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Relationship between Soluble Fms-Like Tyrosine Kinase-1 (Sflt-1) Levels in Preeclamptic Mothers with Asphyxia

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ABSTRACT

Soluble Fms like tyrosine kinase 1 (sFlt-1) is one of the markers that play a role in the pathogenesis of pregnancy-induced hypertension. The research aimed to determine the relationship between sFlt-1 level and asphyxia. The samples were preeclampsia inpartu consisting of 22 people, and normal pregnancy women consisting of 18 people. An analytic observational study with cross-sectional was conducted. The level of sFlt-1 was examined using ELISA. Statistic analysis used Kruskal Wallis test, One-way Anova test and Pearson correlation test. The results showed the facts of the study in the preeclampsia and control groups were not different (p> 0.05). In the preeclampsia group, and the control group (7.876 ± 3.792 ng / mL; p <0.05). There was a difference between sFlt-1 levels and the incidence of asphyxia (p = 0.003) in the preeclampsia group, whereas in the control group no relationship was found between sFlt-1 levels and asphyxia (p> 0.05).

INTRODUCTION

Preeclampsia is a pregnancy-specific condition characterized by placental dysfunction and maternal response to systemic inflammation with endothelial activation and coagulation. The diagnosis of preeclampsia is based on the presence of specific pregnancy-induced hypertension accompanied by other organ system disorders at more than 20 weeks gestation (Airoldi et. al., 2007;. Poon et. al., 2014; Sabrin et. al., 2020).

Preeclampsia is the second leading cause of maternal death. WHO estimates that the incidence of preeclampsia is seven times higher in developing countries than in developed countries. The prevalence of preeclampsia in developed countries is 1.3% - 6%, while in developing countries it is 1.8% - 18%. 5.6 The incidence of preeclampsia in Indonesia alone is 128,273/year or about 5.3% (POGI, 2016).

Complications due to preeclampsia occur not only in the mother but also in the fetus. Fetal complications include an increased risk of intrauterine death, fetal growth restriction, prematurity, and perinatal asphyxia.

Until now, various studies continue to be developed to obtain appropriate and ideal markers in predicting the occurrence of preeclampsia. One of the most studied markers is the anti-angiogenesis factor, namely increased levels of Soluble Fms-like tyrosine kinase 1 (sFlt-1). Increased levels of sFlt-1 in preeclampsia are caused by placental ischemia that causes endothelial dysfunction, resulting in a systemic inflammatory response and organ disorders in the baby.

Based on this description, the researcher intends to conduct a study on the relationship between sFlt-1 levels in preeclamptic mothers and the incidence of asphyxia in newborns.

METHOD

Research Design

This research is a deductive quantitative study using a cross sectional design. The research was conducted at Regional Special Hospital for Mother and Child Siti Fatimah Makassar and Mother and Child Hospital St. Khadijah I Makassar from March to June 2017.

Population and Sample

The examination of serum sFlt-1 levels was carried out at the Hasanuddin University RSP Laboratory Makassar. The population of this study were all pregnant women at Regional Special Hospital for Mother and Child Siti Fatimah Makassar and Mother and Child Hospital St. Khadijah I Makassar. The sample in this study was part of the population who met the inclusion and exclusion criteria of the study. The inclusion criteria of the study were mothers inpartu with preeclampsia. Exclusion criteria are inpartum mothers with intrauterine infection and chronic diseases. The number of subjects in this study was 40 people (consisting of 2 research groups). Sample selection was done by consecutive sampling.

Data Analysis Technique

The examination of serum sFlt-1 levels was carried out by taking 2 cc of blood in the median cubital vein using a 3 ml syringe, then centrifuged to obtain serum ± 100 microns for further examination of serum sFlt-1 levels by ELISA method. Data on sFlt-1 levels were analyzed using One Way Anova test. To determine the relationship between sFlt-1 levels and the incidence of asphyxia, Pearson correlation test was used at the significance level = 0.05.

RESULTS AND DISCUSSION

After observation and selection, 40 postpartum women met the qcriteria, 22 postpartum women with preeclampsia and 18 women with normal pregnancy. The description of the characteristics of the research subjects can be seen in the following table1.

