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RESEARCH

The Mean Difference of Hemostatic Factor in Severe Preeclampsia, Eklampsia and Normal Pregnancy

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Abstract

There will be multiple organs changes in preeclampsia and eclampsia. One of them is a change in hemostasis system which is platelet activation, extrinsic and intrinsic cascade reaction and increasing of fibrinolytic activation. This is a cross sectional study conducted at Obstetric and Gynecologic Departement of Medical Faculty of Andalas University/ M Djamil Central Hospital in Padang on July 2014 with the number of samples are 44 persons. Samples are divided into 3 groups: Severe preeclampsia, eclampsia, and normal pregnancy. Platelet, PT,APTT, and D-Dimer counting were conducted and statistic analyzed was done with Anova dan Post Hoc Bonferoni. The more severe pregnancy, the lower platelet count and PT, but the dif- ference is not statistically significant between three groups: severe preeclampsia, eclampsia, and normal pregnancy ($p < 0,05$). Mean of APTT and D-Dimer is statistically significant due to condition of pregnancy. Post Hoc Bonferroni analysis showed a significant difference of APTT mean in the eclampsia, severe pre-eclampsia, and normal pregnancy ($p < 0,05$). D-Dimer Mean shows a significant difference between normal pregnancy, severe preeclampsia, and eclampsia ($p < 0,05$).

Keywords: *Pregnancy condition, severe preeclampsia, eclampsia, normal pregnancy, platelet, PT, APTT, and D-Dimer*

INTRODUCTION

Preeclampsia is defined as a condition of hypertension and proteinuria after 20 weeks' gestation. Preeclampsia is a major pregnancy complication whose incidence is increasing worldwide and is associated with maternal morbidity and mortality. In hypertension during pregnancy, both pure and superimposed preeclampsia and eclampsia are the most dangerous complications. Preeclampsia and eclampsia are the cause of 30-40% of perinatal deaths in Indonesia.[1,2] The incidence of preeclampsia ranges from 5-15% of all pregnancies worldwide. At Cipto Mangunkusumo Hospital in Jakarta 400-500 cases/ 4000-5000 labor per year were found. In Indonesia the incidence ranges from 7-10%. Research conducted at Perjan RSUP Dr. DR. M. Djamil in 1998-2002 found the incidence of preeclampsia of 5.5% and eclampsia of 0.88% of 12,034 deliveries. During the period of January 1, 2005 to December 31, 2007 at BLU RSUP DR. M. Djamil Padang, there were 220 patients with severe preeclampsia (4.99%) and

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47 people (1.07%) out of 4407 deliveries. From the medical records of RSUP Dr. M. Djamil Padang in 2010 there were 113 cases of severe preeclampsia (PEB) with 2 cases of death, 1 case of death due to DIC and 1 case of death due to intracerebral hemorrhage (PIS). Then there were 37 cases diagnosed as eclampsia with 3 cases of death, 2 cases died due to DIC and 1 case died due to PIS. So in 2010 there were 5 cases of death, 3 people died due to DIC and 2 people died due to PIS. From the data above it was found that there were 60% of cases of death due to DIC in preeclampsia and eclampsia in 2010.[3]

The concept that preeclampsia is a protean syndrome is very important to know, where the pathophysiological mechanism can occur in any organ (cardiovascular system, hematology system, kidneys, liver, brain and eyes). Symptoms that appear on each individual are different, some organ systems are more dominantly affected than other organs, for example patients with preeclampsia with blood pressure of 230/ 120 mmHg do not cause any symptoms to the high tension, but in patients with a slight increase in blood would cause eclampsia to occur immediately.[5]

In preeclampsia and eclampsia there will be anatomic and physiological changes in various organs such as the cardiovascular system, hematology system, kidney, liver, and retina. In the hematological and coagulation system, preeclampsia is associated with a coagulation abnormality complex associated with improved function of platelets, activation of the fibrinolytic system, thrombin formation and accelerated hypercoagulation. Meanwhile, women with minimal preeclampsia have some evidence of disturbance or abnormality from the blood clotting cascade.[5,6]

