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Comparison of D-Dimer Values in Pregnant Women with COVID-19, Preeclampsia and Normal Pregnancy at H. Adam Malik Hospital Medan

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Abstract

Background: Preeclampsia (PE) has been linked to a hypercoagulation state that can be characterized by an increase in D-dimer in the third trimester compared to a normal pregnancy. One of the markers of coagulation abnormalities in hospitalized patients with COVID-19 is with increased levels of D-dimer. The determination of the role of D-dimer levels in pregnancy was impaired due to a substantial increase in D-dimer levels throughout gestational age, and poor standardization of commercial tests available for D-dimers. **Aim:** Comparing the level of D-Dimer in pregnant women infected with Covid-19, preeclampsia and normal pregnant women. **Method:** Analytical research with *case control* method that compares the D-dimer levels of pregnant women with COVID-19 confirmed, preeclampsia, and normal pregnant women who gave birth at H. Adam Malik Medan Hospital with total of 81 subject. **Results:** Of the 81 study subjects, the pregnant women are mostly aged 20-35 years old with 19 subjects (70.4%) normal pregnant women, 24 subjects (88.9%) pregnant women with COVID-19, 16 subjects (59.3%) pregnant women with PE. The parity status of pregnant women is mostly multigravida with 16 subjects (59.3%) normal pregnant women and 17 subjects (63%) pregnant women with PE, 12 subjects (44.4%) pregnant women with COVID-19 are mostly secundigravida. The RT-PCR / Rapid Antigen of pregnant women is mostly resulted negative with 27 subjects (100%) normal pregnant women and 27 subjects (100%) pregnant women with PE, 27 subjects (100%) pregnant women with COVID-19 resulted positive. Urinal examination in the preeclampsia group showed the results of 12 subjects (44.4%) with +3. No urinal examination was carried out in the normal and COVID-19 groups. The average D-dimer in the normal pregnant women group was 1063.37±769.56, the group of pregnant women with COVID-19 1399.22±1136.63, and the group of pregnant women with Preeclampsia 1753.52±1210.63. Kruskal Willis test found a value of $p = 0.116$ ($p>0.05$). **Conclusion:** There was no significant difference in D-dimer levels among the group of normal pregnant women, pregnant women with COVID-19, and pregnant women with preeclampsia.

Keywords: D-dimer, preeclampsia, COVID-19

I. INTRODUCTION

Preeclampsia (PE) has been associated with an even more pronounced hypercoagulable state than in normal pregnancy. Multiple microthrombi usually form in placentas of women with PE and exacerbate tissue ischemia due to failure of spiral artery remodeling. It has been recognized that ischemic placenta releases circulating factors into maternal circulation that cause endothelial dysfunction, oxidative stress, and a worsened inflammatory response.[1]

Hansen et al study, showed that a statistically significant increase in D-dimer was found from first to second trimester ($p < 0.0001$) and from second to third trimester ($p < 0.0001$).[2] During first trimester, 14.78% of uncomplicated pregnant women had concentrations above 0.5 mg/L, which is conventional diagnostic threshold for thromboembolism in nonpregnant women according to reagent manufacturer's recommendations. In second and third trimesters, respectively, 70.82% and 95.94% of uncomplicated pregnant women had concentrations above 0.5 mg/L. Statistical analysis showed differences in D-dimer concentrations between gestational periods ($p < 0.05$).[3]

Coagulation abnormalities are increasingly recognized in hospitalized patients with COVID-19, including increased D-dimer, increased fibrinogen, and increased prothrombin time. D-dimer abnormalities in patients with COVID-19 are associated with increased risk of critical illness and death.[4] Koumoutsea et al. reported two cases of pregnancy with COVID-19 and demonstrated increase in D-dimer levels 17 times above normal

upper limit in pregnancy in the first case and 12 times the above normal upper limit in pregnancy in second case.[5]

Manolov V et al, found that elevated D-dimer levels were associated with development of preeclampsia in third trimester of pregnancy compared with normal pregnancies. The mean levels of D-Dimer were 634 ± 228 ng/ml, 1426 ± 430 ng/ml, 2067 ± 580 ng/ml in control group, preeclampsia and eclampsia patients, respectively.[6,7] Based on background above, the authors would like to conduct research with title Comparison of D-dimer value in pregnant women with COVID-19, preeclampsia and normal pregnancy at H. Adam Malik Hospital Medan.

II. RESEARCH METHODOLOGY

This is analytic study with case control approach at Department of Obstetrics and Gynecology, Faculty of Medicine, University of North Sumatra, H. Adam Malik Hospital, Medan. This research was conducted from March 2021 until sample size was met. Study sample was pregnant women with confirmed COVID-19, preeclampsia and normal pregnant women who gave birth at H. Adam Malik General Hospital, Medan, which were taken using non-probability sampling, which is a consecutive sampling technique.

