

HIGH SERUM RATIO OF SOLUBLE FMS-LIKE TYROSINE KINASE 1 (sFlt-1) TO PLACENTAL GROWTH FACTOR (PIGF) AND HIGH LEVEL OF LOW-DENSITY LIPOPROTEIN (LDL) AS RISK FACTORS OF PREECLAMPSIA

A.A.N. Jaya Kusuma, Endang Sri Widiyanti, I Wayan Megadhana, Putu Doster Mahayasa, Ryan Saktika Mulyana, Kevin Agastya Duarsa

Departement of Obstetrics and Gynecology, Faculty of Medicine, Udayana

University/Prof. IGNG Ngoerah Hospital, Bali, Indonesia

Email: jayakusumakars@gmail.com, endsw@yahoo.com,
megadhana_wayan@yahoo.com, dmahayasa@gmail.com,
ryanmul83@gmail.com, kevin_duarsa@yahoo.com

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ABSTRACT

Preeclampsia is an obstetric disease that is a health problem worldwide, including in Indonesia. Several studies have shown that changes in the maternal spiral arteries are thought to lead to preeclampsia. Preeclampsia in this decade has been associated with changes in angiogenesis regulatory proteins originating from the placenta and circulating in the mother's blood circulation, namely soluble FMS-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PIGF). The author was interested in examining the ratio of sFlt-1/PIGF and low-density lipoprotein (LDL) to the incidence of preeclampsia in pregnant women. This study used a case control analytic observational design. The research sample was selected by consecutive sampling of 20 cases and 20 controls. Univariate analysis was used to describe patient characteristics descriptively, and bivariate analysis was used to determine the relationship between the 2 variables. There is no significant difference in the characteristics of the research subjects. Low PIGF levels are a risk factor for preeclampsia (OR 4.33; p 0.0302) with a cut-off value of 24.5. High sFlt-1 levels are a risk factor for preeclampsia (OR 4.33; p 0.027) with a cut-off value of 869.5. A high sFlt-1/PIGF ratio is a risk factor for preeclampsia (OR 4.33 p 0.030) with a cut-off value of 38. High LDL levels are a risk factor for preeclampsia (OR 6.0; p 0.013) with a cut-off value of 150. Low placental growth factor (PIGF), high levels of soluble FMS-like tyrosine kinase 1 (sFlt-1), and high levels of LDL are risk factors of preeclampsia in pregnant women.

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INTRODUCTION

Preeclampsia is an obstetric disease that has become a health problem throughout the world, including in Indonesia. Preeclampsia is associated with high maternal and infant mortality rates, so early detection of preeclampsia is very important. Various studies to understand early detection in pregnant women suspected of being at risk of preeclampsia before signs and symptoms appear have been carried out, to angiogenic and antiangiogenic protein analysis which is expected to provide innovative input as predictors in more specific early detection of preeclampsia. Biomarkers involved in various complexities of placental abnormalities and endothelial dysfunction have been studied, one of which is still little discussed and studied in Indonesia is the levels of sFlt-1, PlGF, and LDL involved in endothelial dysfunction as the most important etiology in the pathogenesis of preeclampsia.

In 2017, as many as 295,000 women worldwide died during pregnancy and childbirth (Organization, 2011). Hemorrhage, hypertensive diseases, and sepsis contributed to half of maternal mortality worldwide from 2003 to 2009 (Say et al., 2014). Nearly one-tenth of maternal mortality in Asia and Africa, and one-quarter of maternal mortality in Latin America are linked to hypertension during pregnancy. Among these diseases, preeclampsia and eclampsia have the greatest impact on maternal and newborn morbidity and mortality (Organization, 2011).

Proteinuria and elevated blood pressure are diagnostic criteria that have been used, but both criteria are nonspecific. Measurements of proteinuria are of poor accuracy and complications due to proteinuria often arise before proteinuria is significant. Current clinical guidelines suggest that the diagnosis of preeclampsia be made based on the presence of hypertension and signs of multiple organ failure. The clinical manifestations and course of preeclampsia vary widely, suggesting that current diagnostic guidelines are insufficient to cover the entire syndrome (Zeisler et al., 2016).

