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The Correlation of the Lipid Profile and Endothelin-1 with Severe Preeclampsia

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JW, YW, AL, FW and BH were designed the study. Author BK was performed the statistical analysis. Authors JW, YW and BH were wrote the protocol and wrote the first draft of the manuscript. Authors JW, YW, AL, FW and BK managed the analyses of the study. Authors JW, YW, AL, FW and FL managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: To determine the relationship of lipid profile and Endothelin-1 (ET-1) in a severe preeclamptic pregnancy.
Study Design: An observational analytic study using cross-sectional was conducted in Department of Obstetrics and Gynecology, Sam Ratulangi University, in conjunction with the teaching hospital, Prof. Dr. R. D. Kandou General Hospital and the sister hospitals in Manado Hospital. Sixteen woman with normal pregnancy and sixteen others with severe preeclampsia who met the inclusion and exclusion criteria, were tested for lipid profile and 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.
Main Outcome Measures: The comparison and correlation of lipid profile and endothelin-1 (ET-1) plasma level in normal and severe preeclamptic pregnancy.

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Results: Higher cholesterol total, triglyceride, VLDL, ET-1 level were found in severe preeclampsia group. Also, there was a significant correlation between the ET-1 and the triglyceride (r=0589, p=0.016) and VLDL (r=0590, p=0.016) in the normal pregnancy group. In the severe preeclampsia group, there was no significant correlation between the two variables (p>0.05).
Conclusion: There are elevated levels of triglycerides, VLDL and endothelin-1 in the incidence of severe preeclampsia compared with normotensive. This is a small and preliminary observational study, which shows that the older the age and parity the probability of preeclampsia increases and the more ET-1 is produced. But an elevation of the lipid profile is also observed without a proportional relationship with endothelin. This study suggests that lipids are involved in endothelial damage in pre-eclampsia without any relationship between them.

Keywords: lipid profile; endothelin-1; preeclampsia.

1. INTRODUCTION

A woman may die because of pregnancy and labor. The World Health Organization (WHO) stated that hypertension in pregnancy is the most common cause of mortality and morbidity in mother and fetus. The statement was also supported by the American College of Obstetricians and Gynecologist (ACOG), pre-eclampsia usually occurs in extreme maternal age (younger than 18 or over 35). In the United States, it occurs in approximately 5% of all pregnancies. Approximately 86% (254 000) of the estimated global maternal deaths, women died during and following pregnancy and childbirth in 2017. Indonesian Maternal Mortality Rate (MMR) is below from the Millennium Development Goals (MDGs) target. Based on Indonesian National Survey on Demography and Health 2018, Indonesian MMR was 359 per 100,00 live birth while the 2015 MMR target was 102 per 100,000 live births and the infant mortality rate (IMR) target was 23 per 1,000 live births. While, Sustainable Development Goals (SDGs) targeted less than 70 per 100,000 live births [1-5].

Preeclampsia is a specific condition frequently encountered medical complication during pregnancy and is characterized by a rise in systemic vascular resistance with systemic inflammation, hypovolemia, combined with severe proteinuria. Abnormal placentation early in pregnancy is widely assumed to be an important initial event in the onset of preeclampsia. Eventually, this results in the release of anti-angiogenic factors and cytokines, leading to generalized vascular dysfunction. Preeclampsia is responsible for over 500.000 fetal and neonatal deaths and over 70.000 maternal deaths [6-8].

Preeclampsia is started by decreasing in uteroplacental perfusion due to abnormal cytotrophoblast invasion in uterine spiral arteries. In preeclampsia, cytotrophoblast invasion of the interstisial uterine compartment is frequently shallow, although not consistently so. In many locations, spiral artery invasion is incomplete. A placental hypoxia cause a decrease in placental perfusion. In ischemic condition, the placenta will produce lipid peroxide which gets into and binds to lipoproteins, particularly low density lipop rotein (LDL). Under normal circumstances, lipid peroxides is kept in balance by the antioxidants. When the antioxidant level is low, lipid peroxidation becomes uncontrollable and a condition called oxidative stress arises. Once occurred, the process will continue. Because the endothelial cell layer is directly exposed to the arterial blood, the endothelial cells become highly susceptible to lipid peroxidation process. The contact with the lipid peroxide will damage the endothelial cell membrane and cause it to release endothelin-1 (ET-1). The excessive release of ET-1 will cause a capillary vasoconstriction, and will ultimately lead to preeclampsia [9-11].

