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Short Communication

Concentrations of Soluble FMS-Like Tyrosine Kinase 1 and Placental Growth Factor Vary between Early- and Late-onset Preeclampsia

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ABSTRACT

Preeclampsia is a disease with a high mortality rate. The occurrence of preeclampsia based on onset can be detected by examining the biomarkers consisting of Soluble FMS-Like Tyrosine Kinase 1 (Sflt-1) and Placental Growth Factor (PIGF). This study was aimed at determining the concentrations and ratio of Sflt-1 to PIGF in early- and late-onset of preeclampsia. A cross sectional comparative study in General Center Hospital of DR. M. Djamil Padang, Pariaman Regional Hospital, Aisiyah Pariaman Hospital, and Padang Pariaman Regional Hospital was conducted for 2 years. Patients with early- and late-onset preeclampsia who satisfied the inclusion criteria and received treatment in the study sites during that time were recruited. Sampling was consecutive with 28 people per group. The enzyme-linked immunosorbent assay (ELISA) was used to evaluate the levels of Sflt-1 and PIGF. Data normality test was performed using the Shapiro-Wilk test and bivariate analysis with the Mann-Whitney test. The results indicated that there was a significant difference ($p<0.05$) between the mean levels of Sflt-1 at the early- and late-onset of preeclampsia with values of 8.69 and 5.61 ng/mL, respectively. Also, a significant difference between the mean early- and late-onset of PIGF levels was observed with values of 54.98 and 228.78 ng/mL, respectively. The mean early-onset of Sflt-1/PIGF ratio was 0.25 ng/mL, while a value of 0.5 ng/mL was recorded for the late-onset. The findings of the study revealed that there are differences in the levels of Sflt-1, PIGF, and the ratio of Sflt-1/PIGF between the early- and late-onset of preeclampsia.

Keywords: Early-onset preeclampsia, Late-onset preeclampsia, Sflt-1, PIGF, Sflt-1/PIGF

Introduction

The incidence of preeclampsia varies between 2-10% of gestational pregnancies.[1] The World Health Organization (WHO) estimates that preeclampsia in developing countries is about seven times higher than in developed countries.[2] About 5-7% of women in the world go through preeclampsia.[3] Based on the onset of occurrence, preeclampsia can be divided into two categories: early-onset and late-onset. Preeclampsia that develops before 34 weeks of pregnancy is known as early-onset preeclampsia, while preeclampsia that develops after 34 weeks of pregnancy is known as late-onset preeclampsia.[4] The abnormal placentation process has been affirmed as an extrinsic cause of early-onset preeclampsia, while late-onset preeclampsia may be triggered by an intrinsic cause, namely the involvement of very dense microvilli.[5] Investigations using biomarkers for the early identification of preeclampsia have been discovered as science and technology have progressed. Methods for detecting preeclampsia must be able to distinguish preeclampsia from hypertensive disorders in other pregnancies.

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To detect the risk of preeclampsia, several studies recommend examining the ratio of Soluble FMS-Like Tyrosine Kinase 1 (sFlt-1)/Placental Growth Factor (PlGF).[6-10] This examination has high sensitivity and specificity compared to using only one biomarker.[11] There has been a lot of research on the ratio of sFlt-1 to PlGF levels in early and late-onset preeclampsia, but none on the differences in levels of these two variables at early and late-onset.
This study was therefore conducted to evaluate the differences in the ratio of sFlt-1 to PlGF levels in early and late-onset preeclampsia.

Materials and Methods

Study population
Patients with early and late-onset preeclampsia who visited M. Djamil Padang, Pariaman, Aisiyah Pariaman, and Padang Pariaman hospitals during the study period made up the study population. Pregnant women with preeclampsia who met the inclusion criteria were included in the study. The study examined 28 pregnant women, each for early-onset and late-onset preeclampsia. The inclusion criteria were patients diagnosed with preeclampsia by experts based on clinical appearance, obstetric, examinations, and willingness to participate in the study. The exclusion criteria were patients with chronic hypertension, gestational hypertension, malignancy, and severe infections.

