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Original Research Article

Levels of molecular angiogenic and antiangiogenic in pregnant women with risk of preeclampsia

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ABSTRACT

Background: Angiogenic and antiangiogenic imbalances play a major role in the pathogenesis of preeclampsia. Increased production of sFlt-1 by the placenta causes free circulating PIGF and VEGF concentrations to lower because it is bound by sFlt-1. Measuring levels of angiogenic and antiangiogenic proteins as biomarkers indicates placental dysfunction and distinguishes preeclampsia from other disorders. This study aims to analyze the levels of angiogenic and antiangiogenic molecules in pregnant women at risk for preeclampsia.

Methods: The study with a cross-sectional design was carried out in 11-15 weeks gestational age whom had a risk of preeclampsia with 30 samples in primary health care starting April-August 2018. Blood serum was measured by molecular levels of VEGF, PIGF, sFlt-1, and sFlt-1/PIGF ratio using the ELISA method. Data analysis used Pearson product moment test.

Results: The mean of VEGF levels are 15.5 ± 21.6 , PIGF 89.7 ± 55.5 , sFlt-1 11519.4 ± 5126.0 and the ratio sFlt-1/PIGF 166.7 ± 102.1 . Correlation value of risk factors for preeclampsia with molecular levels of VEGF $r = -0.05$; $p = 0.76$, PIGF $r = -0.21$; $p = 0.26$, sFlt $r = 0.01$; $p = 0.99$ and ratio sFlt-1/PIGF $r = 0.10$; $p = 0.58$.

Conclusions: The higher the total score of preeclampsia risk factor, the lower the molecular level of VEGF and PIGF is. Moreover, the higher the total score of preeclampsia risk factor, the higher the molecular level sFlt-1 and the sFlt-1/PIGF ratio is. There are no significant correlation between total score of preeclampsia risk factor and levels of molecule VEGF, PIGF, sFlt-1 and sFlt-1/PIGF ratio.

Keywords: Preeclampsia, PIGF, Risk factors, sFlt-1, VEGF

INTRODUCTION

Preeclampsia is a specific condition in pregnancy which is characterized by the presence of placental dysfunction and maternal response due to systemic inflammation along with endothelial activation and coagulation.¹ The reported incidence of preeclampsia in 2013 in Indonesia was 128,273/year or estimated around 5.3%. Maternal mortality caused by preeclampsia was reported to be

29,000 and as many as 25.8% of the Indonesian population aged more than 18 years old were suffered from hypertension, whereas 6-10% of them were happened during pregnancy.²

Preeclampsia is indeed called as a "disease of theories," because the pathogenesis of preeclampsia has not been well understood. Some of these theories are placental ischemia, oxidative stress and free radicals, and the

theory of VLDL, maladaptive immune, and imbalance of angiogenic and antiangiogenic factors.³⁻⁵ Those the theory of angiogenic and antiangiogenic factors play major role in the pathogenesis of preeclampsia.^{6,7}

The clinical signs of preeclampsia appear after the 20th weeks of pregnancy, however the ischemia and pathogenic processes has begun in the first trimester of the previous few weeks.⁴ Should preeclampsia not well diagnosed or treated, it can cause multiorgan failure, coagulation, eclampsia and even maternal and fetal death.⁸ The National Institute for Health and Care Excellence (NICE) recommended that the high risk of preeclampsia is most effectively identified in the 11-13th weeks of pregnancy in order to make early primary prevention and intervention management.^{1,9}

Risk factors for preeclampsia were assessed through anamnesis as such: age >40 years, nullipara, multiparous with a history of previous preeclampsia, multiparas with pregnancies by new partners, multiparas who had a previous pregnancy 10 years or more, history of preeclampsia in mothers or sisters, multiple pregnancies, diabetes mellitus, chronic hypertension, kidney disease, pregnancy with insemination of sperm, oocyte or embryo donors, obesity before pregnancy, infection during pregnancy, autoimmune diseases such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).^{1,2} Risk factors for pregnant women above can develop into preeclampsia in advanced pregnancy.¹⁰