Until now, the cause of preeclampsia is still not thoroughly understood, but some research suggests that changes in the maternal spiral arteries are thought to lead to preeclampsia (Zeisler et al., 2016). Preeclampsia in this decade is associated with changes in angiogenesis regulatory proteins that originate in the placenta and circulate in the mother's blood circulation, namely soluble FMS-like Tyrosine Kinase 1 (sFlt-1) and Placental Growth Factor (PlGF) (Moufarrej, 2021). In the cases of preeclampsia that have been studied, it was found that there was an increase in sFlt-1 levels and a decrease in PlGF levels in blood serum. sFlt-1 is an antagonist of PlGF and Vascular Endothelial Growth Factor (VEGF), which causes vasoconstriction and endothelial damage leading to fetal growth inhibition and preeclampsia. Therefore, a high ratio of sFlt-1 to PlGF is associated with an increased risk of preeclampsia (Zeisler et al., 2016).

Maynard (2003) research shows that sFlt-1 plays a role in the pathogenesis of preeclampsia, other studies show the usefulness of this angiogenic marker in the diagnosis and prediction and management of preeclampsia and other placental disorders. Other studies have shown that this imbalance of angiogenic and antiangiogenic factors may also describe the prognosis of preeclampsia. An increase in the sFlt-1/PlGF ratio can be detected as early as the second half of pregnancy in pregnant women suffering from preeclampsia

and other placental disorders. This angiogenic factor balance disorder is also known to be detected before the appearance of clinical manifestations of the disease, so it can be used for screening pregnant women who are at risk of complications in their pregnancy, especially preeclampsia).

In preeclampsia, endothelial dysfunction occurs which can be caused by changes in Low Density Lipoprotein (LDL). LDL is a lipoprotein that transports the most cholesterol in the blood. High LDL levels cause deposition of cholesterol in the arteries. In pregnancy there is a change in fat profile, namely an increase in triglycerides followed by an increase in other fats. Hypertriglycerides cause changes in the spectrum of Intermediate Density Lipoprotein (IDL) into LDL particles smaller in size, have higher density and are atherogenic. It is suspected that there is a relationship between preeclampsia and increased LDL levels which causes endothelial dysfunction and causes imbalance in the production of vasodilator substances such as prostacyclin and nitrate oxidants with vasoconstrictors such as thromboxane and endothelin I so that vasoconstriction will occur broadly.

Based on the above exposure, it can be seen that both sFlt-1, PIGF and LDL have an important role in the pathogenesis of preeclampsia. These factors, if expressed in the form of sFlt-1 / PIGF ratio, and LDL have the potential to be used as predictors in the study of pregnant women at risk of preeclampsia because they can be detected before the appearance of clinical manifestations. This is expected to reduce the number of morbidity and death rates arising from late management. Therefore, the authors are interested in examining the ratio of sFlt-1 / PIGF and LDL to the incidence of preeclampsia in pregnant women.

The purpose of this study, to prove low levels of Placental Growth Factor (PIGF) is a risk factor for preeclampsia, proves that high levels of soluble FMS-like Tyrosine Kinase 1 (sFlt-1) are risk factors for preeclampsia. Proving a high ratio of soluble FMS-like Tyrosine Kinase 1 (sFlt-1) to Placental Growth Factor (PIGF) is a risk factor for preeclampsia and proving high levels of Lowdensity Lipoprotein (LDL) is a risk factor for preeclampsia.

The theoretical benefits of this study are expected to contribute knowledge about the ratio of soluble FMS-like Tyrosine Kinase 1 (sFlt-1) levels to Placental Growth Factor (PIGF) levels and high Lowdensity Lipoprotein (LDL) levels to the incidence of preeclampsia.

METHODS

This study uses a case control analytic observational design. This study was conducted to assess the ratio of sFlt-1/PIGF and LDL levels as a risk factor for preeclampsia. The sample of this study were pregnant women who came to the Obstetrics and Gynecology Polyclinic at Prof. Hospital. dr. I.G.N.G Ngoerah Denpasar and the Delivery Room of the Obstetrics and Gynecology IGD Prof. Hospital. dr. I.G.N.G Ngoerah Denpasar with a gestational age of 20-40 weeks and suffering from preeclampsia. While the controls in this study were pregnant women with a gestational age of 20-40 weeks without preeclampsia. For both the case and control groups, 3 cc of venous blood was

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collected for examination of serum PIGF and SFLT-1 levels and 3 cc for examination of LDH. This research was conducted at the Obstetrics and Gynecology Polyclinic, RSUP Prof. dr. I.G.N.G Ngoerah Denpasar and the Delivery Room of the Obstetrics and Gynecology IGD Prof. Hospital. dr. I.G.N.G Ngoerah Denpasar. This research was conducted from December 2021 to December 2022.