Ethical consideration
Ethical clearance was given by Research Ethics Committee, Faculty of Medicine, University of Andalas with Approval number: 609/KEP/FK/2019.

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Blood collection and determination of sFlt-1 and PlGF levels

Blood was collected from the venous blood using a syringe aspiration procedure. An aliquot of 4 ml of blood was taken and placed into a blood chemistry vacutainer. The vacutainer which already contained the sample was labelled with name, medical record number, place of birth, date, and the patient's mother maiden name. The sample was then placed in a vacutainer transport box for later examination in the laboratory. The determination of serum sFlt-1 and PlGF levels was carried out by the ELISA method.[12]

Statistical analysis

The Statistical Package for Social Sciences Software (Version 21.0; SPSS Inc., Chicago, IL) was used for the statistical analysis. A normality test was done using the Saphiro Wilk test. The normality test was based on data SFlt-1 p = 0.00 (p> 0.05) and PlGF p = 0.00 (p> 0.05). The T-test data testing was not performed since the data distribution was not normal, so the data testing was done using a non-parametric test, namely the Mann-Whitney test.

Results and Discussion

Patient characteristics

The results of the patient characteristics are presented in Table 1. The gestational ages of the patients who were sampled in the early- and late-onset preeclampsia categories were 30.85±1.70 and 38.53±1.08, respectively. From both the early- and late-onset results, blood pressure levels in both groups were above 160/100 mmHg.

Concentration and ratio of sFlt-1/PlGF in early- and late-onset preeclampsia

The results of sFlt-1 and PlGF levels in the blood samples of early- and late-onset preeclampsia (Table 2) indicated that there was a difference between the sFlt-1 levels in both. The early-onset preeclampsia sFlt-1 levels were higher than the late-onset preeclampsia. In the early- and late-onset preeclampsia, the average sFlt-1 levels were 8.69±5.76 and 5.61±1.72 ng/mL, respectively. The PlGF levels for the early- and late-onset preeclampsia were 54.98±44.70 and 228.78±4.33 ng/mL, respectively. These observations indicate that the average early-onset preeclampsia PlGF level was lower than the late-onset preeclampsia PlGF level. The sFlt-1/PlGF ratios between the early- and late-onset preeclampsia were 0.25±0.19 and 0.50±0.03, respectively. These results indicate that the early-onset preeclampsia SFlt-1 / PlGF ratio was higher than the late-onset preeclampsia SFlt-1 / PlGF ratio. The test results showed a significant difference (P <0.05) between the sFlt-1 levels of the early- and late-onset preeclampsia, and the PlGF levels of early- and late-onset preeclampsia. Also, there was a significant difference (p < 0.05) between the sFlt-1 / PlGF ratio for the early- and late-onset preeclampsia. Preeclampsia begins in the first trimester with an asymptomatic phase characterized by insufficiency in the trophoblast invasion process and incomplete remodeling of the spiral arteries.[13] Both of these processes play a role in increasing oxidative stress and systemic endothelial dysfunction that will trigger the onset of symptoms of preeclampsia in the final phase of the disease.[14] The role of antiangiogenic proteins in early placental vascularization and trophoblast invasion is unknown. Hypoxia is thought to have an important role in this process.[15] Furthermore, excessive oxidative stress, inflammatory processes, impaired immunological adaptation, and genetic factors are also thought to have a role in the pathogenesis of preeclampsia.[16] Endothelial dysfunction and an imbalance of angiogenic / vasculogenic factors in the blood, such as soluble vascular endothelial growth factor receptor-1 (VEGFR-1, sFlt-1) and PlGF, cause abnormal placentation.[17] Angiogenic and antiangiogenic factors in maternal serum and plasma can be tested as diagnostic biomarkers of preeclampsia for their possible use in predicting the development of preeclampsia.[18] In addition, it can also distinguish between early- and late-onset preeclampsia. This distinction is useful because there are significant differences in the clinical manifestations of early- and late-onset preeclampsia. In the early-onset of preeclampsia, the formation of the spiral arteries is not perfect resulting in hypoperfusion of the placenta, so that the supply of nutrients to the fetus is reduced and eventually fetal growth restriction (FGR) occurs. Meanwhile, there is only a slight decrease in the diameter of the spiral arteries and no evidence of FGR in late-onset preeclampsia.[19] The study analyzed the differences between sFlt-1 levels in early- and late-onset preeclampsia. There was a difference in the levels of the early- and late-onset preeclampsia, where the levels of early-onset preeclampsia were higher than the levels of late-onset preeclampsia. Based on the results of the study, it was found that early-onset preeclampsia was related to fetoplacental conditions. The impaired fetoplacental function allows trophoblast invasion and the formation of spiral blood vessels, causing limited blood flow.[20] This dysfunction causes an increase in the sFlt-1 levels in the early-onset of preeclampsia, which is higher than that of late-onset preeclampsia.

