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The Level of Soluble FMS-Like Tyrosine Kinase 1 (sFlt-1) in the Umbilical Cord in Preeclampsia and its Correlation with Blood Pressure and Baby's Birth Weight

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Abstract
Soluble FMS-like tyrosine kinase 1 (sFlt-1) is one of the markers that plays a role in the pathogenesis of preeclampsia. This study aimed to analyze the levels of umbilical cord sFlt-1 in relation to blood pressure and birth weight in babies on preeclamptic mothers. The study employed an analytical cross-sectional observational design. The sample size for this study consists of 33 participants. The levels of umbilical cord sFlt-1 were examined using the ELISA method. The data were analyzed using the Mann-Whitney U test to determine the differences in sFlt-1 levels, blood pressure, and birth weight. Spearman's rank correlation test was used to determine the correlation between sFlt-1 levels and blood pressure and birth weight. The sFlt-1 examination results indicated a significant difference between the preeclampsia and normal pregnancy groups. The mean sFlt-1 level in the preeclampsia group was 10.693 ng/mL (SD ±6.535 ng/mL), whereas in the normal pregnancy group, it was 3.572 ng/mL (SD ±1.225 ng/mL). This difference suggests that sFlt-1 levels are significantly higher in mothers with preeclampsia compared to those with normal pregnancies. This finding is consistent with the pathophysiology of preeclampsia, which involves endothelial dysfunction and an increase in anti-angiogenic factors such as sFlt-1.

Keywords: Birth Weight, Blood Pressure, Preeclampsia, sFlt-1.

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1. INTRODUCTION

Preeclampsia is a maternal systemic disease characterized by the onset of high blood pressure, with systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg, accompanied by proteinuria after 20 weeks of gestation and organ dysfunction (Prawirohardjo, 2014; Rahmi et al., 2016; Sabrin et al., 2020). Ten million women experience preeclampsia worldwide every year. In Indonesia, the incidence of preeclampsia reaches 128,273 cases or about 5.3% per year (Perkumpulan Obstetri dan Ginekologi Indonesia, 2016; Sirait, 2012). The World Health Organization (2015) records approximately 830 women dying each day due to complications related to pregnancy and childbirth (World Health Organization, 2015). High blood pressure during pregnancy is one of the main causes of maternal mortality, accounting for 75% of cases (Perkumpulan Obstetri dan Ginekologi Indonesia, 2016; Seyom et al., 2015; Sudarman et al., 2021).

Complications of preeclampsia in mothers include oliguria, anuria, placental abruption, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, while for infants, it increases the risk of Intrauterine Growth Restriction (IUGR), Small for Gestational Age (SGA), premature birth, perinatal asphyxia, and fetal death in the womb (Krishnaveni et al., 2018; Sivakumar et al., 2007). The main cause of preeclampsia cannot be determined with certainty. Many theories have been proposed regarding the causes of preeclampsia, but broadly speaking, this condition occurs due to the influence of the placenta (Lindheimer et al., 2008). Preeclampsia is believed to occur in two stages. The first stage involves endothelial dysfunction of cytotrophoblasts and shallow invasion of spiral arteries into the myometrium, leading to ischemia and hypoxia. The second stage involves oxidative stress, triggering the release of anti-angiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt-1), prostaglandins, and cytokines from the placenta into the maternal bloodstream (Moore et al., 2012; Álvarez-Fernández et al., 2016; Rana et al., 2019; Wahida & Gusriani, 2023; Zhao et al., 2010).

Research related to the role of sFlt-1 in the pathogenesis of preeclampsia has been previously conducted using various research methods (Prathima & Anuchitra, 2015; Poon & Nicolaides, 2014; Sibai, 2006) concluded that there is an increase in sFlt-1 in pregnant women with preeclampsia, similar to the findings of Tsao et al., (2005), who also concluded that the levels of sFlt-1 in preeclampsia are significantly higher compared to normotensive mothers. Powers and Varughese measured sFlt-1 levels by taking blood samples from the maternal cubital vein, while Tsao measured sFlt-1 levels through the umbilical cord. Most studies related to sFlt-1 measurement collected blood samples from the maternal cubital vein, which, when compared to human umbilical cord blood serum (HUCBS), should yield more significant results when examining HUCBS because HUCBS is a richer source of various cytokines and growth factors, including proangiogenic factors (PlGF and VEGF) and antiangiogenic factors (sFlt-1 and sEng). To the best knowledge of the researchers, there have been limited studies conducted in Indonesia regarding umbilical cord sFlt-1 levels. Therefore, it is necessary to conduct research on sFlt-1 levels in the umbilical cord of preeclamptic mothers to determine the comparison between sFlt-1 levels in the umbilical cord and the maternal blood of preeclamptic mothers. Based on the above description, the researchers aim to analyze the sFlt-1 levels in relation to blood pressure and birth weight in babies on preeclamptic mothers.

