

Research Article

Endothelin-1 Levels in Pregnant Women with Severe Preeclampsia and Normal Pregnant Women

Kadar Endothelin-1 di Ibu Hamil dengan Preeklamsia Berat dan Ibu Hamil Normal

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Abstract

Objective: To determine the ratio of serum endothelin-1 levels between severe preeclampsia and normotensive pregnancy.

Methods: Observational analytic study using cross-sectional. Sixteen woman with normal pregnancy and sixteen others with severe preeclampsia who met the inclusion and exclusion criteria, were tested for ET-1. The serum was analyzed at Prodia Laboratory, Manado. The ET-1 level was examined using ELISA (R&D Systems, Inc., Minneapolis, MN 55413, USA). The data obtained was analyzed using SPSS software version 20.0 and discussions were held using the existing literature theory.

Results: The mean and median levels of endothelin-1 plasma in patients with severe preeclampsia is 2.46 ± 1.44 pg/ml, 1.09 ± 0.26 pg/ml, whereas in normotensive pregnancy is 1.03 ± 0.26 pg/ml, 1.95 ± 1.44 pg/ml with $p < 0.05$ (0000).

Conclusion: There was a significant difference between endothelin-1 level in severe preeclampsia and normotensive pregnancies.

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Keywords: endothelin-1, normotensive, preeclampsia

Abstrak

Tujuan: Mengetahui perbandingan kadar endothelin-1 antara kehamilan preeklamsia berat dan kehamilan normotensi.

Metode: Penelitian kuantitatif observasional analitik menggunakan pendekatan potong lintang. Dilakukan pemeriksaan kadar endothelin-1 pada 32 sampel ibu hamil yang memenuhi kriteria inklusi dan eksklusi, terdiri atas 16 kehamilan preeklamsia berat dan 16 kehamilan normotensi. Analisis sampel dilakukan di Laboratorium Prodia Manado. Pemeriksaan kadar endothelin-1 menggunakan metode ELISA. Data yang diperoleh diolah dengan menggunakan perangkat lunak SPSS versi 20.0 dan dilakukan pembahasan menggunakan teori kepastakaan yang ada.

Hasil: Rerata dan median kadar endothelin-1 plasma pada penderita preeklamsia berat yaitu $2,46 \pm 1,44$ pg/ml, $1,09 \pm 0,6$ pg/ml, sedangkan pada kehamilan normotensi yaitu $1,03 \pm 0,26$ pg/ml, $1,95 \pm 1,44$ pg/ml dengan nilai $p < 0,05$ (0,000).

Kesimpulan: Terdapat perbedaan signifikan kadar endothelin-1 antara kehamilan preeklamsia berat dengan kehamilan normotensi.

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Kata kunci: endothelin-1, normotensif, preeklamsia

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INTRODUCTION

Two of the maternity care quality indicators are maternal and perinatal mortality. Approximately 600,000 women die from pregnancy-related disorders annually, and 98% of the deaths occurs in the developing countries. The Maternal Mortality Rate (MMR) in Indonesia is still far from the Millennium Development Goals (MDGs) target. The 2015 MMR target was 102 per 100,000 live births, while the infant mortality rate (IMR) target was 23 per 1.000 live births.¹⁻⁴

Preeclampsia is a pregnancy specific condition characterized by placental and maternal response dysfunction to systemic inflammation, accompanied

with endothelial activation and coagulation. Preeclampsia is a major cause of morbidity and mortality of pregnant women and newborns, occurred in approximately 2-8% of all pregnancies in the world. The majority of preeclampsia onset is late (> 34 weeks), and 10% is early (< 34 weeks).⁵⁻⁷

Several risk factors for preeclampsia include primigravida, hyperplacental, aged < 20 years or > 35 years, previous history of preeclampsia/eclampsia, obesity, multiple pregnancies, medical abnormal history due to endothelial dysfunction such as chronic hypertension, and pregestational diabetes mellitus.^{5,7,8}

