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RESEARCH

Differences in protease activated receptor-1 and thrombine levels in preeclampsia and normal pregnancy

Gistin Husnul Khatimah[1], Joserizal Serudji[2], Vaulinne Basyir[2]

Affiliations: *1. Obstetrics and Gynecology Department, Dr. M. Djamil Central General Hospital Padang, West Sumatera, Indonesia; 2. Sub Division of Fetomaternal Medicine, Obstetrics and Gynecology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang, West Sumatera, Indonesia*

Correspondence: *Gistin Husnul Khatimah, email : gistinhk@gmail.com, Hp:081284294488*

Abstract

Introduction*: Preeclampsia is a condition caused by alterations in endothelial function during pregnancy. Changes in endothelial function result in an increase in coagulation and microvascular fibrin accumulation, which results in impaired placental perfusion. Thrombin, which converts fibrin to fibrinogen, as well as platelet activity, the fibrinolytic system, and anticoagulants, are all procoagulant circumstances in preeclampsia. Thrombin contributes to the pathogenesis of preeclampsia by increasing the expression of sFlt-1 thereby providing an antiangiogenic response. Protease Activated Receptor-1 (PAR-1) is a mediator of thrombin for coagulation and inflammation in preeclampsia. Inhibition of Protease Activated Receptor-1 expression in trophoblasts can enhance placental angiogenesis and vascular remodeling. Recently, only few studies have assessed the levels of Protease Activated Receptor -7 and thrombin in preeclampsia.*

Objective: To determine the difference in levels of Protease Activated Receptor-1 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 Protease Activated Receptor-1 in the preeclampsia group were higher at 28.56 ± 7.68 ng/mL while normal pregnancy was 21.67 ± 6.92 ng/mL. The results of statistical tests showed that there was a significant difference in levels of Protease Activated Receptor-1 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 greater levels of Protease Activated Receptor-1 and thrombin than normal pregnancy. There was a significant difference in the mean levels of Protease Activated Receptor-1 and thrombin between preeclampsia and normal pregnancy.*

Keywords**:** *Thrombin, Protease Activated Receptor-1(PAR-1), Preeclampsia*

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INTRODUCTION

Preeclampsia is a major complication of pregnancy and contributes significantly to maternal morbidity and mortality.[1] World Health Organization (WHO) reports the maternal mortality rate due to preeclampsia is 16% in developing countries. Indonesia Health Profile 2014 reported that almost 30% of maternal deaths in Indonesia in 2010 were caused by hypertension in pregnancy.[2] In 2014 the causes of maternal death in Padang City were preeclampsia-eclampsia 31.25%, bleeding 18.75%, and infection 12.5%. Based on data acquired from Medical Record of General Hospital DR. M. Djamil, Padang, that 119 patients with preeclampsia were treated in obstetric inpatient facilities in 2011, 120 patients in 2012, 187 patients in 2013, and 112 patients in 2014.[3]

Finding the etiology of preeclampsia is the best approach in an effort to reduce morbidity and mortality caused by preeclampsia and eclampsia. 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.[4]

Hemostasis changes in a normal pregnancy to support the pregnancy and prepare for the labor.[5] Changes in hemostatic balance occur in normal pregnancy, but they are exaggerated in preeclampsia. The imbalance of hemostatic system is a pathological state, as well as describe the systemic inflammation and endothelial dysfunction that characterize the disease.[6,7]

Thrombin is a serine protease that plays a role in the coagulation, thrombosis, and hemostasis.[7] Thrombin through the activation of Protease activated receptor 1 (PAR-1) stimulates various inflammatory cells such as mast cells, lymphocytes, and neutrophils to release mediators such as histamine, eicosanoids, and cytokines.[8] Erez et al in 2008 reported that PAR-1 expression was significantly increased in preeclampsia. These observations are consistent with the role of PAR-1 as a mediator of thrombin for the coagulation and inflammatory processes in preeclampsia. Thrombin will activate PAR-1 and inhibit the proliferation of extravillous trophoblast. It has been reported that there is an increase in PAR-1 in the placenta of preeclamptic patients compared to the control group. This is because thrombin stimulates the production of PAR-1 mRNA and protein in endothelial cells.[7]

Erez et al in 2008 compared the placentas of preeclamptic patients with placentas in the preterm spontaneous delivery group, the study described a significant increase in the frequency of PAR-1 expression in the placenta of women with preeclampsia. Yin Zhao et al conducted a follow-up study in 2018 to see if inhibiting PAR-1 expression in trophoblast may boost placental angiogenesis and vascular remodeling in preeclampsia.[7,9]

Procoagulant condition in preeclampsia can be caused by activated thrombin through the coagulation cascade, then fibrin is converted to fibrinogen, and activated platelets, the fibrinolytic system and anticoagulants. Thrombin activation is mediated by PAR-1. As the thrombin value increases, the active PAR-1 will also increase.[7,10,11,12]

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In preeclampsia, increased thrombin and PAR-1 are maternal systemic inflammatory responses, and PAR-1 expression is seen not only in the placenta but also in the blood. Inhibition of PAR-1 activation could be a promising therapeutic treatment for preeclampsia in the future. The objective of this study was to see if there are differences in PAR-1 and thrombin levels in preeclampsia and normal pregnancy, so that PAR-1 and thrombin might be utilized as a marker of preeclampsia progression and lower consequences for the mother and fetus.