Table 1 shows that the results of statistical tests on all characteristics showed no significant differences between parity, gestational age, maternal age, education and occupation in the preeclampsia and normal pregnancy groups (p>0.05).

Table 1.
Characteristics of research subjects

Characteristics	Research Group				*P*
	Normal Pregnancy (n=18)		Preeclampsia (n=22)		
	n	%	n	%	
Parity					0,737
Primiparous	8	44.4	11	50.0	
Multiparous	10	55.6	11	50.0	
Pregnancy Age					0,325
Preterm	2	11.1	6	27.3	
Atherm	16	88.9	16	72.7	
Mother's Age					0,346
< 20	0	0,00	4	18.2	
21-35	17	94,4	15	68.2	
>36	1	5,6	3	13.6	
Education					
Low	1	5.6	6	27.3	0,163
High	17	94.4	16	72.7	
Jobs					0,629
Housewife	12	66.7	16	72.7	
Self-employed	3	16.7	5	22.7	
Civil Servant	3	16.7	1	4.5	

Note: Kruskal Wallis test; p value on the basis of p = 0.05 is significant

Table 2.
Mean sFlt-1 levels in both groups

Variables	sFlt-1 level (ng/mL)		*p*
	Mean	Standard Deviation	
Control	3,348	1,653	0,000*
Preeclampsia	7,876	3,792	

* One Way Anova Test

Based on table 2, it can be seen that the mean level of sFlt-1 in the preeclampsia group is 7.876 ± 3.792 ng/mL and in the normal pregnancy group is 3.348 ± 1.653 ng/mL. These results show that the average sFlt-1 level in the preeclampsia group is higher than the average sFlt-1 level in the normal pregnancy group.

Table 3 shows that the greatest incidence of asphyxia occurred in the preeclampsia group, namely 10 cases or 20% and the normal pregnant group as many as 2 cases or 4%. The total incidence of asphyxia in this study was 12 cases from the total sample. The results of the Kruskal-Wallis test showed no significant difference between the two study groups (p>0.05).

Table 3.
Difference in Asphyxia status

Variables		Research group		*p*
		Control	Preeclampsia	
Asphyxia	Yes	2	10	0,066*
	No	16	12	
Total		18	22	

* Kruskal-wallis test

Table 4.
Correlation of sFlt-1 levels and Asphyxia

Variables	Asphyxia r (*p*)
Preeclampsia sFlt-1 levels	-0,597 (0,003)
Normal Pregnant sFlt-1 Level	0,185 (0,462)

* Pearson correlation test

The results of the Pearson correlation test in table 4 show a significant relationship between sFlt-1 levels and the incidence of asphyxia (p=0.003) in the preeclampsia group. While in the normal pregnant group there was no relationship between sFlt-1 levels and the incidence of asphyxia (p>0.05).

Based on the results of statistical tests, it is known that sFlt-1 levels are higher in the preeclampsia group than in the normal pregnancy group. There was also a significant difference between the two research groups. This result answers the research hypothesis that sFlt-1 levels are higher in the preeclampsia group compared to the normal pregnancy group. The serum concentration of sFlt-1 was significantly increased in patients with preeclampsia compared to normal pregnant women (Álvarez-Fernández, 2016).

During normal placental development, cytotrophoblasts invade the maternal spiral artery and degenerate, resulting in low resistance dilatation. This endovascular cytotrophoblast invasion involves replacement, not only of the endothelium, but also of the highly muscular tunica media. During normal differentiation, trophoblast invasion undergoes a process of pseudo-vasculogenesis by changing the expression of adhesion molecules characteristic of epithelial cells (integrins 6/β4, v/β5, and E-cadherin) to endothelial cells (integrin v/β3, platelet adhesion molecule-cell adhesion-1 and E-cadherin) (Foundation P., 2002).