Preeclampsia is usually started by a decrease in utero-placental perfusion due to a cytotrophoblast abnormal invasion in uterine spiral arteries. A placental hypoxia will cause a decrease in placental perfusion. In such circumstances, an imbalance between pro-angiogenic and antiangiogenic factors occur. There are two antiangiogenic proteins produced excessively in preeclamptic patients, which include soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin where ET-1 as a mediator of hypertension. Due to increased free radical and cytokine, decreased proangiogenic factors (VEGF and PIGF), and uncontrolled increase in lipid peroxide, vascular endothelial dysfunction occurs.^{9,10}

ET-1 is a potent vasoconstrictor produced by endothelial cells, macrophages, fibroblasts, and cardiac myocytes. It is a family of peptide composed of 21 amino acids with two intramolecular disulfide bonds. Increased ET-1 level plays an important role in the development of hypertension in pregnancy, which may later progress to preeclampsia.^{6,11,12} Several studies suggested that preeclamptic subjects with higher ET-1 levels had poorer prognosis. We aimed to compare ET-1 serum levels between severe preeclampsia and normotensive pregnancy.

METHODS

We conducted a cross-sectional study to compare the ET-1 serum in severe preeclampsia and nor-

motensive pregnancies. This study was conducted at the Obstetrics and Gynecology Department of the Prof. dr. R. D. Kandou Hospital, Manado, and the sister teaching hospitals in Manado, during the period of October 2015 to November 2015.

The study population were all pregnancy outpatients with severe preeclampsia and those with normal blood pressure at the hospitals. The inclusion criteria were pregnant women with gestational age above 20 weeks, diagnosed with severe preeclampsia and were willing to participate in research. The exclusion criteria were pregnant women with chronic illnesses: diabetes mellitus, chronic hypertension, renal disease, thyroid disease, and patients who had received the cholesterol medication, twin pregnancies, and those who refused to participate in the study. The control group was the normotensive pregnant women with the same gestational age. We collected the sample by consecutive sampling, where every patient who met the study criteria would be included in the study until the minimum number of samples met. Statistical analyses were conducted using SPSS. T test was used for numerical variables.

RESULTS

The total number of subjects was 32, consisted of 16 normotensive pregnant women and 16 severe preeclamptic women. Demographic characteristics of the subjects are presented in Table 1.

Tabel 1. Demographic Characteristics of the Subjects

Characteristics	Normal pregnancy		Severe preeclampsia	
	n	%	n	%
Mother age				
< 35 years old	14	88	8	50
≥ 35 years old	2	12	8	50
Parity				
Primigravida	8	50	6	38
Multigravida	8	50	10	62
Gestational age				
Preterm	5	31	6	38
Aterm	11	69	10	62
Education				
Primary school	0	0	1	7
Junior high	3	19	3	19

Characteristics	Normal pregnancy		Severe preeclampsia	
	n	%	n	%
High school	13	81	10	62
Diploma	0	0	0	0
Graduate	0	0	2	12
Occupation				
Public servant	1	6	2	13
Private employee	0	0	0	0
Student	2	13	1	6
Housewife	13	81	13	81
History of Preeclampsia				
Negative	16	100	13	81
Positive	0	0	3	19
Body Mass Index				
≤ 25	12	75	10	62
> 25	4	25	6	38
Infant Birth weight				
≤ 2500	3	19	6	38
> 2500	13	81	10	62

Table 2. Comparison of the Characteristics between Subjects with Preeclampsia and Normal Pregnancy

Variables	Normal pregnancy			Severe preeclampsia			p
	Mean	Median	SD	Mean	Median	SD	
Age	26.19	27.5	7.26	30.88	34.5	6.95	0.51
Parity	1.75	1.5	1.54	3	2.5	2.03	0.16
Systole	112.5	110	7.75	168.13	160	21.67	0
Diastole	73.13	70	4.79	113.13	110	15.37	0
AST	21	19	6.55	36.44	28.5	31.46	0.138
ALT	12	11.5	3.5	24.81	19.5	21.69	0.043
Hemoglobin	11.41	11.1	1.47	10.66	11.65	3.95	0.669
Platelet	284125	266000	60202	294688	294500	78408	0.672
BMI	22.94	21.5	5.29	24.25	23.5	4.09	0.196
Birth weight	2806.25	3050	831.44	2653.13	2750	642.77	0.16

We found no significant difference between the preeclamptic population and the normotensive group ($p > 0.05$) for the following variables: maternal age, parity, AST, the number of hemoglobin and platelets, BMI and birth weight. There were significant differences between the preeclamptic and normotensive groups for these variables: systolic, diastolic and the levels of ALT ($p < 0.05$).

