Sys Rev Pharm 2021;12(1):1598-1601
A multifaceted review journal in the field of pharmacy

Correlation between Level of Soluble Endoglin and Soluble FMS-Like Tyrosine Kinase-1 on Severe Preeclampsia and Normal Pregnancy

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ABSTRACT

Preeclampsia ranked second as the major causes in maternal death after hemorrhage in Indonesia. Elevated antiangiogenics factor such as soluble endoglin (sEng) andn soluble fms like tyrosine kinase-1 (sFit-1) and reduced proangiogenics such as vascular endothelial growth factor (VEGF), placental growth factor (P1GF), and transforming growth factor-β (TGF-β) have been documented in preeclampsia. Therefore, we aimed to conduct measurement of sEng and sFlt-1 level as early detection of preeclampsia. This was observational analytic study with cross sectional approach. Level of sEng and sFlt-1 was measured with high sensitivity indirect sandwich enzyme-linked immunosorbent assay (ELISA). Results showed that level of sEng and sFlt-1 were higher in severe preeclampsia compared to normal pregnancy. There was significantly positive correlation between level of sEng and sFlt-1 both in severe preeclampsia and normal pregnancy, in which higher sEng level was associated with higher sFlt-1 level.

Keywords: Preeclampsia, sEng, sFlt-1

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INTRODUCTION

Preeclampsia is a complex multisystem disease occurred during pregnancy, as indicated by hypertension (>140/90 mmHg), and proteinuria after 20 weeks of pregnancy.[1-3] Number of preeclampsia cases remain high in developing countries which is about 5-8%.[4,5] In Indonesia, preeclampsia ranked second as the major cause in maternal death after hemorrhage. Preeclampsia in dr. Hasan Sadikin Hospital in Bandung-Indonesia was 7,2% cases of 7.285 birth with mortality number of 0,3% and perinatal 0,21%.[6] Thus, early detection of preeclampsia is required to prevent disease that might endanger both mother and child.

Incomplete trophoblast invasion during placentation is documented in preeclampsia. Endovascular trophoblasts invade to decidua, yet it does not reach miometrium which later reduce the blood vessels diameter.[1] Diminished miometrium arterial causes disturbance in placental circulatory. Furthermore, poor perfusion and hypoxia promotes placental debris release that trigger inflammation along with other pathological proccess.[1,7]

Inflammatory mediators, metabolic, angiogenic and antioangiogenic factors are later present that causes endothelial dysfunction. It stimulates trombocyte activity to undergo adhesion, aggregation, and release. These events are terminated by decrease in vasodilator levels (prostacyclin and nitrite oxide/endothelium-derived relaxing factor) and increase in vasoconstrictor levels (tromboxan and endotelin).[1-8] Extensive angiogenesis chanelling oxygen and nutrient supply to infants in normal pregnancy, is not present in preeclampsia.[9,11] Angiogenesis requires various proangiogenic and antiangiogenic factors to act simultaneously in placental development. Imbalance caused by predominently antiangiogenics over proangiogenics, promotes failure in remodelling that leads to abnormal placentation. Referring to Lim et al, antiangiogenics factor such as soluble endoglin (sEng) andn soluble fms like tyrosine kinase-1 (sFit-1) increase, whilst proangiogenics such as vascular endothelial growth factor (VEGF), placental growth factor (P1GF), and transforming growth factor-β (TGF-β) decrease.[12] sEng inhibits TGF-β binding to endothelial receptor that reduce ability of nitric oxide-dependent endothelial vasodilatation. In preeclampsia, sEng is excessively produced in trophoblast cells along with sFlt-1 and P1GF. Low oxygen promotes synthesis of sEng and sFlt-1 or reduce PlGF otherwise. Preeclamptic placenta also contain higher glycocylated sEng and sFlt-1.[13,15.]

To date, markers of damaged endothelial vessels in preeclamptic patients as the new standard, are sEng, sFlt-1, and PlGF.[16,17] Study regarding correlation between sEng and sFlt-1 serum in severe preeclampsia has never been done in Hasan Sadikin Hospital. Therefore, we aimed to conduct measurement of sEng and sFlt-1 level that hopefully can be early detection on preeclampsia with high sensitivity.