RESULTS AND DISCUSSION

Characteristics of the Research Sample

A total of 40 research samples were collected in this study, each consisting of 20 pregnant women without preeclampsia and diagnosed with preeclampsia. The results of the data normality test using the Shapiro Wilk test showed that the data on maternal age, maternal age, sFlt-1 levels, PIGF levels, and the sFlt-1/PIGF ratio were not normally distributed ($p < 0.05$) while body mass index (BMI) data and LDL levels were normally distributed ($p > 0.05$). There were no differences in basic characteristics such as maternal age, gestational age and BMI before pregnancy between patients with and without preeclampsia. Patients with preeclampsia tend to have an older maternal age, a higher pre-pregnancy BMI and a lower gestational age (Table 1 $< /0,05 >$).

Table 1. Characteristics of Research Samples

Characteristic	Total (N=40)	Preeclampsia Status		P value
		Yes (N=20)	No (N=20)	
Age (years), mean (\pm SD)	30,25 (\pm 3,74)	30,9 (\pm 4,39)	29,6 (\pm 2,92)	0,192
Parity, mean (\pm SD)	1,875 (\pm 0,79)	1,85 (\pm 0,745)	1,90 (\pm 0,852)	0,798
Gestational Age (weeks), mean (\pm SD)	31,5 (\pm 3,37)	30,5 (\pm 3,14)	32,45 (\pm 3,39)	0,091
BMI (kg/m ²), mean (\pm SD)	23,2 (\pm 2,91)	23,58 (\pm 2,8)	22,86 (\pm 3,0)	0,438

Low levels of PIGF as a risk factor for preeclampsia

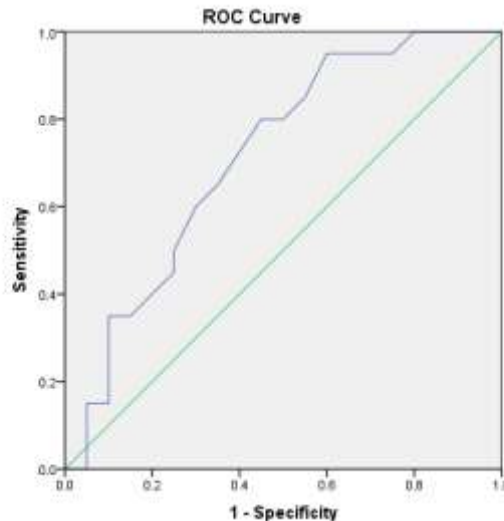
The mean PIGF level in all samples was 26.47 (\pm 9.0). Patients with preeclampsia tended to have lower PIGF levels compared to patients without preeclampsia (24.3 vs. 28.6). The Mann-Whitney test shows this difference is statistically significant ($p = 0.02$) (Table 2).

Table 2 PIGF Levels Based on Preeclampsia Status

Characteristic	Total (N=40)	Preeclampsia status		P value
		Ya (N=20)	No (N=20)	
PIGF, mean (\pm SD)	26,47 (\pm 9,0)	24,3 (\pm 10,5)	28,6 (\pm 6,7)	0,02

A receiver operating characteristics (ROC) curve was created to determine the cutoff point of PIGF levels based on preeclampsia status (Figure 5.2). The cutoff point value of PIGF levels to predict the incidence of preeclampsia was 24.5 with a sensitivity value of 65% and specificity of 65%. The under curve area (AUC) value is 0.714 (p=0.021; Confidence interval [IK] 95% 0.552 – 0.875).

Figure 1. ROC Curve of PIGF Levels by Preeclampsia Status



Patients were then classified into high (>24.5) and low (\leq 24.5) PIGF levels. Preeclampsia patients had a higher proportion of low PIGF levels than non-preeclampsia patients (65% vs. 35%). High PIGF levels tend to be a protective factor for preeclampsia, with patients with low PIGF levels having a 4.33 times higher risk of preeclampsia than high PIGF levels. These results proved to be statistically significant (p = 0.0302).