From Graph 1, the obtained results mean and median distribution of ET-1 appears to be higher severe preeclampsia (2.46 ± 1.44 pg/ml, 1.95 ± 1.44 pg/ml) compared to normotensive pregnancy (1.03 ± 0.26 pg/ml, 1.09 ± 0.26 pg/ml). This result demonstrate increased levels of ET-1 in severe preeclampsia compared to normotensive pregnancy.

The Mann-Whitney statistical test showed that there were significant differences between the levels of endothelin-1 between the severe preeclamptic and the normotensive groups ($p = 0.000$). This means that the concentration of endothelin-1 affects the occurrence of severe preeclampsia.

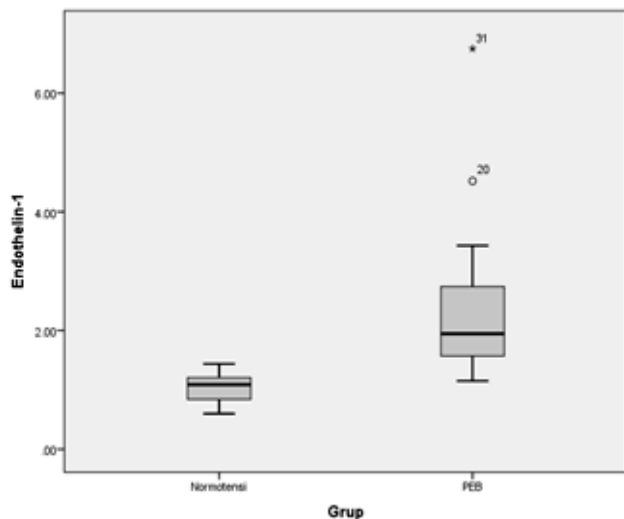


Figure 1. The ET-1 Correlation between Severe Preeclampsia and Normotensive Pregnancy

DISCUSSION

Approximately 5-10% of pregnant women experienced a syndrome known as preeclampsia. In women with normotensive pregnancies, a thorough physiological alterations and body system adaptation occur. In cardiovascular system, ET-1 receptor blockage maintains the vascular tone. Pregnant women with risk factors, such as maternal disease and oxidative stress, the angiogenic factor were dysfunctional.¹⁴

Multiple evidence suggested that ET-1 was one of the preeclampsia pathophysiological factors. When the preeclampsia and the normotensive groups were compared, an elevated ET-1 in preeclampsia group was found. It indicates that the concentration of ET-1 affects the occurrence of severe preeclampsia.¹¹

Early incident in preeclampsia occurs due to decreased utero-placental perfusion, which happens because of remodelling failure of the spiral arteries and endothelial dysfunction.

Placental hypoxia will lead to decreased placental perfusion. In such circumstance, an imbalance factors between proangiogenic and antiangiogenic occurs. In preeclampsia, there are two antiangiogenic proteins produced excessively in the maternal circulation: soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin where ET-1 as a mediator of hypertension. Due to increase in free radical and cytokine causing oxidative stress and decrease in proangiogenic factors VEGF, PlGF and an uncontrolled increase in lipid peroxide. This causes vascular endothelial dysfunction that is disintegration of endothelial structure and function.^{9,10}

Increase in endothelin-1 in the circulation of pregnant women have an important role in the occurrence of hypertension in pregnancy and may develop into preeclampsia. In several different studies, preeclamptic patients with higher ET-1 level in the maternal circulation had poorer prognosis.^{11,15}

The obtained results mean and median distribution of ET-1 appears to be higher in severe preeclampsia compared with normotensive pregnancies. The interpretation result indicates that the presence of increased levels of ET-1 in severe preeclampsia compare with normotensive pregnancies. This means that the concentration of endothelin-1 affects the occurrence of severe preeclampsia.