In preeclampsia, cytotrophoblast endovascular invasion remains superficial and the uterine vasculature does not undergo adequate vascular transformation compared to normal pregnancy. The trophoblast invasion fails to undergo pseudo-vasculogenesis. The spiral arteries are not successfully remodeled and result in resistance. This superficial invasion has been shown to be associated with the failure of cytotrophoblasts to adopt an endothelial adhesion phenotype. Aberrant vascular transformation is thought to cause placental insufficiency and consequent placental hypoxia. This hypothesis is further strengthened by the clinical observation that in women thought to have preeclampsia, uteroplacental blood flow is reduced by 50-70% (Powe et. al., 2011; Maynard et. al., 2011; Hagmann et. al., 2011).

There is indirect evidence that excess sFlt-1 may play a direct role in the pathogenesis of abnormal placentation in preeclampsia. SFlt-1 acts as an antagonistic antiangiogenic molecule, binding to VEGF and PlGF and preventing their interaction with their respective receptors (Flt1 and KDR). Several studies have reported that sFlt-1 is upregulated in the placenta in cases of preeclampsia. Excess sFlt-1 in the bloodstream is associated with decreased free VEGF and free PlGF. In fact, the decrease in free VEGF and free PlGF levels was proportional to the increase in serum sFlt1 levels in preeclamptic patients. These results suggest that the antiangiogenic properties of serum from preeclamptic patients are due to the blockade of VEGF and PlGF by endogenous sFlt1. The changes that occur in angiogenic molecules (increased sFlt-1, decreased free PlGF and free VEGF) give rise to clinical symptoms in preeclampsia (Powe et. al., 2011; Maynard et. al., 2011).

VEGF is known to convert hematopoietic stem cells into endothelial cells, inhibition of VEGF would likely block the endothelial differentiation process found in cytotrophoblast invasion. In vitro, sFlt-1 is known to inhibit placental cytotrophoblast invasion and differentiation in primary cytotrophoblast cultures. Overproduction of sFlt-1 is a consequence of placental hypoxia due to abnormal placentation (Powe et. al., 2011; Maynard et. al., 2011).

In addition, since other cells such as monocytes and endothelial cells also produce sFlt-1, it is thought that trophoblasts may not be the only source of sFlt-1 production during preeclampsia. Recent data from Chaiworaponga and Romero (National Institute of Child Health and Human Development, Detroit, MI) indicate that uterine sFlt-1 concentrations are significantly higher than uterine artery concentrations. This finding, together with other studies, suggests that placental tissue is a major source of excess SFlt-1 production during preeclampsia.

In summary, maternal preeclampsia syndrome is thought to result from abnormal placentation and excessive sFlt-1 production from the placenta. Although it remains unclear whether placental hypoxia or sFlt-1 overproduction is the triggering event in the pathogenesis of preeclampsia, several studies have provided evidence that massive sFlt-1 production during preeclampsia results from placental hypoxia. However, why placental hypoxia leads to predominant production of sflt-1 remains unknown (Karumanchi, 2004).

Thus, the researchers concluded that the differences in sFlt-1 levels in the study groups were caused by differences in placental conditions during pregnancy. In preeclampsia, the placenta is ischemic, thus synthesizing sFlt-1 which causes high levels of sFlt-1 in maternal circulation, whereas in normal pregnancy, the placenta is not hypoxic, so higher proangiogenic factors will be found.

The results of the analysis using the Kruskal Wallis test showed that there was no significant difference between the incidence of asphyxia in the preeclampsia group and the normal pregnant group. The results of the Spearman rank correlation test showed a significant relationship between sFlt-1 levels and asphyxia in the preeclampsia group. While in the normal pregnant group, the statistical test results showed no relationship between sFlt-1 levels with asphyxia in both groups.

The results of this study are supported by Maulik et al (2016) which states the involvement of antiangiogenic factors in the regulation of fetal growth disorders. Similarly, Tsao et al (2005) stated that increased levels of sFlt-1 may play an important role in preeclampsia, SGA and asphyxia.