Table 3 Association Of PIGF Levels With Preeclampsia Status

PIGF levels	Preeclampsia Status		OR value (IK 95%)	P value
	Ya (N=20)	No (N=20)		
Low	13 (65%)	6 (30%)	4,333 (1,150 – 16,323)	0,0302
Tall	7 (35%)	14 (70%)		

Kadar sFlt-1 yang Tinggi Sebagai Faktor Risiko Preeklampsia

The mean sFlt-1 levels in all samples were 873.5 (\pm 439.6). Patients with preeclampsia tended to have higher levels of sFlt-1 compared to patients without preeclampsia (1038.9 vs. 709). The Mann-Whitney test shows this difference is statistically significant (p = 0.026) (Table 4).

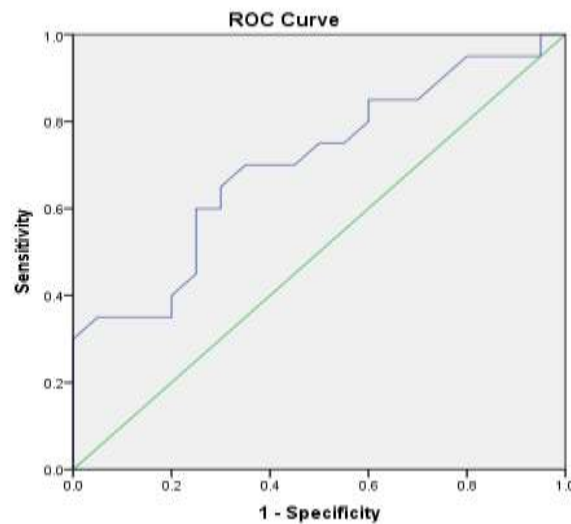
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Table 4. sFlt-1 Levels Based on Preeclampsia Status

Characteristic	Total (N=40)	Preeclampsia status		P value
		Ya (N=20)	No (N=20)	
sFlt-1, mean (±SD)	873,5 (±439,6)	1038,9 (±518,4)	708 (±265,1)	0,026

A receiver operating characteristics (ROC) curve was created to determine the cutoff point of sFlt-1 levels based on preeclampsia status (Figure 5.2). The cutoff point value of sFlt-1 levels to predict the incidence of preeclampsia was 869.5 with a sensitivity value of 65% and specificity of 70%. The area under curve (AUC) value is 0.704 (p=0.027; Confidence interval [IK] 95% 0.541 – 0.866).

Figure 2 ROC Curve of sFlt-1 Levels based on Preeclampsia Status



Patients were then classified into high (>869.5) and low (≤869.5) sFlt-1 levels. As many as 65% of preeclampsia patients and only 30% of patients without preeclampsia have high sFlt-1 levels. Patients with high sFlt-1 levels had a 4.33 times higher chance of developing preeclampsia compared with low sFlt-1 levels (p = 0.027). These results are summarized in Table 5.

Table 5. Relationship of Sflt-1 Levels Category with Preeclampsia Status

sFlt-1 levels	Preeclampsia Status		Value OR (IK 95%)	P value
	Ya (N=20)	No (N=20)		
Tall	13 (65%)	6 (30%)	4,33 (1,15 –	0,027
Low	7 (35%)	14 (70%)	16,32)	

High Sflt-1/PIGF Ratio as a Risk Factor For Preeclampsia

The mean sFlt-1/PIGF ratio in all samples was 36.37 (±22.8). Patients with preeclampsia tended to have a higher sFlt-1/PIGF ratio compared to patients without

preeclampsia (46.56 vs. 26.18). The Mann-Whitney test shows this difference is statistically significant ($p = 0.002$) (Table 6).

Table 6. sFlt-1/PIGF Ratio Based On Preeclampsia Status

Characteristic	Total (N=40)	Preeclampsia Status		P value
		Ya (N=20)	No (N=20)	
Ratio sFlt-1/PIGF, mean (\pm SD)	36,37 (\pm 22,8)	46,56 (\pm 26,62)	26,18 (\pm 12,12)	0,002

The sFlt-1/PIGF ratio was also classified into low (<38) and high (>38). There was a significant difference between the sFlt-1/PIGF ratio in the non-PE and PE groups ($p=0.030$).