MATERIAL AND METHODS

Study design

This was observational analytic study with cross sectional approach. Study was conducted in Dr. Hasan Sadikin Hospital, Bandung, Department of Obstetrics and Gynecology and Cibabat Local Hospital and RSB Astana Anyar. Measurement of ELISA was conducted in Laboratorium Prodia Jakarta. Research subjects involved preeclampsia (18 samples), and normal pregnancies as control (19 samples) in accordance with inclusion criteria. Patients were managed according to the Guidelines of Obstetrics and Gynecology, Faculty of Medicine Padjadjaran University Hasan Sadikin Hospital (FKUP/RSHS), Bandung, through some tests: (1) anamnesis; name, age, address, parity, first day of the last period, gestational age, hypertension history, and current pregnancy disease. (2) blood pressure was measured by using sphygmomanometer. (3) 6 ml blood sample was

taken from peripheral blood before birth, centrifuge at 1,600g 10' 4 °C. Blood sample was withdrawn and then kept in −20 °C temperature. (4) Level of sEng and sFlt-1 was performed by high sensitivity indirect sandwich enzyme-linked immunosorbent assay (ELISA).[18,19]

Data analysis

Data were analyzed with T-test to compare means, and normal distribution; Mann-Whitney test to measure median differences, and abnormal distribution; Chi Square to compare two category groups. Correlation between sEng, sFlt-1, protein, and blood pressure were measured with Rank Spearman test.

Ethical clearance

The study was conducted after the approval from Ethical Review Boards of Health Research, Faculty of Medicine and Dr. Hasan Sadikin Hospital, Bandung. All research subjects were voluntarily required to sign informed consent prior to the study.

RESULTS

There were 37 research subjects involved in accordance with inclusion criteria, consisting of 18 severe preeclampsia and 19 normal pregnancy. Homogeneity was measured based on age, parity, and gestational age. Characteristics of subjects are presented in Table 1. As shown in Table 1, there was no significant difference in age between two groups (p=0,831), as well as in gestational age (p=0,221), dan parity (p=0,105). Therefore, both groups were homogenous to compare.

Table 1. Characteristics of research subjects

	Characteristic	Group		P-value
		Severe preeclampsia (n=18)	Normal (n=19)	
1	Age (th)			0,831
	$\overline{X}$ (SD)	27,4(7,1)	27,0(5,3)	
	Range	17-40	20-36	
	≤ 20	7	8	
	21-34	8	8	
	> 35	3	3	
2	Parity			0,105
	Primi	18	15	
	Multi	0	4	
3	Gestational age (mg)			0,221
	37	8	10	
	38	6	2	
	39	4	7	
	$\overline{X}$ (SD)	37,8(0,8)	37,8(0,9)	
	Range	37-39	37-39	

Note: p-value was measured using T-test, parity was measured using Fisher test, and gestational age was measured using χ^2 test

Table 2 shows there was significant difference in sEng level between severe preeclampsia and normal pregnancy (p=0,001). Level of sEng was higher in severe preeclampsia compared to normal pregnancy. Level of sFlt-1 was also higher in severe preeclampsia than normal pregnancy.

Table 2. Level of sEng and sFilt-1 between severe preeclampsia and normal pregnancy

	Variable	Group		P-value
		Severe preeclampsia (n=18)	Normal (n=19)	
1	sEng			0,001
	$\overline{X}$ (SD)	36,75(25,45)	13,53(10,73)	
	Median	25,81	9,57	
	Range	6,33-78	4,01-45,78	
2	sFlt-1			<0,001
	$\overline{X}$ (SD)	18086,8(8824,4)	7277,36	
	Median	20524,75	6820,4	
	Range	1430,5-28540,5	1657,6-18859,6	

Note: p-value was measured with Mann-Whitney test, and sFlt-1 was measured with T-test

Correlation between sFlt-1 in both treatment groups was also significant (p<0,001). Based on Table 3, sEng and sFlt-1 both in severe preeclampsia and normal pregnancy showed a significant positive correlation in which higher sEng level was associated with higher sFlt-1 level. Correlation between sEng and sFlt-1 in severe preeclampsia and normal pregnancy can be seen in Figure 1 and 2.

Table 3. Correlation of sEng and sFlt-1 between severe preeclampsia and normal pregnancy

Correlation	Group			
	Severe preeclampsia		Normal	
	r_s	p-value	r_s	p-value
sEng and sFlt-1	0,839	<0,001	0,504	0,028

Note : r_s= Rank Spearman coefficient

Based on Figure 2, there was positive correlation between increased sFlt-1 and sEng level (p<0,001) (p<0,05). The correlation was significant both in preeclampsia group (0,839, p>0,05) and normal pregnancy (0,504, p<0,001).

