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THE CORRELATION BETWEEN CRP AND D-DIMER LEVELS IN PREGNANT WOMEN WITH CONFIRMED COVID-19 WITH MILD SYMPTOMS AND MODERATE-SEVERE

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ABSTRACT

Pregnant women are considered to be more susceptible to severe COVID-19 respiratory infections due to physiological and anatomical changes. In addition to its impact on cardiac and pulmonary physiology, pregnancy is also characterized by several changes in the immunological profile or biomarkers. Changes in levels of biomarkers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer have been considered as tools to monitor the severity of COVID-19 infection. This study was conducted to explore the specific role of CRP and D-dimer in COVID-19 pregnant patients. This research is an observational analytical study. The number of research samples was 40 samples consisting of 20 pregnant women with mild COVID-19 symptoms and 20 pregnant women with moderate-severe COVID-19 symptoms who were treated at the obstetric emergency care unit (IRDO) Prof. RSUP. Dr. RD Kandou Manado in August 2021. The data were then analyzed using SPSS 25 software for Windows. In the group of pregnant women with mild COVID-19 symptoms, the mean±SD value of CRP levels was 25.69±3.155 and D-Dimer levels were 2.6956±0.42413; while in the group of pregnant women with moderate to severe symptoms of COVID-19, the mean ± SD value of CRP levels was 42.57 ± 2.615 and D-Dimer levels were 12.3481 ± 1.86270. So from this study it was found that maternal CRP and D-Dimer levels were on average lower in pregnant women with mild COVID-19 symptoms than moderate-severe symptoms. There is a significant relationship between maternal serum CRP levels (p=0.001) and maternal serum D-Dimer levels (p=0.000) against Covid-19 pregnant women with mild and moderate-severe symptoms.

1. INTRODUCTION

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2

infection may range from asymptomatic infection to life-threatening sepsis. COVID-19 was firstly found in December 2019 in a group of patients with pneumonia of unknown causes in Wuhan, China [1]. Genetical analysis showed that SARS-CoV-2 is one of the Beta-Corona virus groups, the same as SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV). Although the transmission is still a mystery, SARS-CoV-2 originated from animal reservoirs, potentially from bats. The clinical features of COVID-19 include fever, cough, dyspnea, and fatigue, similar to most acute respiratory tract infections. Currently, there is no specific medication for COVID-19. Antiviral combined with supportive treatments are the main treatment strategy [2].

Due to the physiological and anatomical changes, pregnant women are considered susceptible to severe viral respiratory infection. During the H1N1 influenza pandemic in 2009, in which early treatment with oseltamivir was shown to reduce complication rates, pregnant women developed severe pneumonia in up to 20% of the total cases. Pregnant women are at risk of severe infection, with a potentially harmful maternal and perinatal outcome. These concerns are based on the experience of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome Corona Virus (MERS), caused by coronavirus and led to poor outcomes during pregnancy [4], [5].

Besides its impact on cardiopulmonary physiology, pregnancy is also characterized by several immunological profile changes. During the labor preparation, a pro-inflammatory state occurs with immune cells migrating to the myometrium and pro-inflammatory cytokines in the cervix or peripheral areas. The characteristic of COVID-19 is the excessive release of inflammatory cytokines, a condition in severe cases mimicking the macrophage activating syndrome. Based on the statement above, we conducted this study to determine the correlation between CRP and D-dimer levels in pregnant women with mild and moderate-severe COVID-19.

2. METHOD

This study was an analytical observational study with a cross-sectional design. This study was conducted from August 2021 to February 2022 in the Hospital and IRDO of Obstetrics and Gynecology of RSUP Prof. Dr. R. D. Kandou Manado. The samples were pregnant women with COVID-19. The subjects were selected using consecutive sampling based on the inclusion and exclusion criteria. A total of 20 pregnant women with mild COVID-19 and 20 women with moderate-severe COVID-19 were included.

The inclusion criteria included pregnant women with COVID-19 confirmed by PCR, agreed to participate in the study, and signed informed consent. The exclusion criteria included incomplete examination, patients with secondary infection, venous/arterial thrombosis, malignancy, chronic inflammation, DIC, vasculitis, and patients who are currently consuming blood thinner medication. The collected data were the serum CRP and D-dimer levels of pregnant women with COVID-19 from the laboratory. This study has been approved by the Health Research Ethics Committee.

Data analysis was carried out using a non-parametric test, the Rank-Spearman correlation test, to determine the association hypothesis of two variables. Analysis was conducted using the SPSS version 25 program for windows. A coefficient correlation score of ≤ 0.05 was considered a significant correlation between the two variables.

3. RESULT

This study was conducted on the population of pregnant women in the Hospital and IRDO Obstetrics and Gynecology of RSUP Prof. Dr. R. D. Kandou Manado from August 2021 to February 20222 with a total of 60 subjects. Most pregnant women with mild COVID-19 were within the age group of 21-34 years, namely

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32 subjects (53%). In the moderate-severe group, most pregnant women were within the age group of 21-34 years, namely 12 subjects (20%).