ET-1 is potent vasoconstrictor that 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. An increased ET-1 in a pregnant woman circulation has correlation preeclampsia. Moreover, it may progress into preeclampsia. In several studies, preeclampsia patients with a higher ET-1 in the maternal circulation to have a poor prognosis [7,12,13].

Therefore, we conducted a research to determine the serum levels of ET-1 relationship with the lipid profile in severe preeclamptic pregnancy.

2. METHODS

We conducted a cross-sectional study to compare the lipid profiles and the ET-1 serum in severe preeclampsia and normotensive pregnancies. The study was conducted from October 2015 through 2016 by Obstetrics and Gynecology Department of Prof. dr. R. D. Kandou Hospital, Manado, and the sister teaching hospitals in Manado.

The Population was 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 willing to participate in research. The exclusion criteria related comorbidities that could bias the results pregnant women with chronic illnesses: diabetes mellitus, chronic hypertension, renal disease, thyroid disease, and patients who have received the cholesterol medication, twin pregnancies, and those who refuse 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 included in the study until the minimum number of samples met.

The number of sample was calculated using a single mean formula with reference to the endothelin levels in patients with preeclampsia 5.48 +/- 0.3 *f*mol/mL, α = 0.05, d=0.15 *f*mol/mL [13].

$$n = \left(\frac{Z_{\alpha}{}^{2}\sigma}{d^{2}} \right) = 15{,}37 = 16$$

The results of the total sample of the study were 32 samples consisting of 16 severe preeclampsia and 16 normotensive pregnant women. We used the t test or non-parametric tests and correlation to statistically test the difference.

3. RESULTS

In this research, there were 32 subjects, consisted of 16 normotensive pregnant women and 16 severe preeclampsia who all meet the inclusion and exclusion criteria. The characteristics are shown in Table 1.

Based on the number of parity, the preeclampsia group consists of 10 cases of multigravida (62%). Based on the maturity of the pregnancy, it has 10 cases of term pregnancies (62%). The most education level was high school education (62%). The most common occupation was housewife (81%). There was 81% that did not have a history of preeclampsia before. The Body Mass Index (BMI) was less than 25 in 10 cases (62%). The infant weight more than 2500 grams in 10 cases. The proportion of the younger than 35 years old was equal to the over 35.

In the group of normotensive pregnant mothers, the numbers of subjects based on the number of parity were equal. There was 69% of term pregnancy. The most education level was high school (81%). The most common occupation was housewife (81%). The BMI was less than 25 in 12 cases (75%). The infant weight more than 2500 grams in 13 cases.

Based on the mean and median of the severe preeclampsia group compared to the normotensive pregnancy group, we concluded that there is no significant difference between the preeclamptic patients with normotensive based on the variables of: maternal age (p=0.510), parity (p= 0.160), AST (p=0138), the number of platelets (p = 0672), IMT (p = 0196), outcomes infants (p=0.160) and LDL (p=0.236). We also found a significant difference between the preeclamptic patients with normotensive for these variables: systolic (p=0.000), diastolic (p=0.000), the levels of ALT (p = 0.043), the levels of total cholesterol (p=0.001), HDL (p=0.035), triglycerides (p=0.000), VLDL levels (p=0.000) and ET-1 (p=0.000).

The Mann-Whitney statistical test showed that there was a significant difference between the levels of endothelin in the <35 years and the ≥ 35 years (p=0.011), inferred that endothelin levels were associated with maternal age.

The Mann-Whitney statistical test showed that there were significant differences between the levels of endothelin between the primipara and the multipara group (p = 0.040).

Based on the tests, it can be concluded that there is no correlation between ET-1 and total cholesterol (r=0.250, p=0.351), HDL (r=0.245, p=0.190) and LDL (r=0.012, p=0.965) in normotensive subjects. We also found moderate correlation with meaningful significance between ET-1 and triglycerides (r=0.589, p=0.016) and VLDL (r=0.590, p=0.016) in normotensive subjects.