Table 7. Relationship of sFlt-1/PIGF Ratio To Preeclampsia Status

Ratio sFlt-1/PIGF	Preeclampsia Status		Value OR (IK 95%)	P value
	Ya (N=20)	No (N=20)		
Tall	12 (70%)	6 (30%)	4.33 (1,15 – 16,32)	0.030
Low	8 (40%)	14 (70%)		

High LDL Levels as a Risk Factor for Preeclampsia

The mean LDL level in all samples was 139.8 (\pm 29.0). Patients with preeclampsia tended to have higher LDL levels compared to patients without preeclampsia (150.2 vs. 129.4). The Mann-Whitney test shows this difference is statistically significant ($p = 0.021$) (Table 8).

Table 8. LDL Levels Based on Preeclampsia Status

Characteristic	Total (N=40)	Preeclampsia Status		P value
		Ya (N=20)	No (N=20)	
LDL levels	139,8 (\pm 29,0)	150,2 (\pm 31,9)	129,4 (\pm 22,0)	0,021

LDL levels are divided into low and high. There was a significant difference in LDL levels between the two groups ($p = 0.013$).

Table 9. Relationship of LDL levels to preeclampsia status

LDL levels	Preeclampsia Status		Nilai OR (IK 95%)	Nilai p
	Ya (N=20)	No (N=20)		
Tall	16 (80%)	8 (40%)	6.0 (1.4583 – 24.6868)	0.013
Low	4 (20%)	12 (60%)		

Low levels of placental growth factor (PlGF) as a risk factor for preeclampsia

Placental growth factor (PlGF) is a member of the vascular endothelial growth factor (VEGF) family that is mostly expressed in the placenta and a small part expressed in other tissues such as the heart, lungs, thyroid, liver, skeletal muscle and bones. This protein is secreted as homodimers PlGF-1 to PlGF-4 (Torry et al., 1998). The isoforms PlGF-1 and PlGF-2 are the most abundant forms of PlGF including pregnancy (Chau et al., 2017).

In a normal pregnancy, PlGF concentrations are initially low in the first trimester of pregnancy and increase from weeks 11 to 12 onwards until peaking at week 30. Normal PlGF concentrations depend on gestational age, with the lower limit of normal peaking at around 141 pg/ml at 30 weeks gestation and then dropping to 23 pg/ml at term (Saffer et al., 2013). In this study, the median PlGF level was 28.5 pg / ml. This result is much lower than the maximum level obtained from the results of the previous study. This difference in results may be explained because after 29-30 weeks gestation, PlGF levels in normal pregnancy have begun to decline (Chau et al., 2017). In this study, the median age in this study was 33 weeks, specifically in the normotensive group. However, the concentration of PlGF is much lower than the results of other studies that get higher concentrations of 175.5 pg / ml in the second trimester and 753 pg / ml in the third trimester (Tidwell et al., 2001).

Serum and urine PLGF were found to decrease in women both at the time of diagnosis and before the onset of preeclampsia syndrome. The decrease in PlGF occurs both in its expression and also in free PlGF levels (Levine et al., 2004). Another study found that PlGF concentrations of less than 62.5 pg/ml increased the risk of preeclampsia. When compared with these concentration limits, we found that the median PlGF level was much lower at 22.5 pg/ml in the preeclampsia group. The risk of preeclampsia increased with a decrease in PlGF concentration, namely 49.6% at levels of 12-99 pg / l and 83.6% at PlGF levels less than 12 pg / l, while the risk of preeclampsia was only 16.1% at PlGF levels \geq 100 pg / ml (Duhig et al., 2019).

The study comparing PlGF levels between normal pregnancy and preeclampsia found patients with PlGF levels less than 62.5 pg/ml had a 3.2 times higher risk than those below that limit. Likewise, the results of this study found that PlGF levels were significantly higher in normal pregnancy than preeclampsia ($p = 0.02$).