In severe preeclampsia or eclampsia, one of the acute worsening of life to the mother and infant is coagulopathy or disseminated intravascular coagulapathy (DIC). DIC is a hematological disorder in which the clotting process occurs along with the occurrence of bleeding due to fibronolysis. Because in DIC there is progressive coagulopathy and conditions, so early diagnosis, treatment and appropriate management are needed to reduce maternal and infant mortality and other complications.[21]

From the information above it is clear that the science of preeclampsia is highly developed and the incidence of eclampsia and preeclampsia in pregnant women is enormous. Plus from the data which states that the complications of preeclampsia that cause most deaths is DIC which is a disease associated with coagulation factors during pregnancy. For this reason, it is important to know how far hemostasis factors such as platelets, PT, APTT and D-Dimer are affected in patients with severe preeclampsia, eclampsia and in normal pregnancy for early diagnosis.[14]

METHOD

This study is a cross-sectional study conducted in the Obstetrics and Gynecology Section at the Faculty of Medicine, Andalas University/ RS. Dr. M. Djamil Padang during the July 2014

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period until the sample was sufficient for 44 patients as research subjects, the sample was divided into 3 groups, namely severe preeclampsia (PEB), eclampsia and normal pregnancy. Then anamnesis and physical examination were performed to obtain clinical data and diagnoses. Data was recorded in a research form that has been provided, then performed a platelet examination, PT, APTT and D-Dimer. Statistical analysis to assess significance use Anova and Post Hoc Bonferoni on SPSS 18.0 for windows.

RESULTS

Basic Characteristics of Research Subjects

The study was conducted in the Obstetrics and Gynecology Section at the Faculty of Medicine, University of Aceh/ RS. Dr. M. Djamil Padang during the period July 2014 to December 2014 of 44 people as research subjects which were divided into 3 groups namely PEB, eclampsia and normal pregnancy. Furthermore, anamnesis and physical examination are performed to obtain clinical data and diagnoses. Data was recorded in a research form that has been provided, then performed a platelet examination, PT, APTT and D-Dimer. The basic characteristics of the research subjects are shown in the table. 1

Based on table 1 there were no statistically significant differences in the basic characteristics of age, parity and gestational age in the normal pregnancy condition group, PEB, and eclampsia. In the PEB pregnancy group and eclampsia, the mean age was 34.30 ± 5.13 years and 33.75 ± 8.84. In the normal pregnancy group, the parity respondents in primipara and multipara 2-3 were the same (35%). In the PEB and Eclampsia groups it was found that multipara 2-3 parity respondents had the highest respondents (45% and 50%). The gestational age of term pregnancy had quite high respondents in the normal pregnancy group, PEB and eclampsia (95%, 80% and 75%).

Table 1. Basic Characteristics of Research Subjects

		Normal n=20	Severe preeclampsia n=20	Eclampsia n=4	P
Age		30.80±8.04	34.30±5.1	33.75±8.84	0.790
Parity	Primipara	7 (35%)	4 (20%)	1 (25%)	0.125
	Multipara 2-3	7 (35%)	9 (45%)	2 (50%)	
	Multipara ≥4	6 (30%)	7 (35%)	1 (25%)	
Gestational age	Preterm	1 (5%)	2 (20%)	1 (25%)	0.052
	Aterm	19 (95%)	18 (80%)	3 (75%)	

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Platelet Average According to Pregnancy Conditions

Table 2. Platelets average according to pregnancy conditions

Pregnancy Condition	Platelet (ẋ±SD)	*P*
Normal	248408 ± 66565.89	
Severe preeclampsia	215200 ± 74293.59	0.271
Eclampsia	210000 ± 40955.26	

In table. 2, there is a tendency that the more severe the condition of pregnancy, the lower the platelet average; however statistically, the difference was not significant (p > 0,05)