Table 1. Characteristics of the subject.

Characteristic	Mild		Moderate-Severe	
	n	%	n	%
Maternal age				
≤20 years	5	8%	1	2%
21 - 34 years	32	53%	12	20%
≥ 35 years	2	3%	8	13%
Education				
Elementary school	1	2%	1	2%
Junior high-school	0	0%	2	3%
High-school	32	53%	14	23%
Diploma	0	0%	1	2%
Bachelor	6	10%	3	5%
Gravida				
Primigravida	18	30%	5	8%
Multigravida	21	35%	16	27%
Occupation				
Houswife	28	47%	18	30%
Civil servants	1	2%	0	0%
Employee	6	10%	0	0%
Entrepreneur	1	2%	1	2%
Students	1	2%	0	0%
Unemployed	2	3%	2	3%

Table 2. The Distribution of Maternal CRP Levels in Pregnant Women with Mild and Moderate-Severe COVID-19.

Descriptives				
Grup			Statistic	Std. Error
CRP	Mild	Mean	25.69	3.155
		95% Confidence Interval for Mean — Lower Bound	19.30	
		95% Confidence Interval for Mean — Upper Bound	32.08	
		5% Trimmed Mean	25.55	
		Median	24.00	
		Variance	388.324	
		Std. Deviation	19.706	
		Minimum	6	
		Maximum	48	
		Range	42	
		Interquartile Range	42	
		Skewness	.164	.378
		Kurtosis	-1.913	.741
	Moderate-Severe	Mean	42.57	2.615
		95% Confidence Interval for Mean — Lower Bound	37.12	

		Upper Bound	48.03	
	5% Trimmed Mean		44.25	
	Median		48.00	
	Variance		143.657	
	Std. Deviation		11.986	
	Minimum		6	
	Maximum		48	
	Range		42	
	Interquartile Range		0	
	Skewness		-2.099	.501
	Kurtosis		3.562	.972

Table 3 The Distribution of Maternal D-dimer Levels in Pregnant Women with Mild and Moderate-Severe COVID-19.

Descriptives					
Grup				Statistic	Std. Error
D-Dimer	Mild	Mean		2.6956	.42413
		95% Confidence Interval for Mean	Lower Bound	1.8370	
			Upper Bound	3.5542	
		5% Trimmed Mean		2.3212	
		Median		1.7300	
		Variance		7.016	
		Std. Deviation		2.64868	
		Minimum		.50	
		Maximum		13.18	
		Range		12.68	
		Interquartile Range		2.56	
		Skewness		2.418	.378
		Kurtosis		6.549	.741
	Moderate-Severe	Mean		12.3481	1.86270
		95% Confidence Interval for Mean	Lower Bound	8.4626	
			Upper Bound	16.2336	
		5% Trimmed Mean		12.5626	
		Median		19.9000	
		Variance		72.863	
		Std. Deviation		8.53598	
		Minimum		.82	
		Maximum		20.00	
		Range		19.18	
		Interquartile Range		17.71	
		Skewness		-.300	.501
		Kurtosis		-1.937	.972

Table 2 shows the distribution of maternal CRP levels in pregnant women with mild COVID-19 and moderate-severe COVID-19. In pregnant women with mild COVID-19, the mean±SD CRP level was 25.69±3.155, while in the pregnant women with moderate-severe COVID-19, the mean±SD CRP level was 42.57±2.615. The mean maternal CRP levels were lower in pregnant women with mild COVID-19 compared to moderate-severe.

Table 3 shows the distribution of maternal D-dimer levels in pregnant women with mild and moderate-severe

COVID-19. In pregnant women with mild COVID-19, the mean±SD D-dimer level was 2.6956±0.42413, while in pregnant women with moderate-severe COVID-19, the mean±SD D-dimer level was 12.3481±1.86270. The mean maternal D-dimer level in pregnant women with mild COVID-19 was lower than in pregnant women with moderate-severe COVID-19.

Table 4 shows the Mann-Whitney U test analysis, which showed a significant difference between the CRP and D-Dimer levels in pregnant women with mild and moderate-severe COVID-19 (p=0.001 and p=0.000).

Table 4 The Correlation Between CRP & D-Dimer Levels in Pregnant Women With Mild and Moderate-Severe COVID-19.