Low PLFGF in pregnancy may be a consequence of abnormal implantations in the placentation and a contributing factor to abnormal placental growth that continues during the second half of pregnancy (Novelia et al., 2019). The hypothesis that PlGF is an indicator of abnormal placentation is supported by also low PlGF levels in women without preeclampsia who give birth to babies with low birth weight (Poon et al., 2008). Other data also postulate that the decrease in PlGF levels in preeclampsia occurs due to persistent placental hypoxia (Chau et al., 2017). But other data got different results, where PlGF expression increased (Regnault et al., 2002) or no change (Hoeller et al., 2017).

In this study, the mean PlGF levels in all samples were 26.47 (\pm 9.0). Patients with preeclampsia tended to have lower PlGF levels compared to patients without preeclampsia

(24.3 vs. 28.6). The Mann-Whitney test shows this difference is statistically significant ($p = 0.02$).

High soluble FMS-like Tyrosine Kinase 1 (sFlt-1) as a risk factor for preeclampsia

Soluble Fms-like tyrosine kinase-1 (sFlt-1) is the soluble form of receptor vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). This vascular endothelial growth factor secretes dimeric glycoproteins that participate in vasculogenesis and angiogenesis (Lecarpentier & Tsatsaris, 2016).

Previous studies found that sFlt-1 levels in non-preeclampsia pregnancies were $3,981.62 \pm 4,921.5$ pg/ml. While in preeclampsia, sFlt-1 levels were $11,231 \pm 8,390.3$ pg / ml. In the study, it was also obtained with a cut off point of $>4,505.50$ pg / ml can predict preeclampsia with a sensitivity of 79.3% and specificity of 82.8% and the risk of preeclampsia increased 18 times at levels above the cut off point (Putra et al., 2016). Other results of other studies obtained lower results, at 29-36 weeks gestation, sFlt-1 levels were 2,641.0 (range 1,811.3 to 12,661.0) in preeclampsia and 1,439.0 (range 428.8 to 4,691.0) (Hanita et al., 2014). In this study, the median sFlt-1 levels were 890 pg / ml in preeclampsia and 754.5 pg / ml in non-preeclampsia.

In preeclampsia, the concentration of sFlt-1 increases in the second trimester, usually 4-5 weeks before the onset of preeclampsia syndrome. The concentration increased 2 to 4 times compared to non-preeclampsia. At the same gestational age, sFlt-1 concentrations were higher in preeclampsia compared to non-preeclampsia (Lecarpentier & Tsatsaris, 2016). In this study, sFlt-1 levels were significantly higher in preeclampsia compared to non-preeclampsia ($p = 0.026$). This result is comparable to the results of the previous Mega Putra et al, (2016) research which also had significant differences between preeclampsia and non-preeclampsia pregnancies ($p < 0.005$). In vivo studies have also explained that high levels of sFlt-1 induce disruption of the spiral artery remodeling process in preeclampsia (Vogtmann et al., 2021).

Preeclampsia is associated with an increase in circulating sFlt-1 protein, as mentioned above. Increased production of sFlt-1 may come from the placenta, this is because the sFlt-1 mRNA of placental preeclampsia levels drop within 48 hours after delivery. In addition, the administration of exogenous sFlt-1 in vivo research also causes clinical and pathological preeclampsia such as hypertension and glomerular endotheliosis (Roberts & Rajakumar, 2009). In addition, sFlt-1 acts as an antagonist of VEGF and PlGF. VEGF plays a role in stimulating angiogenesis and to maintain endothelial integrity, especially in fenestrated endotheliums such as those in glomerular capillaries. Administration of VEGF antagonists as a cancer treatment is also associated with proteinuria and hypertension (Kabbinavar et al., 2003). VEGF also recruits endothelial progenitor cells to the site of endothelial injury (Urbich et al., 2005). So that with an increase in sFlt-1 this will interfere with the remodeling process of the placenta as in preeclampsia.

In this study, the mean level of sFlt-1 in all samples was 873.5 (± 439.6). Patients with preeclampsia tended to have higher levels of sFlt-1 compared to patients without

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preeclampsia (1038.9 vs. 709). The Mann-Whitney test shows this difference is statistically significant ($p = 0.026$).

High ratio of soluble FMS-like Tyrosine Kinase 1 (sFlt-1) to Placental Growth Factor (PIGF) Levels as a Risk Factor For Preeclampsia

Some studies show increased levels of sFlt-1 and decreased levels of PIGF in women with preeclampsia compared to non-preeclampsia pregnancies (Anderson et al., 2012). Thus the sFlt-1:PIGF ratio is also useful in distinguishing preeclampsia patients from non-preeclampsia (Chau et al., 2017).