Some risk factors condition for preeclampsia can cause placental hypoxia. Furthermore this matter triggers the releasing of some markers of placental hypoxia. In the form of increased secretion of sFlt-1 and sFlt-1 serum enter the maternal systemic circulation. Lack of placental perfusion is the main cause of injury to ischemic perfusion in the placenta therefore that all of these processes cause symptoms of preeclampsia.⁹ Increased production of sFlt-1 by placenta preeclampsia causes circulating of free PIGF and VEGF concentrations become low, because it is bound by sFlt-1.¹⁰ Decreasing levels of VEGF and PIGF can cause neovascularization during placentation. Following the result in failure to form normal uteroplacental circulation. As known, the failure indicates infarction of the placenta, arteriosclerosis, superficial cytotrophoblast invasion, and inadequate remodeling of the uterine spiral arteries.¹¹

This study aims to analyze the levels of angiogenic and antiangiogenic molecules in pregnant women at risk for preeclampsia and correlation of total score of preeclampsia risk factor with VEGF, PIGF, sFlt-1 and sFlt-1/PIGF ratios.

METHODS

This study used a cross sectional design, involving subjects who were 11-15 weeks pregnancy whom had a risk of preeclampsia with 30 samples. Sample size was

calculated by obtaining the prevalence of pregnant women whom had a risk of preeclampsia in primary health care. This research was conducted in 10 primary health care facilities, Sleman Yogyakarta, Indonesia starting April-August 2018. The inclusion criteria are first and second trimester pregnant women (gestational age 11-15 weeks), having one of the several high risk of preeclampsia including: multiparas with a history of previous preeclampsia, multiple pregnancy, diabetes melitus (DM), chronic hypertension, kidney disease, antiphospholipid syndrome (APS), and Systemic Lupus Erythematosus (SLE) autoimmune disease) or have more than 2 risks of preeclampsia: nullipara, obesity before pregnancy (BMI > 25 kg/m²), age >40 years, multiparas who have a previous pregnancy 10 years or more, history of preeclampsia in mothers or sisters, multiparous with pregnancy by a new partner, diastolic blood pressure > 80mmHg (MAP > 100. Exclusion criteria are: suffering from infectious diseases, anemia (Hb levels <11gm%), and mothers were on insulin therapy.

Primary data collection begun with anamnesis, physical examination and laboratory examination (urine protein and haemoglobin levels) as a risk screening for preeclampsia.

Each participant measured the total score of preeclampsia risk factor and the levels of VEGF, PIGF, sFlt-1, and sFlt-1/ PIGF ratio. The total score was obtained from the number of risk factor characteristics possessed by each participant multiplied by the weight score of each of the risk factor (Table 1). Participants were measured for blood serum to determine levels of VEGF, PIGF, sFlt-1, and sFlt-1/ PIGF ratio.

Confounding variable includes the immune system, hypoxia and genetics and has been controlled by restriction through the selection of inclusion and exclusion criteria.

Data analysis using Pearson product moment to find out the relationship between the two variables.

VEGF, PIGF and sFlt-1 measurement were done by ELISA and using reagents Quantikine Human VEGF Immunoassay reagents, Cat (R and D systems). No DVE00), Quantikine Human PIGF Immunoassay reagents, (R and D systems) Cat. No DPG00), and Quantikine Human VEGF R1 / Flt-1 Immunoassay, (R and D systems) Cat reagents. DVR No. 100B), respectively. Informed consent was obtained from all study participants.

RESULTS

Most of risk factors for preeclampsia in pregnant women are BMI \geq 25 kg/m², which is 86.7%. The highest score weighting risk factor for preeclampsia is 4 in pregnant women who have hypertension (Table 1).

Some participants have more than 1 risk factor for preeclampsia. The total score was obtained from the number of risk factor characteristics possessed by each participant

multiplied by the weight score of each of the risk factor). Total preeclampsia risk factor scores 2, 3, 4, 5, and 6 were 8 (26.7%), 9 (30%), 8 (26.7%), 3 (10%) and 2 (6.7%).

Table 1 Overview of characteristics of pregnant women and preeclampsia risk factor scores.