Croom et al conducted are search on the serum level of ET-1 in normal pregnancy and preeclampsia. This study demonstrated increased levels of ET-1 in preeclampsia compared to normal pregnancy. In normal pregnancy, the level of ET-1 0.5 pg/ml (1st trimester), 1.1 pg/ml (3rd trimester), and 1.7 pg/ml (at birth). Whereas in patients with preeclampsia, level of ET-1 1.9 pg/ml (before delivery) and 3.5 pg/ml (at birth). Slowinski et al found a very strong relationship between the level of ET-1 in patients and preeclampsia at 24 weeks and 36 weeks of pregnancy compared to normotensive pregnancy. The level of ET-1 was higher in preeclamptic patients at both gestational ages (1.07 ± 2.00 vs 0.54 ± 0.56 pg/ml, $p=0.045$ at 24 weeks and 0.75 ± 1.20 vs 0.44 ± 0.45 pg/ml, $p=0.023$ at 36 weeks).^{16,17}

Several studies have shown that ET-1 is associated with the development of preeclampsia. The levels of ET-1 in preeclamptic patients increased significantly compared to normal pregnancy. ET-1

is a potent vasoconstrictor that can be used as predictors of hypertension and preeclampsia. Increase in ET-1 indicated vasospasm progressivity accompanied with decreased renal plasma flow and utero-placental blood flow. Finally, elevated ET-1 level is responsible for mitogenic activity reported on preeclampsia.^{6,13}

Aggarwal et al found that ET-1 level in preeclampsia was higher compared to normotensive pregnancy (1.52 ± 0.55 vs 0.88 ± 0.35 pg/ml, $p < 0.001$). Nova et al found that ET-1 was highest in patients with HELLP syndrome than without HELLP syndrome and the lowest in normotensive group.^{13,18}

Kamoi et al suggested that ET-1 level in normotensive pregnant women was lower than non pregnant women (0.6 ± 0.1 vs 1.5 ± 0.3 pg/ml) and higher in women with pregnancy-induced hypertension (1.9 ± 0.3 pg/ml). After delivery, increased levels of ET-1 would go back to its normal level in line with decreased blood pressure in all patients. Meanwhile, in pregnant women with chronic hypertension, the ET-1 levels were slightly higher compared to normotensive pregnant women (0.9 ± 0.3 pg/ml, $p < 0.01$). In a study of 6 patients with pregnancy induced hypertension (PIH), 2 patients with pregnancy induced proteinuria (PIP) without hypertension and 7 normotensive pregnant women which was conducted by Ohya et al, subjects with PIP had the highest levels of ET-1, while the normotensive pregnant population had the lowest levels (4.4 ± 0.5 vs 4.5 ± 0.6 vs 1.5 ± 0.2 pg/ml). One week after delivery, ET-1 level in PIH and PIP were still high. After one month, the level of ET-1 in PIH population began to decline, whereas the PIP population still had high ET-1 levels.^{19,20}

In the severe preeclamptic group, four subjects had complications, in which two subjects developed suffered from eclampsia, one subject had eclampsia and one subject suffered from eclampsia with HELLP syndrome. Of these subjects, four them had their ET-1 levels increased significantly, which may indicate further endothelial damage in preeclampsia. These findings are consistent with a study conducted by Nova et al, which found that ET-1 level were significantly elevated in patients with HELLP syndrome compared without HELLP syndrome. However, this needs to be done with greater samples to assess the association between complications of preeclampsia with high levels of ET-1.¹³

This study has some limitations that may affect the results. Confounding factors including level of urea, creatinine and other biochemical mediators as predispositions of preeclampsia, were not controlled. In addition, we did not examine other biochemical factors that were expected to influence ET-1 levels to our subjects. Family physicians and maternity care provider should educate patient and families to do antenatal care regularly to detect high risk pregnancies, including the early signs of preeclampsia, therefore prevention and treatment can be done as early as possible and is expected to reduce maternal and perinatal morbidity and mortality. Further studies with larger sample size are required to obtain the causal association between ET-1 and the complications of preeclampsia.

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