Prothrombin Time (PT) Average According to Pregnancy Conditions

Table. 3. Prothrombin Time (PT) average according to pregnancy conditions

Pregnancy Condition	PT (ẋ±SD)	*P*
Normal	10.70 ± 0.94	
Severe preeclampsia	10.30 ± 0.61	0.233
Eclampsia	10.20 ± 0.88	

Table 3 shows the tendency that the heavier the condition of pregnancy the shorter the mean of PT value; but statistically the difference was not significant (p> 0.05)

Activated Protrombin Time (APTT) Average According to Pregnancy Conditions

Table 4. Activated Prothrombin Time (PT) average according to pregnancy conditions

Pregnancy Condition	APTT (ẋ±SD)	*P*
Normal	32.13 ± 2.48	
Severe preeclampsia	33.48 ± 4.55	0.01
Eklampsia	51.85 ± 30.38	

Based on table 4, it appears that the more severe the pregnancy condition, the longer the mean APTT value, statistically the difference is significant (p <0.05). To see which variables are meaningful, the Posthoc Bonferroni test can be seen which can be seen in table 5.

Table 5. Bonferroni Post Hoc Test

	Normal	Severe preeclampsia	Eclampsia
Normal		1.00	0.001
Severe preeclampsia	1.00		0.002
Eclampsia	0.001	0.002	

The relationship between APTT and new pregnancy conditions was seen to be significant between normal pregnancy and eclampsia, as well as PEB with eclampsia while normal pregnancy with PEB was statistically very insignificant. (p > 0,05).

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D-Dimers Average According to Pregnancy Conditions

Table 6. D-Dimer Average according to pregnancy conditions

Pregnancy Condition	D-Dimer(ẋ±SD)	*P*
Normal	607.77 ± 108,74	
Severe preeclampsia	1903.74 ± 1261.95	0.00
Eclampsia	2413.75 ± 783.85	

Based on Table 6, it looks like the more severe the pregnancy condition, the higher the D-Dimer average, statistically the difference was significant (p < 0,05).

Table 7. Bonferroni Post Hoc Test

	Normal	Severe preeclampsia	Eclampsia
Normal		0.000	0.002
Severe preeclampsia	0.000		0.910
Eclampsia	0.002	0.910	

Based on the table 7 it can be seen that D-Dimer on normal pregnancy and PEB were significant as well as eclampsia while PEB with eclampsia was statistically not significant (p> 0.05).

DISCUSSION

Characteristics of Research Subjects

Characteristics of respondents by age highest obtained at PEB group (34.30 ± 5.13 years), the lowest mean age obtained in normal pregnancy group (30.80 ± 8.04 years), the oldest was 46-year age group obtained Eclampsia and the youngest age was 19 years found in the normal pregnancy group. This was slightly different from the literature which stated that the risk factors for preeclampsia are ≥ 35 years or under 20 years.7 In the normal pregnancy group, the parity respondents in primipara and multipara 2-3 were the same (35%). In the PEB and Eclampsia groups, multipara 2-3 parity was found to have the highest respondents (45% and 50%), this was different from the literature where one of the risk factors for preeclampsia is primigravida.[29] According to gestational age, term pregnancy had quite high respondents in the normal pregnancy group, PEB and eclampsia (95%, 80% and 75%). This is in accordance with the literature where the incidence of preeclampsia is more often found at nearing gestational age.[7]

Strengths and weaknesses of research

This research was cross sectional design where this research can be done with only one time observed, able t see the relationship between variables in the same time and does not take a long time. The limitation of this study was the lack of attention to other factors that can cause

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confusion between disorders of the hemostasis factor due to the process of preeclampsia or due to other diseases, including history or being suffering from vascular disease, kidney disease, liver disease and diabetes mellitus.

