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DIFFERENCES IN PLATELET AND THROMBIN LEVELS IN PREECLAMPSIA AND NORMAL PREGNANCY

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Abstract

Background; Preeclampsia is a pregnancy-specific syndrome that can affect any organ system. The incidence of preeclampsia and eclampsia is different for each country. Changes in endothelial function are considered to be the main cause of symptoms of preeclampsia such as hypertension, proteinuria, and activation of the hemostatic system. Changes in endothelial function that occur in preeclampsia will lead to increased coagulation, fibrin deposition in the microvasculature which results in disruption of placental perfusion. Platelets and thrombin are part of the coagulant factors. Extensive endothelial injury in severe preeclampsia causes a large use of platelets resulting in a decrease in the number of platelets. Thrombin is a serine protease that plays an important role in the coagulation cascade, thrombosis, and hemostasis. Coagulation markers such as platelets and thrombin will affect the coagulation cascade so that they can be used as markers of the progression of preeclampsia. Therefore, it is important to know the extent to which coagulation markers such as platelets and thrombin have an effect in patients with preeclampsia and normal pregnancy. This study to determine the difference in levels of platelet and thrombin in preeclampsia and normal pregnancy Methods: This study is observational with a cross-sectional comparative study design. Sampling was conducted from March 2020 to March 2021. A total of 66 patients were investigated, with 33 samples of preeclampsia and 33 samples of normal pregnancy. The independent sample T-test was used for statistical analysis. Results: The mean levels of Platelet in the preeclampsia group were lower at 214030.3 ± 111128.44 /mm3 while normal pregnancy was 274151.52 ± 88857.02/mm3. The results of statistical tests showed that there was a significant difference in levels of Platelet between the preeclampsia and normal pregnancy groups (p <0,05). The mean thrombin level in the preeclampsia group was higher at 72.23 ± 7.99 ng/mL, while in normal pregnancy it was 63.70 ± 8.92 ng/mL. The difference in thrombin levels between the preeclampsia and normal pregnancy groups was statistically significant (p<0.05) Conclusion: Preeclampsia was associated with Lower levels of Platelet and higher level of thrombin than normal pregnancy. There was a significant difference in the mean levels of Platelet and thrombin between preeclampsia and normal pregnancy.

Keywords: platelet, thrombin, preeclampsia

Introduction

Preeclampsia is a pregnancy-specific syndrome that can affect any organ system.1 The incidence of preeclampsia and eclampsia is different for each country. The United States reported the maternal mortality rate due to preeclampsia or eclampsia from 1998 to 2005 as much as 12.3% of 4693 deliveries. The 2014 Indonesian Health Profile reported that almost 30% of maternal deaths in Indonesia in 2010 were caused by hypertension in pregnancy (Cunningham, Leveno, Bloom, Spong, & Dashe, 2014), (Nursal, Tamela, & Fitrayeni, 2017).

Until now, the pathogenesis of preeclampsia is not completely clear. The development of molecular biology provides a lot of new information to explain the occurrence of preeclampsia. Changes in endothelial function are considered to be the main cause of symptoms of preeclampsia such as hypertension, proteinuria, and activation of the hemostatic system (Levine et al., 2004).

Endothelium functions to maintain the integrity and patency of the vascular compartment, regulate thrombosis, and prevent intravascular coagulation. Changes in endothelial function that occur in preeclampsia will lead to increased coagulation, fibrin deposition in the microvasculature which results in disruption of placental perfusion (Levine et al., 2004), (Heilmann, Rath, & Pollow, 2007), (Pinheiro et al., 2014).

In normal pregnancy, changes in hemostasis occur which aim to maintain pregnancy and prepare for the labor process. During pregnancy, activation of coagulation can help maintain placental function. During labor and beyond, coagulation helps stop blood flow at the wound site during labor, followed by hemostasis by forming a blood clot. Changes in hemostasis in pregnancy include increased coagulation factors, decreased anticoagulant concentrations, and decreased fibrinolytic activity (Marchi et al., 2007), (Solomon, Collis, & Collins, 2012).

