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# Analysis of pregnant women coagulopathy biomarker factors on covid-19 infection in the fetal

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# Abstract

**Background:** Of the 62 babies born, 20 (32 percent) were infected with covid-19, the average age of premature birth. **Purpose:** To analyze the relationship between coagulopathy biomarker factors in pregnant women infected with covid-19 and the incidence of covid-19 infection in newborns.

**Method:** Cross-sectional with the retrospective method. The inclusion criteria were babies born from mothers infected with covid-19, newborns aged 0-28 days. The number of samples is 145. The sampling technique is purposive sampling. The data collection instrument is observation sheet. Data were collected for 12 weeks from hospital medical records. Analysis chi-square test data and independent t test.

**Results:** Participants were young adults as much as 86 (61.4 percent). Gestational age based delivery was premature as much as 55 (37.9 percent). The gestational age range at delivery is 28 weeks to 41 weeks, gestational age when infected with covid-19 trimester III with gestational age range from 29 weeks to 41 weeks. Coagulopathy biomarker values experienced There were 140 abnormal D-dimers with a range of >500 (96.6 percent). All babies are born of mothers infected with covid-19, less than 0 days after birth, 39 were infected (27.1 percent) were infected with covid-19 at <0 days. D-dimer coagulopathy biomarkers exist significant relationship (p-value < 0.05) against infection of newborns from the inside Womb.

**Conclusion:** Coagulopathy biomarker factors in pregnant women are related to the occurrence of babies infected with covid-19. Where the incidence of infection in newborns has occurred since zero days born.

### Keywords: Infant; D-dimer; Infection; Covid-19.

### INTRODUCTION

Illness Coronavirus 2019 or (covid-19) is an infectious disease caused by Severe Acute Respiratory Syndrome 2 (SARS-CoV-2). SARS-CoV-2 is a new type of virus coronavirus which has never been found in humans (Ministry of Health of the Republic of Indonesia, 2020). The Government of the Republic of Indonesia has recorded 4,178,164 positive cases of covid-19. Covid-19 has resulted in 139,682 deaths and 3,953,519 patients have recovered from this condition. Indonesia is the country with the highest number of cumulative cases, ranked 20th (World Health Organization, 2021).

The reproductive tract infection working group of the Indonesian Society of Obstetrics & Gynecology (POGI) reported that there were 536 cases of covid-19 that occurred in pregnant women. According to data, 51.9% of them were pregnant women who showed no symptoms and did not use a respirator. 72% of pregnant women are over 37 weeks old, 3% die from covid-19 and 4.5% are treated in the ICU (Indonesian Society of Obstetrics & Gynecology, 2021).

The Indonesian Obstetrics and Gynecology Association (POGI) reported that there were 536 cases of covid-19 that occurred in pregnant women

(Indonesian Society of Obstetrics & Gynecology, 2021). The results of deliveries in Surakarta stated that of the 62 babies born, 20 babies (32%) were infected with covid-19 (Amorita & Syahriarti, 2021). Data regarding the transmission of covid-19 infection from mother to neonate during pregnancy is still limited to date (Fitriyani, 2021). There are three potential patterns of transmission of covid-19 infection in newborns, namely through the trans placental route, through the birth canal during labor and the puerperium during breastfeeding (Fitriyani, 2021). Other information states that the transmission of the covid-19 virus to newborns can be through splashes of saliva during the delivery process (Hadiyanto, 2021). This condition occurs when newborns are infected through mothers, caregivers, and birth attendants infected with SARS-CoV-2 (Elenga, Wandji, Siban, Nacher, & Demar, 2022). The risk of transmitting covid-19 infection to newborns is an issue that needs attention.