Risk factor of preeclampsia	(Weighted score of risk factor)	n (%) (n=30)
Age > 40 years old	1	3 (10%)
Primigravida	2	8 (16.7%)
BMI \geq 25kg/m ²	2	26 (86.7%)
History of preeclampsia:	3	4 (13.3%)
Pregnancy intervals > 10 years	1	2 (6.7%)
Family history	1	7 (23.3%)
Hypertension	4	2 (6.7%)
Diabetes mellitus	2	1 (3.3%)

Table 2: Correlation of total score of preeclampsia risk factor with VEGF, PlGF, sFlt-1 and sFlt-1/ PlGF ratios.

Levels of molecular	Mean \pm SD	r	p-value
VEGF	15.5 \pm 21.6	-0.05	0.76 ^a
PlGF	89.7 \pm 55.5	-0.21	0.26 ^a
sFlt-1	11519.4 \pm 5126.0	0.01	0.99 ^a
Rasio sFlt-1/ PlGF	166.7 \pm 102.1	0.10	0.58 ^a

^aPearson product moment.

Then a correlation analysis was performed between the total score of preeclampsia risk factor with the levels of molecular VEGF, PlGF, sFlt-1 and sFlt-1/ PlGF ratio, results in Table 2.

The mean VEGF levels are 15.5 \pm 21.6, PlGF 89.7 \pm 55.5, sFlt-1 11519.4 \pm 5126.0 and the ratio sFlt-1/ PlGF 166.7 \pm 102.1 (Table 2).

Based on the weight of risk factors and the calculation of the total score of preeclampsia risk factors, the results showed that there are no significant correlation between total score of preeclampsia risk factor and levels of molecular VEGF, PlGF, sFlt-1 and sFlt-1/ PlGF ratio. However, there is a negative correlation on the level of VEGF and PlGF molecules and a positive correlation on the level of the sFlt-1 molecule and the sFlt-1/ PlGF ratio. The higher the total score of preeclampsia risk factor the lower the levels of VEGF and PlGF molecules, the higher the total score of preeclampsia risk factor the higher the level of sFlt-1 molecule and sFlt-1/ PlGF ratio.

DISCUSSION

This study shows that the characteristics of the research subjects are risk factors for preeclampsia. Most of risk factors for preeclampsia in pregnant women are BMI \geq 25kg/m², which is 86.7% (Table 1). Risk factors for pregnant women above are at risk of developing

preeclampsia in advanced pregnancy. These risk factors, which have been identified, can help in assessing the risk of pregnancy at the initial antenatal.¹⁰

Risk factor of preeclampsia

Primiparity is significantly associated with the incidence of preeclampsia with a risk of increasing 2x (OR2.39; 1.23-4.65) compared to multiparity.¹¹ In primiparity there is a reaction of maternal adaptation to trophoblast invasion in early pregnancy. Normal invasion failure of trophoblast cells causes maladaptation of the spiral arteries, which is associated with the causes of preeclampsia.¹² Based on Dekker's research in Esplin et al, it was stated that first or multiparous pregnancies with new partners showed that there were interactions between maternal antibodies and fetal antigens derived from paternal genes, where father's genetic contribution to fetal genotypes could contribute to the development of preeclampsia.¹³

Based on the Duckitt report, 2005, preeclampsia occurred doubled at the age of mothers over 40 years. The risk of preeclampsia in the second pregnancy increases with the age of the mother (1.3 times every 5 years of age).¹⁴ The more mature a woman in age, the higher the risk factors will be, which may be caused by an increase in the reaction of the villi which leads to the occurrence of preeclampsia.¹¹

Obesity increased the risk of preeclampsia by 2.47 times (95% CI, 1.66-3.67), whereas women with BMI before pregnancy >35 compared with BMI 19-27 had a fourfold risk of preeclampsia (95% CI, 3.52-5.49).¹⁴ Obesity leads to lipotoxic conditions characterized by decreased angiogenic regulation and increased pro-inflammatory cytokines. Proinflammatory cytokines, especially TNF- α through the process of apoptosis can limit the invasion of cytotrophoblast cells into the spiral arteries.¹⁵ Increased triglyceride levels in obesity due to the production of VLDL in the liver because of the increase in free fatty acids entering the liver. This causes oxidative cell regeneration resulting in endothelial cell dysfunction and causing preeclampsia. Obesity causes changes in the body's metabolism in the form of increased inflammation of the cardiovascular system, oxidative stress and decreased PlGF. The high level of fat reserves increases leptin levels and decreases in adiponectin which causes insulin resistance, endothelial dysfunction and impaired vasodilation in order that increased blood pressure vasoconstriction interferes with the distribution of nutrients to the fetus.^{16,17}