A shift in the hemostatic balance occurs in a normal pregnancy but is in stark contrast to preeclampsia. This imbalance of the hemostatic system is a pathological condition and reflects the systemic inflammation and endothelial dysfunction that are characteristic of this disease (Gardiner & Vatish, 2017), (Erez et al., 2008).

Platelets and thrombin are part of the coagulant factors. Thrombocytopenia can be found in normal pregnant women. Therefore, thrombocytopenia in severe preeclampsia is considered significant if the platelet count is <100,000/µL. The frequency and severity of thrombocytopenia vary and depend on the severity and duration of the preeclampsia syndrome. The lower the platelet count, the higher the maternal morbidity and mortality rate (Yusrawati, 2015).

The decrease in the number of platelets in preeclampsia is thought to be related to the endothelial damage that occurs. In hemostasis, platelets have an important role, namely in the formation of the stabilization of the platelet plug in endothelial injury. Extensive endothelial injury in severe preeclampsia causes a large use of platelets resulting in a decrease in the number of platelets (Cunningham et al., 2014), (Baskett & Talaulikar, 2014).

Thrombin is a serine protease that plays an important role in the coagulation cascade, thrombosis, and hemostasis. Once generated in the blood from the inactive precursor prothrombin, thrombin has a procoagulant function when converting fibrinogen to insoluble fibrin clots that anchor platelets to the lesion site and initiate the wound repair process. at the implantation site will result in an excess of thrombin in the first trimester associated with the later development of preeclampsia.

Coagulation markers such as platelets and thrombin will affect the coagulation cascade so that they can be used as markers of the progression of preeclampsia. Therefore, it is important to know the extent to which coagulation markers such as platelets and thrombin have an effect in patients with preeclampsia and normal pregnancy.

Research Methods

The research design was an analytical observational study with a cross-sectional approach to determine the difference between platelet and thrombin levels in preeclampsia and normal pregnancy. The research was conducted at the Department of Obstetrics and Gynecology, Dr. M. Djamil Padang. Sample collection was carried out from March 2020 to March 2021. The samples studied were 66 people, consisting of 33 samples with a diagnosis of preeclampsia and 33 with normal pregnancy samples. This study has been approved by the health and research ethics committee, Faculty of Medicine, Andalas University Padang (323/KEP/FK/2020). This study presents the characteristics of research respondents, maternal age, difference in the parity, and body mass index. Data analysis was carried out with the help of SPSS version 23 software. The univariate analysis was used to see the characteristics of the sample. The data consisted of levels of platelet, thrombin, normal pregnancy, and preeclampsia. Categorical data was presented in the form of a frequency distribution, while numerical data is presented in the form of mean and standard deviation Bivariate analysis was carried out using the independent sample T test because the data distribution was normally distributed after the Saphiro Wilk test was performed. ($p>0.05$).

Results and Discussion

A. Results

1. Characteristics of Research Subjects

Table 1
Characteristics of Research Respondents

characteristics		Pregnancy Status		*P value*
	n	Preeclampsia	Normal Pregnancy	
		(Mean ± SD)	(Mean ± SD)	
Maternal age (Years)	33	31,52 ± 5,32	30,79 ± 5,46	0,585
Parity	33	12 (57,1 %)	9 (42,9 %)	

	Primipara				
0,597					
	Multipara	33	21 (46,7 %)	24 (53,3 %)	
	Body mass index	33	27,59 ± 5,04	25,54 ± 3,83	0,066

Based on Table 1, it can be concluded that the mean age of mothers with preeclampsia was higher, namely 31.52 ± 5.32 years, while normal pregnancies had a mean age of 30.79 ± 5.46. The results of statistical tests showed that there was no difference in the characteristics of maternal age between preeclampsia and normal pregnancy ($p > 0.05$). In this study, multigravida suffered more from preeclampsia than primigravida, namely 21 people (46.7%) compared to 12 people (57.1%). The results of the analysis were obtained ($p>0.05$) so it was concluded that there was no difference in the parity characteristics of preeclampsia and normal pregnancies. BMI in the preeclampsia group was higher at 27.59 ± 5.04 and normal pregnancy was 25.54 ± 3.83, but the statistical test results showed no significant difference in BMI characteristics between preeclampsia and normal pregnancy ($p > 0.05$).