Research conducted by Chen et al (2010), showed a significant decrease in villous density in ischemic placentas leading to decreased branching angiogenesis. Another report stated that there was a decrease in surface area, volume and number of villi as well as a decrease in the number of capillaries in the stroma of ischemic placentas compared to placentas from normal pregnancies. These findings suggest that aberrant vascular formation may be a factor associated with impaired umbilical blood flow. Although the exact cause of abnormal vascularization in ischemic placenta is not known with certainty, deficiency of angiogenic factors and increase of antiangiogenic factors are thought to be one of the main factors 12.

sFlt-1 binds to VEGF and PlGF, decreasing their free blood concentration, thereby inhibiting the interaction of growth factors with their receptors. This leads to endothelial dysfunction and disrupts vasculogenic and angiogenic processes. These results together suggest that abnormal levels of angiogenic and antiangiogenic growth factors are responsible for the pathophysiology associated with preeclampsia.

Tapanainen et al (2008) showed an association between hypoxia, decreased placental size, and the incidence of neonatal asphyxia. Other studies suggest that uteroplasmic hypoxia is the cause of intrauterine hypoxia. During preeclampsia, trophoblast cells fail to fully transform the uterine spiral artery into a high-capacity, low-resistance blood vessel. This leads to constricted and narrow blood

vessels and the development of local hypoxia. In vitro studies show that hypoxia can affect the proliferation, differentiation and invasion of cytotrophoblast cells. This suggests that superficial invasion may be a factor involved in intrauterine hypoxia (Arroyo, 2008).

Impaired placental circulation due to placental ischemia has long been proposed as a major mechanism underlying fetal growth disorders. In line with this concept, Doppler ultrasound studies have shown that increased impedance of the umbilical circulation associated with fetal decompensation results in the absence of end-diastolic flow in the umbilical artery. This hemodynamic disturbance is associated with poor perinatal outcomes including stillbirth and perinatal asphyxia. However, the molecular mechanisms underlying fetal angiogenesis still require further research (Maulik et al., 2016).

Angiogenesis is a complex biological process controlled by agonists and antagonists that directly or indirectly promote or inhibit angiogenic activity. Normal pregnancy is a balanced angiogenic state. Current evidence suggests the presence of an antiangiogenic state in some complications of pregnancy. Maynard et al (2011), first proposed an antiangiogenic state in preeclampsia involving placental phase-like sFlt-1 in maternal plasma, which opposes vascular proagogenic endothelial growth factor (VEGF) and placental growth factor (PlGF). Furthermore, Romero et al (2008), have provided an overview of the effects of antiangiogenic factors in the maternal circulation that are associated with low birth weight, fetal death, asphyxia and are placenta-related. 9

Mediator sFlt-1 levels in the maternal circulation are predominantly derived from the placenta. However, the explanation of the antiangiogenic circulation mechanism in the placenta is still limited. Elucidation of specific placental angiogenic mechanisms will not only expand our understanding of the causative pathways of restricted fetal growth but may also lead to the development of biomarkers for possible FGR 8.

Thus, the researchers concluded that elevated sFlt-1 levels do have an association with the incidence of asphyxia in preeclamptic mothers but are not the main causative factor. Further research is still needed to determine the role of each factor in maternal circulation related to perinatal asphyxia.

CONCLUSIONS AND RECOMMENDATION

The mean level of sFlt-1 in preeclampsia was higher than the mean level of sFlt-1 in normal pregnancy. There was a significant relationship between sFlt-1 levels and asphyxia in the preeclampsia group, while in the normal pregnancy group there was no relationship between sFlt-1 levels and asphyxia. It is recommended to further researchers to develop this research with other variables.

Ethics approval and consent to participate

Researchers have obtained research permits from the Salatiga City health office and have also obtained consent from the research participants prior to conducting in-depth research.

Consent for publication

I fully agree that this thesis can be published for academic purposes and I am ready to provide support and additional information needed to facilitate the publication process.

Availability of data and material (ADM)

All of the data and materials used in this research have been collected well and are available for those who need them, both for academic purposes and further research.

Competing interests

The authors declare that they have no involvement with any external parties and this paper is purely from the sources listed in the bibliography and does not contain plagarism from any journal article. All sources of writing have been listed in the bibliography

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Authors' contributions

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