Table 1. The sample characteristics

Characteristics	Normal Pregnancy		Severe Preeclampsia	
	N	%	n	%
Mother age				
< 35 year old	14	88	8	50
≥ 35 year 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
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 Birthweight				
≤ 2500	3	19	6	38
> 2500	13	81	10	62

Table 2. The Comparison of the Preeclampsia and the Normal Pregnancy Characteristics

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
Birthweight	2806.25	3050	831.44	2653.13	2750	642.77	0.16
Total Cholesterol	192.06	193.5	40.93	241.19	247	33.47	0.001
HDL	55.31	49.5	17.3	42.75	40.5	10.4	0.035
LDL	119.5	114	32.51	131.88	140	24.88	0.236
Triglyceride	165.63	169.5	31.48	322.81	313	95.88	0
VLDL	33.13	33.9	6.3	64.56	62.6	19.18	0
ET-1	1.03	1.09	0.26	2.46	1.95	1.44	0

Table 3. ET-1 distribution based on age

Characteristic	n	ET-1 mean (pg/mL)	ET-1 median (pg/mL)	P
Mother age				0.011
< 35 years	10	1.65 ± 1.46	1.12 ± 1.46	
≥ 35 years	22	1.93 ± 0.58	1.65 ± 0.58	

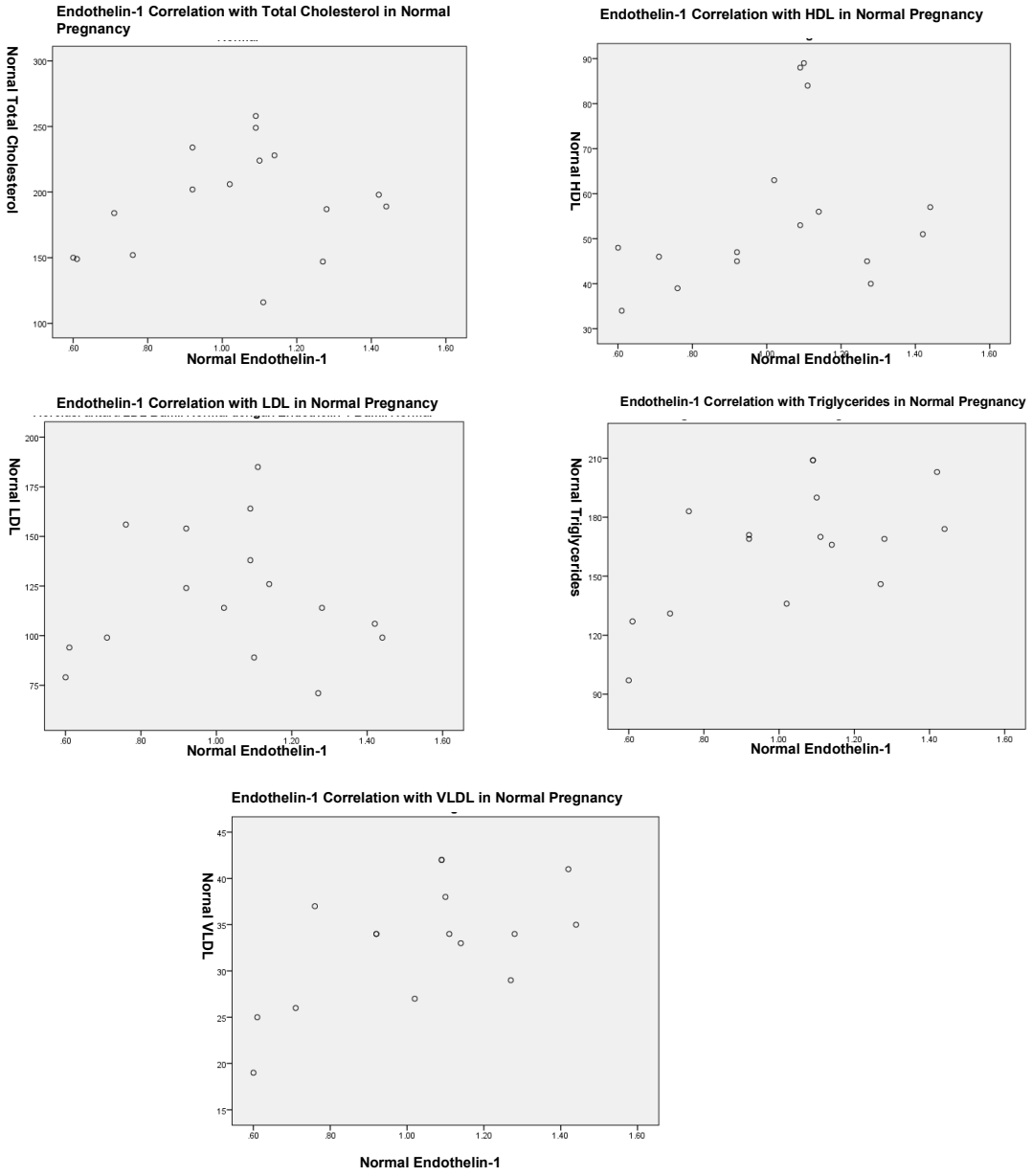

Fig. 1. ET-1 Correlation with lipid profile in normal pregnancy group

Table 4. ET -1 Distribution based on the number of parity

Characteristic	n	ET-1 mean (pg/mL)	ET-1 median (pg/mL)	P
Parity				0.040
Primipara	14	1.70 ± 1.53	1.13 ± 1.53	
Multipara	18	1.82 ± 0.58	1.57 ± 0.58	