The results of the study are in agreement with the findings of Aksornphusitaphong and Phupong.[21]

Table 1: Characteristics of patients with early- or late-onset preeclamsia

	Early-onset Preeclamsia n = 28 (Mean ± SD)	Late-onset Preeclamsia n = 28 (Mean ± SD)
Age (y)	32.92 ± 6.06	32.57 ± 6.61
Body Weight (kg)	77.32 ± 5.26	82.99 ± 5.40
Height (cm)	157.9 ± 4.09	157.75 ± 3.08
Gestational age (week)	30.85 ±1.70	38.53 ± 1.08
Systolic Pressure (mmHg)	160.85 ±13.93	166 ± 10.3
Diastolic Pressure (mmHg),	106.85 ± 5.59	107.64 ± 6.32

Table 2: Levels of sFlt-1 and PlGF in blood samples of early- and late-onset preeclampsia patients

Groups	Serum sFlt-1 level (ng / mL)		Serum PIGF levels (ng / mL)		SFlt-1 / PlGF level ratio	
	Mean	SD	Mean	SD	Mean	SD
Early-onset Preeclampsia	8.69	5.76	54.98	44.70	0.25	0.19
Late-onset Preeclampsia	5.61	1.72	228.78	267.57	0.50	0.03
Total	7.15	4.49	141.88	209.32	0.15	0.17

They reported that a history of chronic hypertension was significantly associated with an increased risk of early-onset preeclampsia, while a family history of chronic hypertension was associated with the risk of late-onset preeclampsia.[21] Furthermore, the study also analyzed the differences in the levels of PlGF early- and late-onset preeclampsia. PlGF was evaluated in each sample from the early- and late-onset preeclampsia groups. The results of the statistical analysis using SPSS revealed that there was a significant difference in the levels of the PlGF early- and late-onset preeclampsia. Also, the PlGF level at the early-onset of preeclampsia is lower than the PlGF level at the late-onset of preeclampsia. This is related to sFlt-1, where increasing levels of sFlt-1 as an antiangiogenic proteins inhibit angiogenic protein, such as PlGF. When sFlt-1 levels rise in the bloodstream, the angiogenic factor PlGF falls, which helps to prevent endothelial dysfunction from worsening.[22]

This study showed that there was a significant difference between the levels of the sFlt-1 / PIGF ratio in early- and late-onset preeclampsia. Stefan Verlohren's study found implications of the sFlt-1 / PIGF ratio on preeclampsia. The sFlt-1 / PIGF ratio is an appropriate examination and is of sufficient significance for preeclampsia. In a subgroup analysis consisting of normal pregnancy and preeclampsia, the sFlt-1 / PIGF ratio was better than a single examination in a diagnostic test. Furthermore, this test has a high sensitivity and specificity in detecting preeclampsia at an early stage.[23]

Conclusion

The findings of this study indicate that the levels of Sflt-1 and PIGF, as well as the ratio of Sflt-1/PIGF differ significantly between the early- and late-onset of preeclampsia.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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