2. Platelet Levels In Respondents

Platelet levels in the preeclampsia and normal pregnancy groups can be seen in Table 2 below:

Table 2
Platelet Levels in Preeclampsia and Normal Pregnancy

Pregnancy status	**Platelet level (/mm^3)**		***P value***
	n	**(Mean ± SD)**	
Preeclampsia	33	214030,3 ± 111128,44	0,009
Normal Pregnancy	33	274151,52 ± 88857,02	

Based on Table 2, it is known that the mean platelet level in the preeclampsia group was lower at 214030.3 ± 111128.44 /mm^3 while in normal pregnancy it was 274151.52 ± 88857.02/mm^3. The results of statistical tests showed that there was a difference in the mean thrombin levels between the preeclampsia and normal pregnancy groups ($p < 0.05$).

3. Thrombin Levels in Respondents

Thrombin levels in the preeclampsia and normal pregnancy groups can be seen in Table 3 below:

Table 3
Thrombin Levels in Preeclampsia and Normal Pregnancy

Pregnancy status	**Thrombin level (ng/mL^3)**		***P value***
	n	**(Mean ± SD)**	
Preeclampsia	33	72,23 ± 7,99	0,009
Normal Pregnancy	33	63,70 ± 8,92	

Based on Table 3, it is known that the mean thrombin level in the preeclampsia group was higher at 72.23 ± 7.99 ng/mL while in normal pregnancy it was 63.70 ± 8.92 ng/mL. The results of statistical tests showed that there was a difference in the mean thrombin levels between the preeclampsia and normal pregnancy groups ($p < 0.05$).

B. Discussion

1. Characteristics of Research Subjects

Based on the results of the study, it was found that the mean age of pregnant women with preeclampsia was higher, namely 31.52 ± 5.32 years, while in the group with normal pregnancies it was 30.79 ± 5.46 years, but the results of statistical tests showed that there was no significant difference in age characteristics. Mothers between preeclampsia and normal pregnancy ($p > 0.05$).

The results of research conducted by Vincent et al (2018) at Sanglah Hospital found that the most cases of preeclampsia were found in pregnant women with an age range of 20-35 years, namely 65.6% and at least 7.8% in pregnant women aged less from 20 years (Vincent, Darmayasa, & Suardika, 2017).

The results of the study by Kumari et al (2016) showed different things, in which cases of preeclampsia were more commonly found in pregnant women aged less than 20 years and more than 30 years. Women younger than 20 years of age do not yet have a normal uterine size for pregnancy, so the risk for disturbances during pregnancy is greater. In women who are less than 20 years old, immunological maladaptation occurs, the adaptation of the process of forming antibody blocking is not optimal so it is formed in very small quantities. This causes an autoantibody reaction to placental antigens. Women over the age of 35 when they enter labor are at greater risk for medical disorders, such as degenerative diseases or endothelial vascular damage.