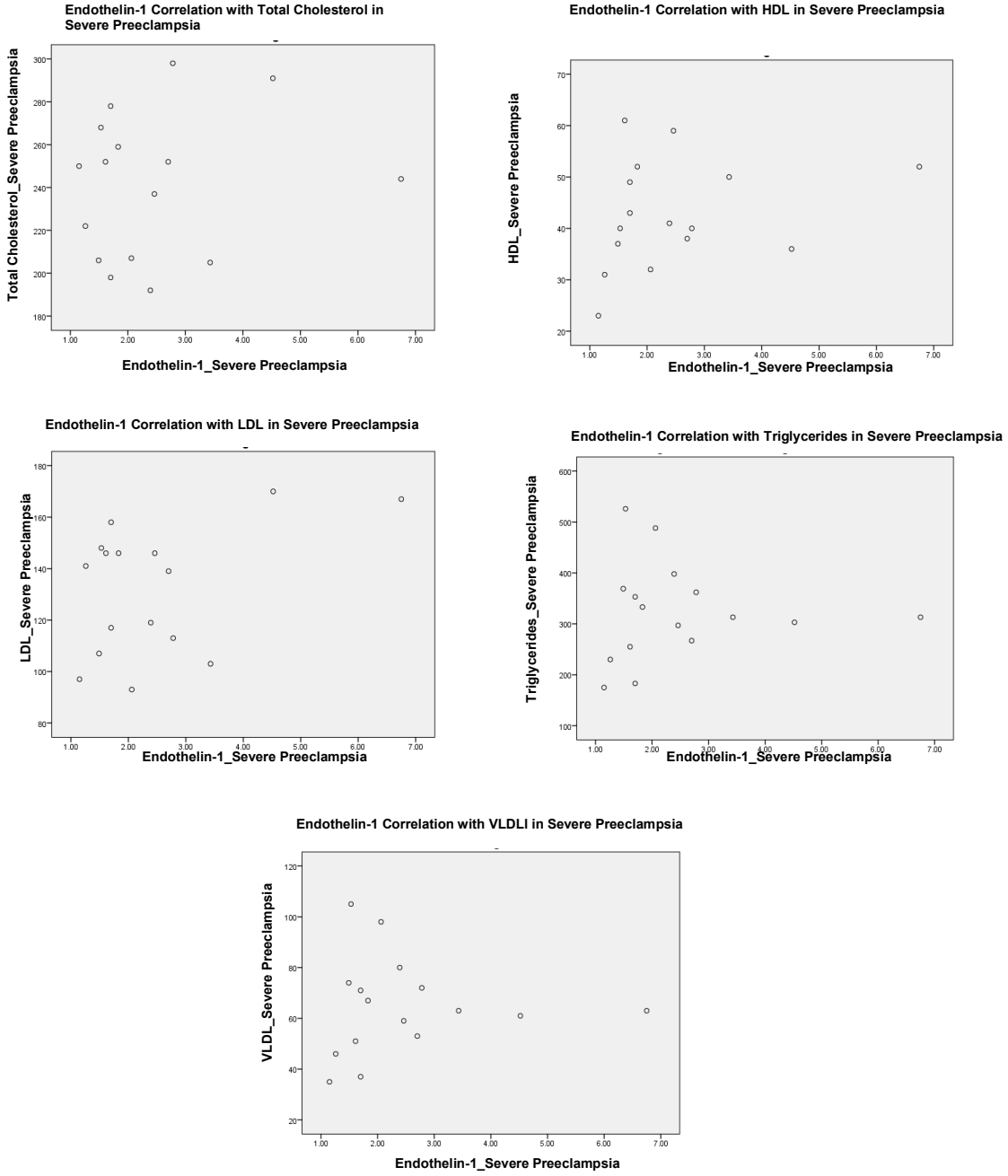

Fig. 2. ET-1 Correlation with Lipid Profile in Severe Preeclampsia Group

Because ET-1 in the severe preeclampsia group were not normally distributed, then we conducted a non-parametric Kendall's tau and Spearman's rho. We found no correlation between ET-1 and total cholesterol (r=0.084, p=0.652), HDL (r=0.262, p=0.162), LDL (r=0.153, p=0.416), triglycerides (r=0.101, p=0.588) and VLDL (r=0.108, p=0.588) in preeclampsia.

4. DISCUSSION AND CONCLUSION

Preeclampsia, a hypertensive disorder peculiar to pregnancy, is a systemic syndrome that appears to originate in the placenta and is characterized by widespread maternal endothelial dysfunction. Until recently, the molecular pathogenesis of phenotypic

preeclampsia was largely unknown, but recent observation support the hypothesis that altered expression of placental anti-angiogenic factors are responsible for the clinical manifestation of the disease. These anti-angiogenic factors produce systemic endothelial dysfunction, resulting in hypertension, proteinuria, and the other systemic manifestation of preeclampsia [10,14]. That systemic disorders lead to decreased uteroplacental perfusion due to a cytotrophoblast abnormal invasion in uterine spiral arteries. A placental hypoxia will cause a decrease in placental perfusion. When placenta is ischemic condition, the placenta will produce lipid peroxide which gets into and binds to lipoproteins, particularly low LDL [9].