METHODS

This study is a cross-sectional comparative study with an observational study design. The mean difference in levels of Protease Activated Receptor-1 and thrombin in preeclampsia and normal pregnancy was investigated in this study. The research was carried out at Dr. M. Djamil Padang's Department of Obstetrics and Gynecology. Samples were collected between March 2020 and March 2021. A total of 66 patients were studied, with 33 having been diagnosed with preeclampsia and 33 having a normal pregnancy

DISCUSSION

Normality test was carried out using the Shapiro Wilk test to determine whether the data were normally distributed or not. It can be concluded that the mean age of mothers with preeclampsia is higher; 31.52 ± 5.32 years while normal pregnancy has 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 had more preeclampsia than primigravida, 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. Systolic and diastolic blood pressure in the preeclampsia group was higher than in normal pregnancies; 180.88 ± 25.02 mmHg and 108.76 ± 11.43 mmHg. The results of statistical tests showed that there were differences in the characteristics of systolic and diastolic blood pressure in women with preeclampsia and normal pregnancies ($p < 0.05$). 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 ($p > 0.05$).

It is known that the mean level of Protease Activated Receptor-1 in the preeclampsia group was higher at 28.56 ± 7.68 ng/mL while in normal pregnancy it was 21.67 ± 6.92 ng/mL. The results of statistical tests showed that there was a difference in the mean levels of Protease Activated Receptor-1 between the preeclampsia and normal pregnancy groups ($p<0,05$).

This study 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

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statistical tests showed that there was a difference in the mean thrombin levels between the preeclampsia and normal pregnancy groups (p<0,05).

Based on the results of the study, it was found that the mean age of pregnant women with preeclampsia was higher; 31.52 ± 5.32 years, while the group with normal pregnancy was 30.79 ± 5.46 years, but the results of statistical tests showed that there was no significant difference in maternal age characteristics between preeclampsia and normal pregnancy (p>0.05). Perucci et al (2017) also found in their research that the mean age of pregnant women with preeclampsia was 26 years, whereas in normal pregnancies it was 23 years, but statistical test results showed that there was no difference in the mean age between the two groups.[13]

The findings of Kumari et al (2016) showed that preeclampsia was more common in pregnant women aged less than 20 years and more than 30 years. Because women under the age of 20 do not yet have a proper uterine size for pregnancy, the risk of complications during pregnancy is higher. Immunological maladaptation occurs in women under the age of 20, when the process of producing blocking antibodies is adapted to produce relatively modest levels of antibodies.[14,15]

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, 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. 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 vascular endothelial damage.[14]

This matches the findings of Giurgescu et al (2015), who discovered that up to 83.3 percent of multigravida experienced preeclampsia. Preeclampsia is more commonly encountered by primigravida, according to theory. This is because preeclampsia is more common in pregnant women who have been exposed to the chorionic villi for the first time. 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 into the maternal decidual tissue. As a result of the immune response in the previous pregnancy, blocking antibodies will be created more completely during the next pregnancy, lowering the risk of preeclampsia in multigravida.[1,16,17]

The results of this study showed that the mean systolic and diastolic blood pressure in preeclampsia was higher than the group with normal pregnancy, and from the results of statistical tests there was a significant difference (p < 0.05). This result is similar with a study conducted by Singh et al (2018) where the mean systolic blood pressure in preeclampsia patients was 138.12 ± 8.81 mmHg while in normal pregnancy it was 114.37 ± 0.29 mmHg. Likewise with the results of research by Mumtaz et al (2008) which found the mean systolic

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and diastolic blood pressure in preeclampsia was 150.35 ± 7.67 mmHg and 98.94 ± 7.03 while in normal pregnancy it was 122.79 ± 9.08 mmHg and 80.23 ± 6.26 mmHg. The theory of Cunningham et al (2014) states that in patients with preeclampsia incomplete trophoblastic invasion occurs. The deeper myometrial arteries do not lose their endothelial lining and musculoelastic tissue. As a result, the muscle layer of the spiral arteries becomes stiff and hard so that the lumen of the spiral arteries does not experience vasodilation. The outer diameter of blood vessels in women with preeclampsia is half that of patients with normal pregnancies. Hypertension is caused by a blockage of blood flow caused by constriction of blood vessels.[1]