Transmission of the SARS-CoV-2 virus to infants can occur during pregnancy through the placenta (Auriti, De Rose, Santisi, Martini, Piersigilli, Bersani, Ronchetti, & Caforio, 2021). The SARS-CoV-2 virus initiates infection in infected infants through increasing the angiotensin-2 (ACE2) converting enzyme receptor protein in the placenta which is expressed in the presence of ACE2 on the surface of the placental membrane and cells (Jing, Run-Qian, Hao-Ran, Hao-Ran, Ya-Bin, Yang, & Fei, 2020). So it is stated that the transmission of SARS-CoV-2 from mothers who are infected with covid-19 is via trans placenta (Jing et al., 2020). Other information stating that SARS-CoV infection can occur via transplacental basiscoexpression from transmembrane protease serine 2 (TMPRSS2) which initiates the entry of SARS-CoV-2 through the placental cell membrane and replicates the virus (Beeraka, Sadhu, Madhunapantula, Pragada, Svistunov, Nikolenko, Mikhaleva, & Aliev, 2020), The entry of the SARS-CoV-2 virus causes lesions in the placenta and causes fetal and maternal vascular dysfunction as well as signs of inflammation (Adams, Rekawek. Vahanian. Akerman. Hernandez. Rapkiewicz, Ragolia, Sicuranza, Chavez, Vintzileos, & Khullar, 2021) If the viral load is checked in pregnant women and fetuses, the virus will be found to be very

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Department Keperawatan Poltekkes Kemenkes Jakarta I Corresponding author: E-mail: yani\_manru@yahoo.co.id high (Patberg et al., 2021). Viruses examined in the mother through the blood or nasopharynx will describe a high increase and are at risk of transmission via delivery (Patberg et al., 2021).

Pregnant women are one of the population groups that are vulnerable to being infected with covid-19. Physiological changes in an effort to adapt to intrauterine fetal growth continue until the mature gestational age. These changes include an increase in the volume of fluid in the body so that the tidal volume of the heart increases as well as blood concentration which tends to experience heme concentration. Likewise, blood composition also increases, including clotting factors in anticipation of bleeding during pregnancy and childbirth. One of these changes requires preventive measures against the transmission of covid-19 to the fetus as well as prevention of symptoms that may occur in pregnant women when exposed to covid-19 (Schwartz, 2020). This is due to physiological changes in the body systems of pregnant women which tend to cause a decrease in body resistance (Auriti et al., 2021; Wastnedge, Reynolds, Van Boeckel, Stock, Denison, Maybin, & Critchley, 2021) Previous information suggests vertical transmission in the third trimester of pregnancy (Nokhostin, Saffarieh, & Sharami, 2020). The impact is growth retardation in the uterus (10%) and in the last trimester of pregnancy fetal tachycardia and fetal distress occur (Elenga et al., 2022; Nurdamayanti, & Riafisari, 2020).

There are various risks that can occur to the fetus and newborn. Fetal distress and intrauterine death are the impacts of Covid-19 on the fetus (Rumfabe, Herlina, & Pande, 2020). Of the 31 babies who were exposed to Covid-19, the most frequent symptoms were fever 17 (54.8%), shortness of breath 11 (35.4%), vomiting or food intolerance 11 (35.4%), cough 9 (29%), tachycardia 5 (16.1%), rhinorrhea 3 (9.7%), pneumonia 3 (9.7ARDS%), skin rash 2 (6.5%), diarrhea 1 (3, 2%), and cyanosis 1 (3.2%) %) (Rampengan, Rompis, & Umboh, 2021).

Based on the examination of coagulopathy and inflammatory biomarkers, it has been shown that there is a process of damage to the placenta. However, how much the value of these biomarkers is related to the transmission of infection to newborns needs to be

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studied. So that the vertical transmission of SARS-CoV-2 from mother to fetus, including the relationship of coagulopathy biomarkers to transmission of infection based on the magnitude of the biomarkers that cause transmission of infection to the fetus until the baby is born (Vivanti, Vauloup-Fellous, Prevot, Zupan, Suffee, & Cao, 2020). So the purpose of this study was to explore the relationship between coagulopathy biomarkers in pregnant women infected with covid-19 and the transmission of covid-19 infection in newborns.