The relationship between the lipid profile and preeclampsia had been studied. Prasetyo et al reported that there was significant correlation with total cholesterol & LDL in the risk of preeclampsia. High triglyceride increases the risk of vascular disorder of the placenta, which triggers endothelial dysfunction, atherosclerosis and thrombosis and the formation of atherosclerosis in the placental spiral arteries in women with preeclampsia [15,16].

In this study, the characteristics of the sample include the age, parity, gestational age, education, occupation, previous preeclampsia history, body mass index and infant birthweight, are listed in Table 1. The distribution based on the age was similar in both groups. Severe preeclampsia had more multiparous patients (62%), more gestation > 37 weeks (62%) and more normal body mass index (62%), more baby with weight >2,500 g (62%). This result is slightly different from existing theories, possibly due to random sampling within a relatively short period.

From mean difference test (Table 2), the score was higher in severe preeclampsia in regards to the mother age, parity, AST, level of haemoglobin, platelet, and BMI. In contrast, the infant birthweight was lower. The differences were not significant ($p>0.05$). The result confirms the previous studies. In preeclamptic patients, other studies found an older maternal age, lower infant birthweight, and higher AST and ALT [17].

In Table 2, the LDL and HDL were higher ($p>0.05$) in the preeclampsia than in the normal pregnancy, eventhough the differences are not significant. The total cholesterol, triglycerides and VLDL in the preeclampsia are significantly higher compared to the normal pregnancy ($p<0.05$). It suggests that the lipids are involved in endothelial damage in the preeclampsia.