In this study, the median ratio of sFlt-1: PIGF in preeclampsia was 40.1 while in non-preeclampsia it was 23.7. The difference between the two ratios is statistically significant ($p = 0.002$). These results are also supported by other studies, but with more striking results. In the study of Nikuei et al, (2020) obtained a ratio of 91.33 in preeclampsia patients and 17.62 in non-preeclampsia ($p < 0.001$).

In addition, this ratio also serves as a good predictive factor against preeclampsia. The results of this study are supported by the results of other studies that obtained an sFlt-1: PIGF ratio of more than 38 has a 2.8 times higher risk of preeclampsia (Ohkuchi *et al*, 2021). Another study also found that a ratio of more than 38 had a positive predictive value of 36.7% experiencing preeclampsia in 4 weeks, and sensitivity of 66.2% and specificity of 83.1%.

In this study, the mean ratio of sFlt-1 / PIGF in all samples was 36.37 (± 22.8). Patients with preeclampsia tended to have a higher sFlt-1/PIGF ratio compared to patients without preeclampsia (46.56 vs. 26.18). The Mann-Whitney test shows this difference is statistically significant ($p = 0.002$).

High Levels of Low Density Lipoprotein (LDL) as a Risk Factor For Preeclampsia

In this study, LDL levels in preeclampsia were 150.2 (± 31.9) mg / dl while in non-preeclampsia pregnancies were 129.4 (± 22.0) mg / dl. The same results were also obtained in previous studies that found LDL levels in preeclampsia 133.92 (± 38.77) mg / dl higher than normotensive which was 112.41 ± 36.08 mg / dl (Tesfa et al., 2020). So is research (Kozan et al., 2015) received 147 ± 61 mg/dl in preeclampsia and 135 ± 59 mg/dl in non-preeclampsia. Another study also found pregnant women who had LDL levels of >50 U/l had a 2.9 times higher risk of developing preeclampsia compared to levels below (Qiu et al., 2006). Other studies have had similar results.

Several other studies have had different results. Research by Rajyalakshmi and Rao, (2016) shows no significant increase in LDL in preeclampsia and eclampsia. Likewise, the results of research Harmi et al (2012) found no difference in LDL cholesterol levels between preeclampsia and overweight pregnant women with non-preeclampsia blood pressure.

Although some data show an association between LDL levels and preeclampsia, it is still unclear whether high cholesterol levels are a predisposing factor that occurs before preeclampsia or vice versa increases after preeclampsia. Theories that explain the

relationship are the occurrence of hemodynamic disorders, oxidative stress, exposure to inflammatory cytokines and hypercholesterolemia. In the pathogenesis of preeclampsia, characteristic lesions of the placenta are fibrin deposits, acute atheros, and thrombosis. These lesions are almost the same shape as lesions found in atherosclerosis. Based on these findings, there may be pathophysiological similarities between preeclampsia and atherosclerosis. An abnormal fat profile is also a risk factor for preeclampsia (Lowe et al., 2015). Several factors such as fatty acids, lipoproteins, lipid peroxidases, TNF α , fibronectin products and microvilli fragments from syncytiotrophoblast cells, all of these factors are the result of intravascular inflammatory responses encountered in pregnancy and have increased preeclampsia (Lowe et al., 2015).

In this study, the mean LDL levels in all samples were 139.8 (\pm 29.0). Patients with preeclampsia tended to have higher LDL levels compared to patients without preeclampsia (150.2 vs. 129.4). The Mann-Whitney test shows this difference is statistically significant ($p = 0.021$).

CONCLUSION

Low levels of placental growth factor (PIGF) are a risk factor for preeclampsia (OR 4.33; p 0.0302). High levels of soluble FMS-like Tyrosine Kinase 1 (sFlt-1) are a risk factor for preeclampsia (OR 4.33; p 0.027). A high soluble FMS-like Tyrosine Kinase 1 (sFlt-1) / Placental Growth Factor (PIGF) ratio is a risk factor for preeclampsia (OR 4.33 p 0.030). High levels of Low Density Lipoprotein (LDL) are a risk factor for preeclampsia (OR 6.0; p 0.013).

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