Preeclampsia patients have a higher BMI (27.59 5.04 kg/m2) than women who have normal pregnancies, according to the findings of this study. 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 similar with research conducted by Taebi et al (2014) who found BMI in preeclampsia; 28.56 ± 3.4 kg/m2 while in normal pregnancy 25.45 ± 4.5 kg/m2. 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.[17]

It showed that the mean levels of Protease Activated Receptor-1 in the preeclampsia group were higher; 28.56 ± 7.68 ng/mL, while in normal pregnancy it was 21.67 ± 6.92 ng/mL. Statistical test results obtained $p = 0.0001$ ($p < 0.05$), it can be concluded that there is a significant difference in levels of Protease Activated Receptor-1 between preeclampsia and normal pregnancy.

This study is similar to that of Erez et al (2008) which compared 26 placental tissues from preeclampsia patients and 26 placentas from deliveries without infection. Based on these results, it was found that PAR-1 was found in 92% of placentas from preeclampsia patients and 88.5% of control group. 7 The percentage of placentas from preeclampsia patients with strong PAR-1 immunoreactivity was higher than the control group, which was 37.5% and 8.7%. Histological findings of the preeclampsia patient's placenta found intervillous infarction, increased intervillous fibrin deposition and distal villous hypoplasia caused by maternal hypoperfusion. It can be concluded that the placenta from preeclampsia patients has a significantly higher frequency of PAR-1 expression than the placenta from normal women. These observations are consistent with the role of PAR-1 as a mediator of the coagulation and inflammatory effects of the preeclampsia syndrome.[7]

PAR-1 is involved in trophoblast invasion and placentation in the first trimester of pregnancy. In the presence of thrombin, PAR-1 activation inhibits trophoblast proliferation. Excessive thrombin generation in preeclampsia also causes an increase in PAR-1 expression in the trophoblast villi in patients with preeclampsia.[7,15]

The biological activity of thrombin is mediated by protease-activated receptors (PAR). PAR-1 is the main receptor for thrombin in mediating the effects of thrombin on platelet activation, proinflammatory cytokine secretion, local tissue remodeling after irritation and

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fetal vascular development and stabilization. Hypoperfusion and responsive hypoxia due to vasospasm and vasoconstriction lead to activation of the coagulation system in the intervillous space and trophoblast ischemia.[8]

This is due to the expression of soluble Fms-like tyrosine kinase 1 (sFLT-1) which is initiated by PAR-1 activity in response to thrombin receptors. 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. Thrombin produced by the placenta activates PAR-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. An imbalance of antiangiogenic (sFLT-1) and proangiogenic (VEGF and PlGF) proteins contributes to the pathogenesis of preeclampsia.[8]

A study conducted by Yin Zhao et al (2017) on 12 mice which were grouped into 3 groups, group 1 was control that was given only normal saline, group 2 was induced by preeclampsia without being given a PAR-1 antagonist and group 3 was induced by preeclampsia given PAR-antagnosia. 1. As a result, the control mouse placenta showed normal arterial remodeling and the endothelial lining was identified. Group 2 showed endothelial disruption at the base and infrequent trophoblast invasion. In group 3, the process of remodeling the muscle layer of blood vessels and deeper trophoblast invasion was seen. Thus, it was concluded that PAR-1 inhibition may promote placental angiogenesis and vascular remodeling in preeclamptic samples.[7,8]

The study that has been conducted shows that the average thrombin level in the preeclampsia group is higher, 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) which states that there is a significant difference in thrombin value between preeclampsia 8173.1 nM compared to normal pregnancy 7231.0 nM ($p < 0.05$). there was a significant difference in thrombin generation time between normal pregnancies of 7.0 ± 1.2 minutes and preeclampsia 8.5 ± 2.0 minutes ($p < 0.05$).[18]

CONCLUSIONS

Hemostatic shifts occur in a normal pregnancy to maintain the pregnancy and prepare for labor. Coagulatory activation can aid placental function and minimize bleeding during pregnancy.[5,20] A shift in the hemostatic balance occurs in normal pregnancy, but contrasts greatly in preeclampsia.[6]

Impaired trophoblast penetration into the myometrium in the first trimester triggers the coagulation pathway, leading in hypoperfusion and hypoxia, which triggers the release of inflammatory cytokines, resulting in systemic endothelial dysfunction. Tissue factor (TF) is activated by inflammatory cytokines, resulting in the activation of the coagulation cascade and

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the production of fibrin.[21] In preeclampsia, placental thrombosis is a common histologic finding. Intervillous fibrin deposition, fetal thrombotic vasculopathy, and decidual vascular thrombosis are all more common in preeclampsia than in normal pregnancies. Antithrombin formation differs significantly in preeclampsia, and this condition also demonstrates that thrombin formation differs significantly in preeclampsia and normal pregnancy.[22,23,24]

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