause premature rupture of membranes are external factors such as viral infections (Barokah and Agustina, 2021). Physiological and immunological changes during pregnancy can increase the risk of pregnant women being infected with the virus (Wang et al., 2020). Pregnant women are more susceptible to infection, cause more severe complications and have a higher mortality rate than the non-pregnant population. More than 100 million pregnant women worldwide are at high risk of being infected with COVID-19 (Yu et al., 2020).

Based on this, it is in line with the results of this study that mothers infected with COVID-19 have a risk of complications of premature rupture of membranes as much as 2.26 times compared to pregnant women who are not infected with COVID-19.

The incidence of premature rupture of membranes has become a global concern for maternal health, neonatal mortality, and is the most common cause of morbidity and mortality in neonates worldwide, both short and long term. Because the immunological immaturity of neonates makes them susceptible to infection, vertical transmission is a particularly worrying complication of viral infection occurring during pregnancy (Huleihel et al, 2004). The first report on obstetric outcomes for pregnant women with COVID-19 revealed a significant increase in the incidence of premature rupture of membranes (Knight et al., 2020).

The limitations of this study are that there is a language bias because it only uses

English articles, and a search bias because it only uses three databases.

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#### AUTHORS CONTRIBUTION

Hepti Widia Ningsih as the main researcher who chose the topic, conducted a search for data collection in this study. Bhisma Murti and Uki Retno Budihastuti conducted data analysis and reviewed research documents.

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This study is self-funded.

#### CONFLICT OF INTEREST

There is no conflict of interest in this study.

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