# **RESEARCH METHOD**

Research design cross sectional using a retrospective approach, that is aims to determine the relationship of coagulopathy biomarkers of pregnant women infected with covid-19 in the perinatal period to newborns. The population in this study were new babies born to mothers who were infected with covid-19 and had been taken to the PCR swab were hospitalized 2021. The sample inclusion criteria are babies born to mothers infected with covid-19, newborns 0-28 days old. The exclusion criteria were babies with birth defects and complications. Determination of the number of samples using the

Slovin formula, in order to obtain a total of 145. The sampling technique is purposive sampling, choose by characteristics inclusion criteria (Masturoh & Anggita, 2018).

Data collection was carried out for 12 weeks, starting from March-May 2022. Data was collected based on participant status taken from medical records. The data collection instrument was an observation sheet containing: 1) maternal data: demographics (maternal age, gestational age at delivery and gestational age at exposure to Covid-19). coagulopathy biomarker value, namely D-dimer). The research hypothesis is that there is a relationship between coagulopathy biomarkers against covid-19 infection in newborns. Data analysis using SPSS for windows. The statistical test used was the chi square test for data that categorical, and test Mann Whitney for numeric-categorical data. Statistical test results test the hypothesis using the p-value with a significance level of 0.05 (Dahlan, 2011).

This research was carried out after obtaining a proper ethical certificate from the committee Ethics Poltekkes Kemekes Jakarta 1. Statement of proper written ethics with number 010/KEPK/II/2022.

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# **RESEARCH RESULTS**

Variables	Results (n/%)	(Mean ±SD) (Range)	p-value
Age Teenager (17-25 years) Young adults (26-35 years) Adult (36-45 years)	33/22.7 89/61.4 23/15.9	(29.87±5.8)(17-42)	
<b>Gestational age at birth</b> Premature (<37 week) Enough months (37-41 week)	55/37.9 90/62.1	(37.52±2.1)(28-41)	
<b>Gestational Age</b> First trimester (0-13 week) Second trimester (14-28 week) Third trimester (29-41 week)	0/0 0/0 145/100	(37.45±2.111)(28-41)	
Newborn Baby Infected Not infected	40/27.6 105/72.4		
Time of exposure to covid-19 infection <0 day >0 day	144/99.3 1/0.7		
<b>Category D-dimer</b> Normal (<500 ng/ml) Abnormal (>500 ng/ml)	5/3.4 140/96.6	(3006.86±3006.88)(0-20000)	0.027
Analysis of Inflammation biomarkers Leukosit NRL(Neutrofil Limfosit Rasio) CRP (C-Reactive Protein)		(12,48±6,30)(3,8-41,1) (7,65±7,46)(1,30-52,3) (3,50±5,42)(0,10-41,09)	0.211 0.361 0.837

#### Table 1. Characteristics of Respondents (N=145)

From table 1. above it can be seen that the participants were young adults as much as 89 (61.4%). Gestational age based on preterm labor was 55 (37.9%). The gestational age range at delivery is 28 weeks to 41 weeks. All participants were of gestational age when infected with covid-19 in the third trimester with a gestational age range of 29 weeks to 41 weeks. The majority of newborn baby were not infected 105 (72.4%) and time of exposure to covid-19 infection <0 day 144 (99.3%). Almost all pregnant women with coagulopathy biomarker values had abnormal D-dimers with a range of >500 in 140 (96.6%). P-value of 0.027 (p-value < 0.05) indicates that there is a significant relationship between D-dimer coagulopathy biomarkers and infection of newborns from the womb. The results of the analysis of inflammatory biomarkers found no significant relationship between leukocytes, NRL and CRP on exposure to covid-19 infection in infants from inside the womb because of the p-value > 0.05.