Based on the results of this study, it was known that 46.7% of multiparas had preeclampsia and 57.1% were primiparas with preeclampsia. Research conducted by Utama (2008) stated that cases of preeclampsia were more commonly found in multiparous pregnant women, namely 61.2% while in primiparas 38.8%, but from this study, it was found that there was no relationship between parity and the incidence of preeclampsia. In theory, preeclampsia is more common in primigravida. This is because the incidence of preeclampsia often occurs in pregnant women who are first exposed to the chorionic villi. The existence of an immunological mechanism in the process of forming blocking antibodies against placental antigens by Human Leukocyte Antigen-G (HLA-G) which is not yet fully formed in primigravida, causes this group to have a high risk of developing preeclampsia. This mechanism results in the disruption of the trophoblast implantation process to the maternal decidual tissue. During the next pregnancy, the formation of blocking antibodies will be formed more completely as a result of the immune response in the previous pregnancy, so the risk of preeclampsia in multigravida will be lower. Stress during labor is more common in primigravida,

so the body will be stimulated to excrete cortisol which can increase the sympathetic response so that cardiac output and blood pressure increase. This mechanism results in the disruption of the trophoblast implantation process to the maternal decidual tissue. During the next pregnancy, the formation of blocking antibodies will be formed more completely as a result of the immune response in the previous pregnancy, so the risk of preeclampsia in multigravida will be lower. Stress during labor is more common in primigravida, so the body will be stimulated to excrete cortisol which can increase the sympathetic response so that cardiac output and blood pressure increase. This mechanism results in the disruption of the trophoblast implantation process to the maternal decidual tissue. During the next pregnancy, the formation of blocking antibodies will be formed more completely as a result of the immune response in the previous pregnancy, so the risk of preeclampsia in multigravida will be lower. Stress during labor is more common in primigravida, so the body will be stimulated to excrete cortisol which can increase the sympathetic response so that cardiac output and blood pressure increase (Cunningham et al., 2014), (Bastani, P., Kobra, H., Hossein, 2008), (Denantika, O., Serudji, J., Revilla, 2015).

From the results of this study, it was known that the BMI of preeclampsia patients was higher than the group with normal pregnancies, namely 27.59 ± 5.04 kg/m2 and 25.54 ± 3.83 kg/m2. The results of statistical tests showed no difference in BMI characteristics between preeclampsia and normal pregnancy ($p > 0.05$). The results of this study are in line with research conducted by Taebi et al (2014) who found the BMI in preeclampsia was 28.56 ± 3.4 kg/m2 while in normal pregnancy it was 25.45 ± 4.5 kg/m^2. Women who are overweight tend to increase the inflammatory response as a result of more adipose tissue being a supplier of inflammatory mediators. This is the reason for the close relationship between a BMI of more than 35 kg/m^2 with cases of preeclampsia. High BMI can trigger an increase in blood pressure through the secretion of angiotensinogen by adipocytes, blood viscosity also increases due to the secretion of profibrinogen and plasminogen activator inhibitor (PAI) by adipocytes and an increase in blood volume due to an increase in BMI (Sohlberg, Stephansson, Cnattingius, & Wikström, 2012).

2. Differences in Platelet Levels Between Preeclampsia and Normal Pregnancy

The research that has been done shows that the mean platelet level in the preeclampsia group is lower, namely 214030.3 ± 111128.44 / mm3 while in normal pregnancy it is 274151.52 ± 88857.02 / mm3. Statistical test results obtained $p = 0.009$ ($p < 0.05$), it can be concluded that there is a significant difference in platelet levels between preeclampsia and normal pregnancy.

This study is in line with that studied by Sultana (2014), as many as 245 patients were analyzed, of which 82 people were diagnosed with preeclampsia, 63 with eclampsia, and 100 normal pregnancies as controls. The number of platelets in preeclampsia and eclampsia patients decreased significantly when compared to

the control group. The decrease in the number of platelets is directly proportional to the severity of hypertension (Sultana, Karim, Atia, Ferdousi, & Ahmed, 2012).

The decrease in the number of platelets in preeclampsia is thought to be related to the endothelial damage that occurs. In hemostasis, platelets have an important role, namely in the formation of the stabilization of the platelet plug in endothelial injury. Extensive endothelial injury in severe preeclampsia causes a large use of platelets resulting in a decrease in the number of platelets (Cunningham et al., 2014), (Baskett & Talaulikar, 2014), (Vincent et al., 2017).