2. RESEARCH METHOD

The research design of this study is an analytical observational cross-sectional design. In this design, data is collected at a single point in time from a predetermined sample to analyze the relationship between umbilical cord sFlt-1 levels, blood pressure, and birth weight in mothers with preeclampsia. The population in this study consisted of all delivering mothers at RSKDIA Siti Fatimah and RSIA Siti Khadijah, Makassar. The sample size in this study consisted of 33 pregnant women. A total of 33 individuals who met the inclusion criteria, which

included delivering mothers with preeclampsia and mothers with normal pregnancies without chronic diseases or intrauterine infections, were included in the study. The sample was divided into 18 individuals in the preeclampsia group and 15 individuals in the normal pregnancy group. The sampling technique used in this study was accidental sampling.

Several instruments were used in this study, including observation sheets to determine asphyxia status, observation sheets to measure the baby's birth weight, and an examination tool using a microplate reader with the ELISA method (unit: ng/mL) to measure sFlt-1 levels. Data collection and processing were conducted over a period of 12 weeks. Blood samples for sFlt-1 level examination were collected and analyzed in the laboratory by the researcher with assistance from laboratory staff.

The data in this study were further processed using the SPSS program. To determine the mean sFlt-1 levels in each research group, the Mann-Whitney U test was used, with a significance value of $p<0.05$ indicating a significant difference. To indicate the relationship between sFlt-1 levels and the occurrence of asphyxia and birth weight, the Spearman rank correlation test was used, with significance values of $p=0.05$ for systolic blood pressure, $p=0.05$ for diastolic blood pressure, and $p=0.05$ for birth weight, all of which showed statistically significant correlations. This research was conducted after obtaining ethical clearance with reference number 11/KEPK-FIKES UBT/VIII/2019, issued by the Ethics Committee of the Faculty of Health Sciences, Universitas Borneo Tarakan.

3. RESULTS AND DISCUSSION

Table 1. Frequency Distribution of Sample Characteristics.

Characteristics	Research Group			
	Normal Pregnancy (n=15)		Preeclampsia (n=18)	
	n	%	n	%
Parity				
Primigravida	6	35,3	11	64,7
Multigravida	9	56,3	7	43,8
Gestational Age (weeks)				
Preterm	2	50,0	2	50,0
Aterm	13	44,8	16	55,2
Education				
Low	1	14,3	6	85,7
High	14	53,8	12	46,2
Age (years)				
< 20	0	0,00	1	100
20 – 35	14	48,3	15	51,7
>35	1	33,3	2	66,7
Occupation				
Housewife	9	39,1	14	60,9
Enterpreneur	3	42,9	3	57,1
Civil Servant	3	75,0	1	25,0

Table 1 shows the mothers' characteristics included in this study sample. The majority of the mothers were between 20-35 years old (87.9%), which falls within the reproductive age group. Most of the pregnancies were observed to be at term (78.8%), with a lower proportion of multigravidas (48.5%) compared to primigravidas (51.5%). The socioeconomic factors, assessed based on the mothers' education level and occupation, indicated that the majority of participants had a high level of education (78.8%), and most were homemakers (69.7%).

Table 2. Distribution of mean sFlt-1 levels in umbilical cord.

sFlt-1 Level (ng/mL)	Research Group		
	Normal Preganancy	Preeclampsia	*p-value*
Mean ± SD	3,572±1,225	10,693±6,535	0,000

Table 2 shows that the mean sFlt-1 levels, with the highest concentration found in the preeclampsia group (10,693 ng/mL) compared to the normal pregnancy group (3,572 ng/mL). The Mann-Whitney U test results showed a highly significant difference between the preeclampsia group and the normal pregnancy group (p=0.000).

Table 3. Distribution of Blood Pressure Differences and Birth Weight of Infants in the Research Group.

Variable	Normal Preganancy	Preeclampsia	*p-value*
	Mean±SD	Mean±SD	
Systolic Blood Pressure	115,33±5,164	146,11±8,498	0,000
Diastolic Blood Pressure	80,67±4,577	97,22±7,519	0,000
Birth Weight	2973,33±301,109	2672,22±386,242	0,026

Table 3 shows the differences in systolic blood pressure, diastolic blood pressure, and birth weight between the two study groups. Systolic blood pressure showed a significant difference (p=0.000), as did diastolic blood pressure (p=0.000) and birth weight (p=0.026).

Tabel 4. The Correlation between Umbilical Cord sFlt-1 Levels and Blood Pressure and Birth Weight.

Variable	Statistical Value			
	sFlt-1 Normal Preganancy		sFlt-1 Preeclampsia	
	r	*p-value*	r	*p-value*
Systolic Blood Pressure	-0,372	0,172	0,793	0,000
Diastolic Blood Pressure	-0,413	0,127	0,711	0,001
Birth Weight	-0,765	0,001	-0,603	0,008

Table 4 shows the correlation between sFlt-1 levels and systolic blood pressure (p=0.000), diastolic blood pressure (p=0.001), and birth weight (p=0.008) in the preeclampsia group. Conversely, in the normal pregnancy group, no relationship was found between systolic blood pressure (p=0.172) and diastolic blood pressure (p=0.127) with sFlt-1, while a significant relationship was found with birth weight (p=0.001).