Test Statistics[a]		
	CRP	D-Dimer
Mann-Whitney U	222.000	136.000
Wilcoxon W	1002.000	916.000
Z	-3.240	-4.249
Asymp. Sig. (2-tailed)	.001	.000

a. Grouping Variable: Grup

4. DISCUSSION

C-reactive protein or CRP is a protein secreted in the liver during inflammation. The production of this acute protein is induced by the action of IL-6 in genes for transcription of CRP during inflammation and/or infection. CRP has pro- and anti-inflammatory properties. This protein plays a role in recognizing and excreting pathogens and dead cells by binding phosphocholine, phospholipid, histone, chromatin, and fibronectin. Due to its acute nature, CRP levels may reflect an inflammation condition more sensitive and specific. The normal level of CRP in an adult is <0.3 mg/L. The presence of at least one comorbid may lead to increased CRP levels to 1 mg/L. An increase of over 10 mg/L tends to reflect viral or bacterial infection. In pregnant women without complications, CRP levels may be increased during the first trimester. This is potentially due to the pregnancy condition, which is often associated with the activation and proliferation of immune cells. This condition may be exacerbated by other stimuli such as smoking exposure, an imbalanced diet, and other diseases like preeclampsia and gestational diabetes mellitus. The highest normal level of CRP in pregnant women is 18 mg/L. One factor leading to such a high level is the adipose tissue in the patient. The higher amount of adipose tissue, the higher risk of the immune response against excessive nutritional conditions across the pregnancy. Another cause of this condition is infection. Chronic, low-grade inflammation is often associated with an increased risk of asthma and allergy in children because high CRP levels may indicate high circulation of immune cells, cytokines, and chemokines that can cross the placenta, affecting multiple phases of growth and development of the baby, including the immune system [6- 8].

In the COVID-19 pandemic situation, CRP has been widely studied as one of the biological markers to determine the severity and prognosis of the patients. The mean CRP level in survivors is 40 mg/L, and this level is increased up to three-folds to 125 mg/L in COVID-19 patients who passed away. Based on the severity of COVID-19 according to the CT scan grading, the increase in CRP occurs gradually. In grade II, the mean CRP level is 11.47 mg/L and in grade III, it is almost 23.40 mg/L. After further sensitivity test, the cut-off of CRP levels considered to be dangerous is ≥ 16.6 mg/L. Besides inflammation, such high CRP levels can also be caused by nosocomial infection; therefore, antibiotics can be considered. In another study in 2020, a similar trend was also seen. The higher the CRP levels, the wider the lung lesion's diameter. In the group with mild COVID-19, the mean CRP level was 1.5 ± 1.56 mg/L with lung tissue damage of 1.23 ± 1.43. In the group with moderate COVID-19, the range of CRP was 16.76 ± 18.38 mg/L with a lesion size of 2.94 ± 1.91. While

in the group with severe COVID-19, the CRP level exceeded 50 mg/L (54.15 ± 1.06 mg/L) with a lesion size of 9.15 ± 1.20. Treatment should be fast and appropriate to avoid complications such as cardiovascular complications, acute respiratory distress syndrome (ARDS), and death [9- 12].

D-dimer is an end-product after a cleavage of the blood clot. An important note in the treatment of COVID-19 is to prevent subsequent complications such as disseminated intravascular coagulation (DIC), which could lead to death. In healthy adults, the normal level is <0.5 mg/L. Higher levels of D-dimer may be present in several conditions such as pregnancy, malignancy, smoking history, history of surgery, and autoimmune disorders. In a 2019 study in RSUP Cipto Mangunkusumo, the average increase of D-dimer in the first trimester was 0.58 ± 0.36 mg/L; in the second trimester, 0.83 ± 0.46; and in the third trimester, 1.16 ± 0.57 mg/L. Increased coagulation cascade since the first trimester can be caused by thromboplastin released by the placenta. This substrate induces a coagulation cascade by activating factor VII. In addition, the pregnancy process also alters the homeostasis of coagulation and fibrinolysis process due to increased fibrinogen, factor VII, factor VIII, X, von Willebrand, and decreased protein S [13], [14].

Besides CRP, D-dimer levels in patients with COVID-19 are often associated with poor prognosis and clinical outcomes. In deceased COVID-19 patients, there is an increased serum D-dimer level causing fibrin degradation and prolonged prothrombin time, leading to DIC. D-dimer level of >1 ug/L is one of the mortality predictors in patients not-influenced by gender and age. The D-dimer levels also vary according to the severity of COVID-19. In patients with mild COVID-19, D-dimer level is still under 0.5 mg/L. In patients with moderate COVID-19, the level may reach the normal cut-off with a range of 0.35 ± 0.25 mg/L. The highest increase is seen in severe COVID-19, reaching over 3 (3.15 ± 3.31 mg/L). In another study, D-dimer level over 1 mg/L in pregnant or nonpregnant individuals was not associated with poor prognosis, and antithrombotic such as enoxaparin can reduce the incidence of thromboembolic events. Another study reported that D-dimer level of ≥ 3 ug/mL is an indication of anti-heparin administration to prevent sepsis and reduce the risk of further coagulation dysfunction, especially in the alveoli, which may lead to death [9], [15-17].

5. CONCLUSION

There is a significant correlation between maternal serum CRP levels in pregnant women with mild and moderate-severe COVID-19. There is a significant correlation between maternal serum D-dimer levels in pregnant women with mild and moderate-severe COVID-19.

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