Vasospasm that occurs in preeclampsia also plays a role in reducing the number of platelets. Continuous vasospasm will damage the endothelial integrity of blood vessels, causing increased capillary permeability, and blood plasma will shift to the inertial space. Blood components including platelets will accumulate in the subendothelium which will then worsen the endothelial dysfunction itself (Labelle & Kitchens, 2005).

Other platelet abnormalities are also found in preeclampsia besides thrombocytopenia. These disorders include platelet activation with increased degranulation, the release of thromboxane A2, and decreased platelet lifespan. Although the cause is unknown, immunologic processes or simple deposition of platelets at the site of endothelial damage may be involved in the development of this disorder (Cunningham et al., 2014).

3. Differences in Thrombin Levels Between Preeclampsia and Normal Pregnancy

The research that has been carried out shows that the average thrombin level in the preeclampsia group is higher, namely 72.23 ± 7.99 ng/mL, while in normal pregnancy it is 63.70 ± 8.92 ng/mL. Statistical test results obtained p = 0.0001 (p <0.05), it can be concluded that there is a significant difference in thrombin levels between preeclampsia and normal pregnancy.

This study is in line with Erez et al (2017) who stated that there was a significant difference in thrombin values between preeclampsia at 8173.1 nM compared to normal pregnancy at 7231.0 nM ($p < 0.05$) (Egan et al., 2017). Karl Egan et al (2017) stated that there was a significant difference in the time of thrombin formation between normal pregnancy 7.0 ± 1.2 minutes and preeclampsia 8.5 ± 2.0 minutes ($p < 0.05$) (Egan et al., 2017).

In normal pregnancy, changes in hemostasis occur which aim to maintain pregnancy and prepare for the labor process. During pregnancy, activation of coagulation can help maintain placental function, and prevent bleeding (Solomon et al., 2012), (Gardiner & Vatish, 2017). A shift in the hemostatic balance occurs in a normal pregnancy but is in stark contrast to preeclampsia (Gardiner & Vatish, 2017).

The coagulation pathway is induced by impaired trophoblast invasion into the myometrium in the first trimester, causing hypoperfusion and hypoxia, which in turn causes the release of inflammatory cytokines, resulting in systemic

endothelial dysfunction. Inflammatory cytokines induce tissue factor (TF) so that the coagulation cascade is activated to form fibrin.1 Placental thrombosis is a frequent histologic finding in preeclampsia. Preeclampsia has higher rates of intervillous fibrin deposition, fetal thrombotic vasculopathy, and decidual vessel thrombosis than normal pregnancies. There is a significant difference in the formation of antithrombin in preeclampsia, this situation also proves that there is a difference in the formation of thrombin in preeclampsia and normal pregnancy (Liu, Gurung, & Qiu, 2019), (Rosero, Villares, & Bar-Eli, 2016).

Thrombin is produced at the site of vascular injury, in the presence of thrombin mobilization of adhesive molecules such as thromboxane A2 and P selectin to the endothelial surface so that it can bind to fibrinogen and von Willebrand Factor (VWF) to mediate platelet aggregation and stimulate the production of autocoids and cytokines (Cunningham et al., 2014).

Thrombin produced by the placenta activates Protease-Activated Receptors-1 which acts as a cause of the secretion of sFLT-1 by endothelial cells which is the basis of the antiangiogenic and proangiogenic imbalance. sFLT-1 is an antiangiogenic protein that is increased in uteroplacental ischemia. This protein will inhibit the interaction of endothelial receptors with placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) on the cell surface which ultimately causes cell damage. Antiangiogenic (sFLT-1) and proangiogenic (VEGF and PlGF) protein imbalances contribute to the pathogenesis of preeclampsia (Denantika, O., Serudji, J., Revilla, 2015), (Rosero et al., 2016).

Conclusion

Preeclampsia was associated with Lower levels of Platelet and higher level of thrombin than normal pregnancy. There was a significant difference in the mean levels of Platelet and thrombin between preeclampsia and normal pregnancy

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