This research reveals a significant difference in sFlt-1 levels between the preeclampsia group and the normal pregnant group. Additionally, a correlation was found between sFlt-1 levels and blood pressure and birth weight in the preeclampsia group. The high blood pressure in preeclampsia is caused by vasoconstriction of blood vessels. This is due to placental ischemia and endothelial damage (Lam et al., 2005). One substance that plays a crucial role in endothelial damage is sFlt-1. Various studies have concluded that the antiangiogenic factors produced by the placenta play an important role in the pathogenesis of preeclampsia. Preeclampsia is believed to occur in two stages (Chen et al., 2009; Chen, & Wang, 2013; Xiao et al., 2014). The first stage involves endothelial dysfunction from inadequate cytotrophoblast invasion of spiral arteries into the myometrium, resulting in remaining small-caliber resistance vessels. Insufficient placental invasion can cause ischemia and hypoxia. The second stage occurs towards the end of pregnancy, where oxidative stress triggers the placenta to release anti-angiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), prostaglandins, and cytokines into the maternal circulation. The high production of sFlt-1 and sEng leads to hypoxia and reduced levels of proangiogenic factors, namely placental growth factor (PIGF), and vascular endothelial growth factor (VEGF). These changes result in

systemic endothelial dysfunction and an inflammatory response that leads to increased systemic vascular resistance, vasoconstriction, activation of the coagulation cascade, and clinical manifestations such as hypertension, proteinuria, liver dysfunction, neurological disorders, hematological disorders, and impaired fetal growth (Moore et al., 2012; Kajdy et al., 2020; Maynard & Karumanchi, 2011; Poon & Nicolaides, 2014; Zhao et al., 2010).

The findings from this study are supported, who reported elevated levels of sFlt-1 in women with preeclampsia compared to those without preeclampsia, demonstrating a significant role of antiangiogenic factors in the disease's pathophysiology (Karumanchi, 2016; Helmo et al., 2018; Tendean & Wagey, 2021). Moreover, studies by Levine et al., (2006) have indicated that increased sFlt-1 levels precede the onset of preeclampsia symptoms, suggesting that sFlt-1 could serve as an early biomarker for preeclampsia. Furthermore, Rana et al., (2019) highlighted that the rise in sFlt-1 levels was strongly correlated with disease severity, reinforcing its role in the clinical progression of preeclampsia.

sFLT-1 protein is one of the membrane-bound FLT-1 receptors. sFLT-1 circulates freely in the serum and functions to bind and neutralize VEGF and PlGF. Several studies have found a relationship between increased sFLT-1 levels and preeclampsia. sFLT-1 levels begin to rise at 5 weeks gestation before the onset of preeclampsia, and they remain elevated compared to women without preeclampsia. sFLT-1 is believed to be closely related to the severity of the disease. sFLT-1 levels in pregnant women with preeclampsia decrease after delivery of the baby and placenta (Maynard & Karumanchi 2011).

In hypertensive conditions, there is an increase in vascular resistance. However, the most important aspect of the progression of preeclampsia is the increased resistance in the uterine arteries that supply blood to the placenta. If the increase in arterial resistance is significant, it can affect the condition of the fetus in the womb. The fetus can experience hypoxia in cases of acute insufficiency, leading to fetal distress (Rana et al. 2019; Seyom et al. 2015).

Preeclampsia is a multisystem disorder in pregnant women that can affect the condition of the fetus through placental insufficiency, resulting in intrauterine growth restriction. In cases of preeclampsia, placental dysfunction occurs, leading to inadequate nutrient supply to the fetus during pregnancy, resulting in lower birth weight than expected for the gestational age (or small for gestational age) (Moore et al. 2012; Poon and Nicolaides 2014; Roberts & Escudero, 2012). These findings are consistent with the research by Sibai (2006), which indicated that fetuses from preeclamptic pregnancies often exhibit growth restriction due to compromised placental function and nutrient transport.

4. CONCLUSION

There is a significant difference in sFlt-1 levels between the group of mothers with preeclampsia and the group of mothers with normal pregnancies, where the preeclampsia group had higher sFlt-1 levels (10.693±6.535 ng/mL) compared to the normal pregnancy group (3.572±1.225 ng/mL). The elevated sFlt-1 levels in mothers with preeclampsia were associated with increased systolic and diastolic blood pressure, as well as lower birth weight of the infants. The analysis results indicated a significant correlation between sFlt-1 levels and systolic blood pressure ($p=0.000$), diastolic blood pressure ($p=0.001$), and birth weight ($p=0.008$). These findings suggest that increased sFlt-1 levels are linked to worsening maternal hypertension and adverse perinatal outcomes, including lower birth weight.

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