In a normal pregnancy, an elevated lipoprotein level and composition may occur as a result of the hormonal changes. However, physiological changes can be well-tolerated by a pregnant woman. High triglycerides is required for fetal growth. The research concluded that a non-preeclampsia pregnancy had an increase in low density and larger diameter of LDL, whereas in preeclampsia the LDL was smaller and had a high density, and the LDL was more easily to be oxidized. The study also found a significant association between triglycerides and VLDL. The fact that patients with preeclampsia experiencing dyslipidemia, characterized by high levels of triglycerides and VLDL, suggests a correlation between preeclampsia and endothelial lesions that causes the atherosclerosis [18-20].

Jeyabalan et al. reported a platelet membrane study found an increase in fluid and cholesterol concentrations occurred in preeclampsia. A woman with a history of preeclampsia had a higher total cholesterol, LDL, and triglycerides, although the differences were not always statistically significant. Low HDL concentration among women with a history of preeclampsia had been reported by several studies [21].

In preeclampsia patients, the increase in triglycerides and free fatty acid increased two fold compared to uncomplicated pregnancies. In consequence, it increases the amount of fatty acids in the visceral adipocytes, triggers the liver VLDL production, and suppresses the lipoprotein lipase activity, which causes an increase in triglycerides serum concentrations. Triglyceride is contended as a major risk factor in endothelial dysfunction, arteriosclerosis, and thrombosis in preeclampsia [20].

Multiple evidence suggests that ET-1 is 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. In addition, in some other studies have shown elevated levels of ET-1 in various pathological conditions such as

hypertension, uremia, ischemic heart disease and Atherosclerosis [12,22].

Endothelium plays an important role in vascular homeostasis through substance synthesis and release. The substances synthesized and released modulate the vascular tone and structure, and modulate the interaction of the circulated cells with the blood vessel wall. A hypercholesterolemia patient with endothelial dysfunction expresses a decrease in nitrogen oxide (NO) and experience a vasodilation by the presence of acetylcholine. These contribute to a premature atherosclerosis. In some studies, ET-1 was also argued to cause a vasomotor dysregulation in dyslipidemia [23].

Fig. 1 showed in the normal pregnancy group, there was a significant correlation between ET-1 with triglyceride and VLDL. Fig. 2 showed it in the severe preeclampsia, there was no association between ET-1 with the lipid profile. In a 2014 study, the result was not much different. The study examined ET-1 in patients with myocardial infarction with or without coronary artery bypass. It found no significant correlation between ET-1 and the lipid profile [24].

Jenkins et al. [25,26] reported a research on the triglyceride and insulin relationship with ET-1 showed a significant correlation between the variables. Another study that examined whether physical activity will increase the levels of endothelin-1 in patients with coronary artery disease (CAD), found a correlation between LDL and ET-1, which LDL were high in CAD patients. It showed that the regulation of in vivo ET-1 secretion involves LDL.

Ellatif et al. [27] conducted a research on the effect of altitude on endothelial dysfunction in cardiovascular patients. The study showed an increased ET-1 in patients with cardiovascular disease in a higher altitude and had an abnormally higher lipid profile (total cholesterol, LDL, HDL, triglycerides).

In the severe preeclampsia group, 4 subjects had complications: 2 had an impending eclampsia, 1 sample progressed to eclampsia, and 1 suffered eclampsia with HELLP syndrome. In these for subjects, both of ET-1 and lipid profile (except HDL) were quite high. It may indicate further endothelial damage in preeclampsia. These findings were consistent with a research, which found ET-1 significantly elevated in preeclampsia patients with HELLP syndrome compared to those without HELLP syndrome. Unfortunately, the study did not include the lipid profile [28].

Our study had some limitations. This study cannot control the confounding factors such as urea, creatinine and other biochemical mediators. There was no examination of other biochemical factors that could affect the ET-1 level in this research.

As conclusion, in a normal pregnancy, there is a correlation between the ET-1 and the triglyceride and VLDL, where an elevated ET-1 was followed by an increase in triglyceride and VLDL. However there is no relationship between the level of endotheliln-1 with the lipid profile in a severe preeclampsia.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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