The history of preeclampsia is a major risk factor or high risk. Based on the research of Cincotta RB and Arngrimsson R in Esplin et al, showed that in primigravidas with a family history of preeclampsia, the incidence of preeclampsia increased threefold compared to primigravida without a family history. Other studies also mention the risk of increasing the prevalence of preeclampsia and eclampsia significantly higher in children of women with families with a history of preeclampsia (23%) than in daughter-in-law (10%).¹³ According to Duckit and Hanington, 2005 the risk increased by 7-fold (RR 7.19 95% CI 5.85-8.83). Pregnancy in women with a history of preeclampsia is associated with a high incidence of severe preeclampsia, early onset preeclampsia, and poor perinatal effects.¹⁴

A study involving 760,901 women in Norway, showed that multiparous women with a previous pregnancy distance of 10 years or more had a risk of preeclampsia about the same as nullipara.¹⁴ Robillard et al reported that the risk of preeclampsia increased according to the length of the interval with the first pregnancy (1.5 times every 5 years the distance of the first and second pregnancies). NICE reports that the <10 year pregnancy interval does not increase the risk of recurrent preeclampsia, but some reports suggest an increased risk of recurrent preeclampsia at <2 years or > 10 years of pregnancy.¹⁸

A history of family preeclampsia also increases the risk almost 3-fold (RR 2.90 95% CI 1.70-4.93). The history of maternal preeclampsia increases risk by 3.6 times (RR 3.6 95% CI 1.49-8.67).¹⁴ In the previous study it was found 26% of the incidence of preeclampsia in girls and women with preeclampsia but only 8% of incidents in daughter-in-law. The increasing prevalence of preeclampsia in girls born to preeclamptic mothers, associated with non-preeclamptic pregnancies from the

same mother, may indicate a fetal genotypic influence on the reliability of preeclampsia.¹⁹

Shibuya et al, conducted a study on a population of 56,968, indicating that the risk of preeclampsia increased almost four-fold if diabetes occurred before pregnancy (RR 3.56; 95% CI 2.54 - 4.99).¹⁴ Chappell et al, study of 861 women with chronic hypertension, found an incidence of superimposed preeclampsia of 22% and almost half of those with early onset preeclampsia (<34 weeks) with worse maternal and perinatal output.¹⁰ Karumanchi et al, said that women with DM and hypertension increased the incidence of preeclampsia and also showed the presence of several factors in the maternal risk of preeclampsia. In addition to increased vascular reactivity, vasoconstriction is mediated in part by changes in local concentrations of several vasoactive molecules, including vasoconstrictor norepinephrine, endothelin, and thromboxane, and vasodilator prostacyclin and nitric oxide.¹⁸

Angiogenic and antiangiogenic in pregnant women with risk of preeclampsia

Pregnant women at risk of preeclampsia cause changes in levels of VEGF, PlGF, sFlt-1 and the ratio of sFlt-1/PlGF levels, have low levels of angiogenic molecules, and high antiangiogenic levels (Table 2). This study showed that the VEGF and PlGF correlation values showed a negative correlation, namely the higher the total score of preeclampsia risk factor the lower the levels of VEGF and PlGF molecules. While the sFlt-1 correlation value and sFlt-1 / PlGF ratio showed a positive correlation, namely the higher the total score of preeclampsia risk factor the higher the level of sFlt-1 molecule and sFlt-1/PlGF ratio. There are no significant correlation between total score of preeclampsia risk factor and levels of molecule VEGF, PlGF, sFlt-1 and sFlt-1/PlGF ratio (Table 2).