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Variable -	Newborn Baby		n valuo	ΛP	95% C I	
	Infected (n=40)	not infected (n=105)	p-value	UK	lower	upper
Exposure time						
<0 day	39 (97.5%)	105 (100%)	0,276	0,27	0,20	0,35
>0 day	1 (2.5%)	0 (0%)				

Table 2. Time of Exposure to Covid-19 Infection of Newborns (N=145)

The table 2. informs that all babies born to mothers who were infected with covid-19, less than 0 days after birth, were infected as many as 39 (97.5%) were infected with covid-19 at <0 days. Analysis of the relationship between exposure time and infant infection immediately after birth was not significant (p-value > 0.05). Based on an OR of 0.27 with a 95% Cl of 0.20 to 0.35, it means that newborns are born less than zero (0) days, have a 0.27 times chance of experiencing covid-19 infection compared to more than zero (0) days from infected pregnant women.

### DISCUSSION

The gestational age when participants were infected with covid-19 ranged from 29-41 weeks' gestation, with an average gestational age of 37.5 weeks. This incident refers to previous information which explains that there are reports of vertical transmission of covid-19 in the third trimester of pregnancy (Nokhostin, Saffarieh, & Sharami, 2020). The gestational age of participants with covid-19 at delivery was the third trimester (29 weeks-41 weeks), namely pregnancies and preterm labor. Pregnant women without a viral infection are at increased risk of developing thromboembolic complications. This is due to an increase in blood concentration, namely coagulation factors during pregnancy as an effort to adapt to physical conditions (Facciolà, Micali, Visalli, Rullo, Russotto, Laganà, Laganà, Nunnari, & Pietro, 2022).

The average gestational age of mothers with Covid-19 at delivery is the third trimester. The current research is in accordance with what was stated by previous researchers which stated that pregnant women who are infected with covid-19 have a 1.33 times higher risk of giving birth normally compared to pregnant women who are not infected (Widiyanto, Atmojo, Livana, Fajriah, Putri , Nahak, & Anulus,

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Department Keperawatan Poltekkes Kemenkes Jakarta I Corresponding author: E-mail: yani\_manru@yahoo.co.id 2021). The gestational age when the mother was infected with covid-19 ranged from 29-41 weeks' gestation, with an average gestational age of 37.5 weeks. This is also supported by research in Iran where there are reports of vertical transmission of covid-19 in the third trimester of pregnancy (Nokhostin et al., 2020). However, the physiological adaptations that occur in the body of pregnant women have the opportunity to experience preeclampsia and are at high risk of increasing coagulopathy biomarker factors when infected with covid-19 (Koumoutsea, Vivanti, Shehata, Benachi, Le, Celine, Whittle, Snelgrove, & Kinga, 2020).

The coagulopathy biomarker value, namely the Ddimer of mothers who are exposed to covid-19 infection, has a value that tends to be high > 500. In addition, infection biomarkers also tend to increase in pregnant women infected with covid-19. Correlation analysis showed that there was a significant relationship between the incidence of COVID-19 infection in newborns. This is in accordance with a Canadian study of acute progressive coagulopathy that has problems with Covid-19 in full-term pregnant women showing a significant increase in D-dimer (12-17 times the normal value) (Koumoutsea et al., 2020). Pregnant women have a conventional D-dimer value of 0.5 mg/L, because D-dimer tends to increase during pregnancy. This increase in D-dimer levels is most likely caused by continuous coagulation and fibrinolysis during placental development (Hedengran, Andersen, Stender, & Szecsi, 2016).

Inflammatory biomarker values, namely leukocytes, NLR, CRP, mothers who were exposed to covid-19 infection in this study had no relationship to covid-19 infection in newborns, but had abnormalities. The average pregnant woman infected with covid-19 experiences abnormal blood biomarker values such as leukocytes, D-dimer, CRP, and NLR (Koumoutsea et

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al., 2020). Laboratory parameters of increased CRP, NLR, and leukocytosis can help predict the severity of covid-19 (Pribakti, 2020).