The inclusion criteria of this study were patient with complete data examination of D-dimer, RT-PCR/Rapid Antigen data, pregnant women who have been diagnosed with preeclampsia (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg in twice measurements with proteinuria $\geq$300 mg/24hr or protein/creatinine ratio $\geq$ 0.3 or dipstick reading 1+). While the exclusion criteria were pregnant women with venous thrombosis, DIC, myocardial infarction, infection, sepsis, cancer, and postoperative stroke, bleeding.

Data will be collected and analyzed using statistical software. The data will be analyzed descriptively to evaluted frequency distribution based on characteristics. Data on a categorical scale will be displayed in percentage values while data on a numerical scale will be displayed in mean and standard deviation value. Then it will be analyzed inferentially to see difference of mean D-dimer in both groups. Inferential analysis begins with normality test, if data is normally distributed, independent t test will be used, whereas if data are not normally distributed, Mann Whitney test will be used.

III. RESULTS

The study data consisted of primary data for normal pregnant women group and secondary data from medical records for pregnant patients with COVID-19 and preeclampsia group. Both primary and secondary data consist of patient identity (name, age, parity, gestational age), results of physical examination (blood pressure) and results of laboratory tests, namely D-dimer levels, proteinuria on urinalysis, ultrasound examination and results of PCR or rapid antigen.

Table 1. Distribution of research subject characteristics

Variable	Group		
	Normal (n, %)	COVID (n, %)	Preeclamsia (n, %)
Age (years old)			
< 20	3 (11,1%)	0 (0%)	1 (3,7%)
20-35	19 (70,4%)	24 (88,9%)	16 (59,3%)
> 35	5 (18,5%)	3 (11,1%)	10 (37,0%)
Parity			
Primigravida	7 (25,9%)	7 (25,9%)	3 (11,1%)
Secundigravida	4 (14,8%)	12 (44,4%)	7 (25,9%)
Multigravida	16 (59,3%)	8 (29,6%)	17 (63,0%)
RT-PCR/Rapid Antigen			
Positive	0 (0%)	27 (100%)	0 (0%)
Negative	27 (100%)	0 (0%)	27 (100%)
Urinalysis			
Not examined	27 (100%)	27 (100%)	0 (0%)
+1	0 (0%)	0 (0%)	9 (33,3%)
+2	0 (0%)	0 (0%)	6 (22,2%)
+3	0 (0%)	0 (0%)	12 (44,4%)
Total	27 (100%)	27 (100%)	27 (100%)

After examining D-dimer on all research samples, it was found that mean D-Dimer in normal group was 1063.37+769.56; COVID group was 1399.22+ 1136.63 and Preeclampsia group was 1753.52+1210.63. Then Kruskal Willis test was carried out to assess comparison of D-dimer levels between groups and found a p value = 0.116 (p> 0.05) which indicated that there was no significant difference in D-dimer levels between

normal, COVID and preeclampsia groups.

Table 2 Comparison of D-dimer levels between groups

Variable	Group			p
	Normal	COVID	Preeclampsia	
D-dimer (ng/L)				0,116*
Mean ± Standar deviation	1063,37 ± 769,56	1399,22 ± 1136,63	1753,52 ± 1210,63	
Median	920	950	1400	
Maximum	>4.000	>4.000	>4.000	
Minimum	154	10	350	

* Kruskal Wallis test

IV. DISCUSSIONS

The exaggerated immune response due to COVID infection causes a systemic cytokine storm that triggers systemic inflammatory response syndrome (SIRS). An exaggerated systemic inflammatory response can lead to systemic endothelial injury (endotheliopathy) and a hypercoagulable state that increases the risk of systemic macrothrombosis and microthrombosis. Manifestations of macrothrombosis can be either venous thromboembolism (eg deep vein thrombosis and pulmonary embolism) or arterial thromboembolism (eg stroke). Microthrombosis plays a role in ARDS process and multi-organ failure.[8]

Plasma fibrin monomer complexes increase with maternal weight and are lower in women with history of chronic hypertension. D-dimer increased with gestational age and maternal weight. In Grossman's study using STA-Liatest test (Diagnostica Stago), median D-Dimer at 11-13 weeks of gestation was 0.31 mg/L. Several previous studies in a small number of cases ranging from 5-350 normal pregnancies at <16 weeks of gestation reported that median D-Dimer varied between 0.1-0.8 mg/L.[9] D-Dimer (DD) was the smallest fragment of fibrin degradation product (FDP); Small protein fragments present in blood after a blood clot are degraded by fibrinolysis. Pregnancy is characterized by a hypercoagulable state, which has been the subject of extensive investigation in the last 2 decades. It has been reported that 78% and 99% to 100% of pregnant women experience higher-than-standard DD in second and third trimesters.[10]