Platelet Average According to Pregnancy Conditions

Statistically, there was a tendency that the more severe the condition of pregnancy, the decreasing platelet average decreased, but the difference was not statistically significant (p> 0.05). According to the literature it is stated that the reduction in the number of platelets in preeclampsia is related to endothelial damage in all blood vessels where platelets are used as the primary mechanism of the hemostasis system.[4] The disruption process of hemostasis can cause multiple organ failure, where the activation of massive clotting factors can cause a decrease in the number of platelets and coagulation factors resulting in bleeding/ consumption coagulopathy.[19] In pregnant women with preeclampsia/ eclampsia the platelet count will be lower than normal pregnant women.[7] From this description it can be understood that there was relevance between the severity of the pregnancy condition and the degree of endothelial damage.

Prothrombin Time (PT) Average Value According to pregnancy conditions

Statistically, it seemed that the more severe the condition of pregnancy, the shorter the mean of PT value, but statistically the difference was not significant (p> 0.05). PT is part of the mechanism of secondary hemostasis through the extrinsic pathway in which endothelial damage that continues to occur in patients with preeclampsia will trigger activation of the pathway, at an early stage it will be seen as a tendency to shortened PT values. Activation of the extrinsic pathway is triggered by trauma to the tissue structure or against the walls of blood vessels.[35] From this description it can be understood that there is relevance between the severity of the condition of pregnancy with the degree of endothelial damage and also plays a role as a cause of hypercoagulable state in the hemostasis system.

Activated Protrombin Time (APTT) Value Average According to Pregnancy Conditions

Decreased due to activation of endothelial damage. The mean of APTT value was seen that the more severe the condition of pregnancy the higher the APTT mean value, statistically the difference was significant (p <0.05). Endothelial damage in preeclampsia that occurs will lead to activation of the intrinsic pathway which will be seen as an elongated APTT value. The intrinsic pathway is initiated by trauma to the blood cells themselves, or exposed to collagen walls of the arteries which cause this pathway to activate.[35] APTT values vary according to the severity of the progression of preeclampsia itself and may be prolonged in the final process when the clotting factor drops very low.[17]

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Statistically, there were significant differences in the mean of APTT values in normal pregnancies and eclampsia as well as PEB and eclampsia ($p < 0.05$) but not significant in normal pregnancies and PEB ($p > 0.05$). Based on these data, the APTT value can be used as an indicator of the tendency for eclampsia. This change towards the APTT value tends to be elongated showing that the intrinsic pathway has no role in the hypercoagulable state but has a tendency towards DIC. This change in APTT value can also be used as a reference in getting to know DIC earlier in preeclampsia thus patients will not enter coagulopathy consumption later.

D-Dimer Levels Average According to Pregnancy Conditions

The average value of D-Dimer showed that the more severe the condition of pregnancy, the higher the mean value of D-Dimer, statistically the difference was significant ($p < 0.05$). This increase in D-Dimer was a description of the amount of thrombus that occurred due to the process of fibrinolysis to control thus coagulation activity was not excessive, Plasmin caused degradation of fibrin, increased the amount of dissolved fibrin degradation products, high levels indicate the presence of a lot of thrombus in the blood.[41]

A significant difference was seen in the mean D-Dimer in normal pregnancy and PEB as well as in eclampsia ($p < 0.05$). However, PEB and eclampsia were not significant ($p > 0.05$). This can explain the mechanism of damage in preeclampsia in which tertiary hemostasis due to fibrinolysis played an important role in the response to endothelial damage so that coagulation activity is not excessive.4 From this description it can also be understood that the heavier the conditions of pregnancy the higher thrombus levels in blood due to activation of the clotting cascade through extrinsic and intrinsic pathways where platelets as the main ingredient that made up the thrombus were also seen to be experiencing.

CONCLUSION

There is a tendency to reduce the average platelet count based on the severity of the condition of pregnancy, but it is not statistically significant. There is a tendency to shorten the mean of PT value based on the increasingly severe conditions of pregnancy but statistically not significant. The mean of APTT with pregnancy condition was seen to be significant between normal pregnancy and eclampsia, as well as PEB with eclampsia while normal pregnancy with PEB is statistically very insignificant. The mean of D-Dimer levels in normal pregnancy and PEB are seen to be as significant as eclampsia, while PEB with eclampsia is statistically not significant.

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