Another factor that influences the process of activation of the fibrinolytic system is very quickly concentration the of infection initiated by proinflammatory cytokines such as interleukins (IL). namely IL 1 and six (Levi, Thachil, Iba, & Levy, 2020). The concentration of this cytokine as the main mediator that promotes coagulation activation and thrombin formation is cancer necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-1. This biomarker element can be found in patients who are very severely infected with covid-19 (Levi et al., 2020). The high level of coagulopathy biomarkers reflects the condition of plasma viral load. Previous information suggests that plasma viral load in covid-19 cases is positively correlated with disease severity (Wong, Khong, & Tan, 2021). Where viremia can trigger a cytokine storm with a spike in proinflammatory cytokines, including interferon-y (IFN y), interleukin-2 (IL-2) , IL-6, IL-7, IL-10 (Wong et al., 2021). Production of inflammatory biomarkers that trigger coagulation activation can damage the placenta / placental ischemia.

This is as stated by previous researchers that transplacental transmission of COVID-19 infection through SARS-CoV-2 in neonates is caused by very high immunohistochemistry and viral load resulting in viremia in the mother and infection in the placenta (Vivanti, Vauloup-Fellous, Prevot, Zupan, Suffee, Do Cao, Benachi, & De Luca, 2020). This information requires histological testing of the placenta immediately after birth (Mazur-Bialy, Kołomańska-Bogucka, Tim, & Opławski, 2020). Based on histological examination of the placenta and immunohistochemistry, previous information indicated the presence of placental inflammation. However, the current study has not examined the covid-19 virus in the placenta and as well as histological examination of the placenta.

Study participants at the hospital, where data were collected, had not found any examination of the value of biomarkers as the main mediator of coagulation activation. So that in answering the hypothesis assumptions only refers to the value of coagulopathy biomarkers. However, based on the exploratory results

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Department Keperawatan Poltekkes Kemenkes Jakarta I Corresponding author: E-mail: yani\_manru@yahoo.co.id of previous studies, it can support current findings where there is a significant relationship of coagulopathy biomarkers to newborn infection that has taken place since pregnancy. Thus it can be stated that there is a relationship between coagulopathy biomarkers as a medium that initiates the occurrence of covid-19 infection in infants since in the mother's womb. This is supported by data from research and the results of previous studies.

### CONCLUSION

The demographics of pregnant women who are exposed to covid-19 infection are mostly young adults with all gestational ages in the third trimester and most of the delivery ages are full term. The value of the Coagulopathy Biomarker, namely D-dimer, in pregnant women exposed to covid-19 infection is very high. High coagulopathy biomarkers can be initiated by inflammatory biomarkers.

Newborns (neonates) experience covid-19 infection immediately after birth at zero days. The value of coagulopathy biomarkers is related to exposure to covid-19 infection in infants over time zero day. However, the amount of viral load in the placenta has not yet been identified. So to get certainty of covid-19 infection in newborns is due to coagulopathy biomarkers namely D Dimer need identification of placental histology.

Patient data, namely maternal cervical viral load and placental viral load need to be evaluated so that it can be seen how much influence cervical and placental viral load has on exposure to infection in newborns. Viral load values in newborns when babies are born both spontaneously and by cesarean section need to be studied so that the relationship between maternal viral load values and viral load values in newborns can be known.

Likewise, the value of inflammatory biomarkers has increased from normal values, so it can be assumed that there is a high probability of damage to the placental membrane thereby triggering coagulopathy factor biomarkers, referring to previous findings. Although currently the outbreak of the covid-19 Virus pandemic cases has not increased much but you still need to watch out for the condition of the mother during pregnancy. In addition, it is necessary to

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evaluate pregnant women who have received the covid-19 booster vaccine, considering that pregnant women are one of the vulnerable populations apart from the population with Co-Morbid.

# DECLARATION OF CONFLIC INTEREST

The researcher states that there are no competing financial interests or personal relationships that might affect the completion of the articles presented in this paper.

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