This elevated D-dimer level is most likely due to continued coagulation and fibrinolysis during normal placental development, leading to a high frequency of false-positive results. D-dimers are further elevated during pregnancy. At beginning 13-20 weeks of gestation, more than 25% of pregnant women have D-dimer levels $\geq$ 0.5 mg/L, and by 36-42 weeks of gestation, nearly all pregnant women have values above this conventional threshold. The D-dimer reference interval increases every trimester, especially upper reference limit, which reaches 2.8mg/L during third trimester. D-dimer values peak on first postpartum day, indicating that coagulation and fibrinolytic systems quickly return to their normal states, in accordance with previous findings.[11]

The effectiveness of D-dimer of pulmonary embolism (PE) diagnosis in pregnancy has been investigated, with conflicting results. The DiPEP group (diagnosis of PE in pregnancy) concluded, using D-dimer measurement by ELISA (counted negative if <400 ng/ml) and using Innovance technology (reference range 1-1.3 mg/L), D-Dimer is not useful for PE diagnosis in pregnancy context. However, Van der Pol et al. reported that D-dimer measurements could be used to rule out PE in this group, using a cut-off value > 1000 ng/ml if none of clinical criteria were met, or < 500 ng/ml where there were good clinical signs of deep vein thrombosis; hemoptysis or where PE is most likely diagnosis.[12]

The results of this study are in line with Tanjung et al study who reported that D-dimer levels were higher in preeclamptic women than normal and non-pregnant pregnant women (2,316 ng/ml vs 1,604 ng/ml) and there was no significant difference between two groups. D-dimer levels were also higher in term preeclampsia than in preterm (2,316 ng/ml vs 1,283 ng/ml), and there was no significant difference between two groups.[13] D-dimer is involved in dynamic balance between plasminogen activator (t-P) and uPA) and plasminogen inhibitors (PAI-1) in women with preeclampsia. Therefore, concentration of D-dimer may reflect dynamic changes in both superhypercoagulable state and active fibrinolytic state.[14]

Manolov V et al, found that elevated D-dimer levels were associated with preeclampsia development in third trimester of pregnancy compared with normal pregnancies. Mean D-dimer levels were 634 ± 228 ng/ml, 1426 ± 430 ng/ml, 2067 ± 580 ng/ml in control group, patients with preeclampsia and eclampsia.[6,7] Women with PE had higher D-dimer levels. higher at 30-34 weeks compared with pregnant women who remained normotensive during gestation and this level continued to increase until late gestation.[1] The frequency of high D-dimer levels in case group (preeclampsia) was seen in 14 women (46.67%) whereas in control group

(normotension) was seen in 4 (13.33%) women with p-value of 0.005 and a significant odds ratio of 5.69 and showed a positive relationship between pre-eclampsia and high levels of D-dimer (>0, 5µg/ml). In current study, the D-dimer levels of preeclamptic women compared with normal controls were significantly high which correlates with study conducted by Z Tacoosian et al. Similar results were also reported by Kucukgoz Gulec U et al, where D-dimer level was significantly higher in patients with severe pre-eclampsia compared with mild pre-eclampsia.[15] The meta-analysis by Pinheiro et al showed that elevated plasma D-dimer concentrations were associated with preeclampsia in third trimester of pregnancy compared to normotensive pregnant subjects.[16] The proportion of pregnant women who had elevated d-dimer concentrations in severe gestational hypertension group was significantly higher than in non--severe gestational hypertension group. (89.8% vs. 53.7%; P<0.01). Patients with severe gestational hypertension had significantly higher median d-dimer concentrations compared with non-severe gestational hypertension (median [range], 2.00 mg/L [0.11 to 7.49] vs. 0.71 mg /L [0.09 to 5.39]; P<0.01). Using ROC curve analysis, cut-off value of 1.19 mg/L (ROC area under the curve, 0.71; 95% confidence interval, 0.60 to 0.82; P=0.001) for maternal d-dimer concentration had 63.3% sensitivity and 65.9% specificity for identification of severe gestational hypertension.[17] There was a significant increase in urinary D-dimer levels in patients with severe preeclampsia complicated by acute kidney injury (AKI) compared with patients with normotensive pregnancies (2503 ng/mL vs 236.2 ng/mL; p = 0.001). Based on ROC, cut off urinary D-dimer levels >818 ng/dL with ROC curve being 0.819 (81.9%), showed sensitivity 80%, and specificity 73%. The severity of thrombotic microangiopathy involving renal arteries due to worsening of preeclampsia can be observed clinically as AKI and biochemically as elevated urinary D-dimer levels.[18]

CONCLUSION

There was no significant difference in D-dimer levels among the group of normal pregnant women, pregnant women with COVID-19, and pregnant women with preeclampsia

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