The pathogenic process of preeclampsia begins during the first trimester, long before clinical signs appear clearly.⁴ In the early stages of the pathogenesis of preeclampsia there is a decrease in placental perfusion, asymptomatic (placental). This decrease is characterized by abnormal placentation, followed by elaboration of certain soluble factors that enter the maternal circulation and cause widespread development of endothelial dysfunction.⁶ At this stage, there is a decrease in VEGF which will lead to disruption of endothelization and invasion of the spiral arteries to the myometrium, leading to increased vascular resistance, this will be followed in the second stage, where ischemia occurs in the placenta, causing oxidative stress on the placenta and releasing proteins such as sFlt-1, prostaglandin, and cytokines.²⁰

Measuring the levels of angiogenic and antiangiogenic proteins in the bloodstream as biomarkers indicates placental dysfunction and differentiates preeclampsia from other disorders, such as gestational hypertension

and chronic glomerulonephritis.⁴ Angiogenic factors (VEGF, PlGF) correlate with disease severity, can be detected several weeks before clinical presentation of the disease and have a predictive value for the diagnosis of early onset preeclampsia.²¹

Vascular endothel growth factor

VEGF is bound by sFlt-1 in preeclampsia, resulting in low levels of circulating free VEGF.²² VEGF induces vasculogenesis and angiogenesis and plays an important role in endothelial cell proliferation. VEGF inactivation can cause lethal effects on the embryo and vascular defects in the placenta. Decreased VEGF levels due to binding with receptors in the circulating increase indicate angiogenic and antiangiogenic imbalances which subsequently trigger endothelial dysfunction.²³ This results in failure to form normal uteroplacental circulation. The failure indicates infarction of the placenta, arteriosclerosis, superficial cytotrophoblast invasion, and inadequate remodeling of the uterine spiral arteries.²⁰

Placental growth factor

Several studies have shown the important role of PlGF in regulating angiogenesis under pathological.²⁴ In women who subsequently experience preeclampsia, serum PlGF concentrations do not increase when compared to the age of 10-13 weeks of pregnancy and experience a significant decrease 5 weeks before the appearance of clinical manifestations.²⁵ Serum PlGF examination at 11-13 weeks pregnancy can identify a high proportion of high-risk pregnancies for early onset PE.²⁶ PlGF concentrations begin to decrease 9-11 weeks before hypertension and urine protein are seen, with an increase of 5 weeks before the onset.²⁵

Soluble fms like tyrosine kinase-1

Increased expression of sFlt-1 can interfere with trophoblast function and endothelial cells in preeclampsia.²⁷ An increase in sFlt-1 in the serum of pregnant women is associated with endothelial dysfunction that occurs in preeclampsia, which is characterized by the emergence of clinical manifestations.²⁸ Levels of sFlt-1 in the serum of pregnant women with preeclampsia are high at 20 weeks' gestation and increase significantly within 5 weeks before hypertension and preeclampsia arise.²⁹

The sFlt-1 / PlGF ≤ 38 ratio can be used to predict the absence of short-term preeclampsia in women with suspected clinical syndromes. Preeclampsia often occurs in patients with a ratio of sFlt-1 / PlGF ratio ≥ 85 (40.5%) compared to 33 to 85 (28.1%) and < 33 (9.8%). The Zeisler et al, study found that the sFlt-1 / PlGF ratio with a cutoff of 38 had an important predictive value.³⁰

The strengths of this study is to analyze the angiogenic levels of VEGF and PlGF, antiangiogenic sFlt-1 and sFlt-1/PlGF ratios in pregnant women with the risk of preeclampsia measured in one study of the four measured markers which describe changes that can occur in spiral arteries (imbalance theory pathway angiogenic and anti angiogenic factors).

CONCLUSION

There are no significant correlation between total score of preeclampsia risk factor and levels of molecule VEGF, PlGF, sFlt-1 and sFlt-1 / PlGF ratio.

The higher the risk factor score, the lower the molecular level of VEGF and PlGF will be. Furthermore, the higher the total score of preeclampsia risk factor, the higher the molecular level sFlt-1 and the sFlt-1 / PlGF ratio is.

Recommendations

Based on the results of the study, recommendations that can be suggested are: Early risk factors detection and screening for preeclampsia in < 16 weeks of gestation is very necessary, the need of regular monitoring of weight gain during pregnancy based on pregnancy BMI, especially in pregnant women with BMI $> 25 \text{ kg/m}^2$ and advanced researchers to be able to prove the circulation of antiangiogenic and angiogenic levels in each trimester in pregnant women with risk factors for preeclampsia pregnancy and in normal pregnancy.

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