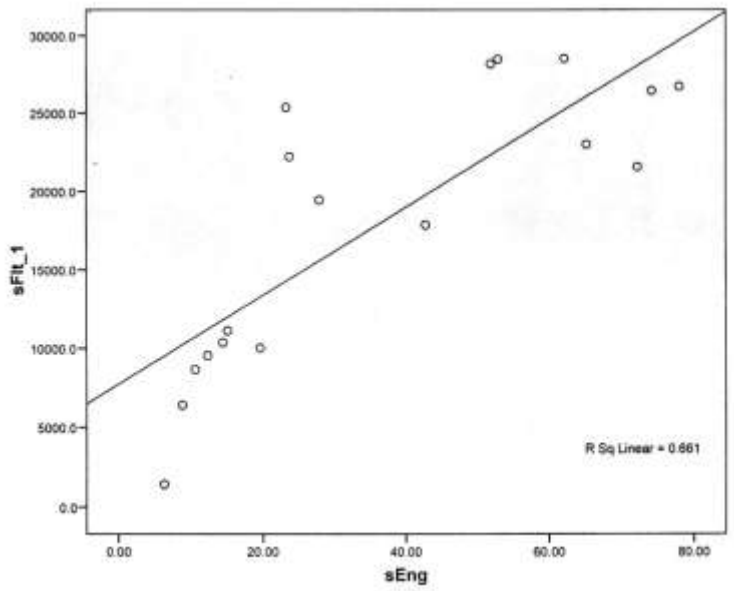

Figure 1. Correlation between sEng and sFlt-1 in severe preeclampsia

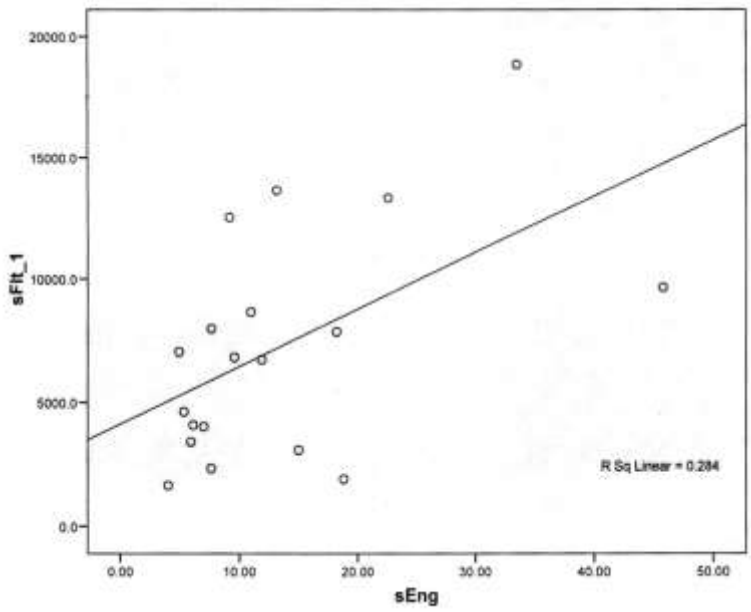

Figure 2. Correlation between sEng and sFlt-1 in normal pregnancy

DISCUSSION

Characterization of research subjects showed no significant difference in age and gestational age. Effect of maternal age, parity, and gestational age in preeclampsia occurence has been reported in previous studies. Young

age, primigravida and gestational age have higher risk of preeclampsia.[1,20.]

In this study, sEng level was positively associated with increased sFlt-1 both in severe preeclampsia and normal pregnancy. In severe preeclampsia, sFlt-1 and sEng were higher than that in normal pregnancy. Correlation between level of sEng and sFlt-1 is very important to be noted as patophysiology of preeclampsia in which imbalance of pro- and antiangiogenics occurs. Alteration in pro- and antiangiogenic is associated with damaged endothelium in placenta. Level of sEng and sFlt-1 as antiangiogenics increase in preeclampsia. These results are in accordance with study done by Chen Y., that compared level of sFlt-1, PlGF, and sEng in preeclamptic patients and normal pregnancy. It was revealed that sFlt-1 was significantly higher in preeclamptic patients than normal. Referring to Levine et al., sFlt-1 elevate about five weeks prior to preeclampsia onset. Average of sFlt-1 level in women with clinical disease is three-fold higher than that in normal pregnancy at the same gestational age, and also associated with its severity.[17] According to Chen Y., sEng was significantly higher prior to preeclampsia onset. They suggest that sEng should be measured at second trimester as a marker to predict severe preeclampsia.[21] In this study, increased sFlt-1 was positively correlated with increased sEng.

CONCLUSION

Level of sFlt-1 in severe preeclampsia was higher than that in normal pregnancy. Level of sEng in severe preeclampsia was also higher than that in normal pregnancy. There was positive correlation between sFlt-1 and sEng in severe preeclampsia.

ACKNOWLEDGEMENTS

This research was supported by the Department of Obstetrics and Gynecology Dr. Hasan Sadikin Hospital (RSHS), Bandung. We would also like to thank PT. Prodia for the aid in providing research materials.

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