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Research Article
Relationships of Malondialdehid and Sflt-1 with Maternal and Neonatal Outcome in Preeclampsia: An Observational Analytic Study

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Abstract

Background and Objective: Increased Malondialdehyde (MDA) will cause endothelial damage and dysfunction. Soluble fms-like tyrosine kinase-1 (sFlt1) is known increase in amniotic fluid in preeclamptic patients. This study was aimed to determine the relationship between MDA and sFlt1 with maternal and neonatal outcome in preeclampsia. **Materials and Methods:** This was an observational analytic study with cross sectional study design. The sample size was 35 samples of pregnant women with preeclampsia. Sampling was done by consecutive sampling, from obstetrician's practice at RSUP. Dr. M. Djamil Padang, RSI. Ibnu Sina Padang and RSU. BMC Padang. After maternal and neonatal examination and measurements MDA and sFlt1 levels of cubital venous blood by using Enzyme-Linked Immunosorbent Assay (ELISA) method, Pearson correlation was performed to assess the relationship between variables for normally distributed data and Spearman's correlation for abnormal distribution data with significance level $p<0.05$. **Result:** This study found MDA associations with maternal and neonatal outcomes were systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), infant weight, infant length, apgar score I and apgar score II which obtained $p<0.001$, $r = 0.587$, $p = 0.011$, $r = 0.356$, $p<0.001$, $r = 0.497$, $p = 0.005$, $r = 0.393$, $p = 0.001$, $r = 0.448$, $p = 0.063$, $r = 0.265$ and $p = 0.020$, $r = 0.328$. The relationship of sFlt1 with maternal and neonatal outcome found $p = 0.984$, $r = 0.003$, $p = 0.783$, $r = 0.040$, $p = 0.758$, $r = 0.045$, $p = 0.471$, $r = 0.104$, $p = 0.292$, $r = 0.152$, $p = 0.639$, $r = 0.068$ and $p = 0.707$, $r = 0.055$. **Conclusion:** There was relationship between MDA with maternal and neonatal outcomes except for apgar score in the first minute. There was no relationship between sFlt1 with materal and neonatal outcome.

Key words: Malondialdehid (MDA), soluble fms-like tyrosine kinase-1 (sFlt1), preeclampsia, maternal outcome, neonatal outcome

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Preeclampsia was an important issue in the field of obstetrics because it was still the main cause of maternal death compared to bleeding and infection. Preeclampsia also caused perinatal death and premature birth[1]. The overall incidence of preeclampsia was 5-14% of all pregnancies. It was later found out that the incidence of preeclampsia ranged from 15.9% of all maternal deaths in the United States and was the greatest causes of perinatal morbidity and mortality[2]. The exact cause of preeclampsia was not known until today. Many factors were thought to be associated with the pathogenesis of preeclampsia, such as genetic factors, immune disorders, vascular disorders and oxidative stress[3].

Several studies had identified markers expressed on trophoblasts as well as decidua that were thought to play an important role in the failure of trophoblast invasion which in turn played a role in the pathophysiology of preeclampsia[2]. An imbalance between antioxidants and free radicals in pregnancy was thought to lead to pathological changes that could lead to complications in pregnancy such as preeclampsia[4]. One of the free radicals known to increase during preeclampsia was Malondialdehyde (MDA). MDA is a dialdehyde compound that is a lipid peroxidation end product in the body that was thought to be associated with preeclampsia and was also associated with IUGR and gestational diabetes. However, the relationship between MDA and various complications of pregnancy had not been fully accepted globally for its conflicting study results[5].

Soluble fms-like tyrosine kinase 1 (sFlt1), a potent antagonist compounds from VEGF and placental growth factor (PIGF), had been known to increase levels of amniotic fluid in patients with preeclampsia. VEGF is an angiogenesis promoter and inhibition of VEGF signals that will cause hypertension and proteinuria[6].

Preeclampsia was associated with increased morbidity and mortality rates of new borns[2]. IUGR was a pregnancy complication that had been known to be associated with maternal preeclampsia. Birth length and apgar scores were also found to be lower in infants born to mothers with preeclampsia compared to mothers with normal pregnancies. Pregnancy complications occurred were usually caused by premature birth and uteroplacental insufficiency that caused disruption of blood flow to the fetus[2]. Given the hypothesis about relationship between MDA and sFlt1 as a marker of preeclampsia which would lead to poor outcomes in neonates, authors were interested to investigate whether there was a relationship between MDA and sFlt1 with neonatal and maternal outcomes in preeclampsia.

MATERIALS AND METHODS

This was an observational analytic study with cross sectional study design. This study was conducted at RSUP. Dr. M. Djamil Padang, RSI. Ibnu Sina Padang, RSU. BMC Padang as well as sample examination conducted in Biomedical Laboratory FK Unand in August, 2017 - November 2017. Library search and proposal writing conducted during August, 2017 with duration 28 h week^{-1}. Data collection and analysis was conducted during September 2017 with a duration of 28 h week^{-1}. A sample size of 35 samples consisted of 30 samples of preeclamptic pregnant women plus 15% to avoid drop outs which had met inclusion criteria and passed exclusion criteria. Sampling was done by consecutive sampling.

The population of this study were all pregnant women who suffered from preeclampsia a term who did antenatal care on obstetrician's practice at RSUP. Dr. M. Djamil Padang, RSI. Ibnu Sina Padang and RSU. BMC Padang. The inclusion criteria in this study were women with preeclampsia, neonates born alive and willing to participate in the study.

After signing informed consent, history, clinical examination and obstetric examination and ultrasound were performed. Blood pressure were obtained and then MAP was calculated. A cubital venous blood were sampled to check the levels of MDA and sFlt1 in the mother. MDA was examined using spectrophotometric method with spectrophotometer and NWLSS TM Malondialdehyde Assay reagent and sFlt1 was examined by ELISA. After the child was born either per vaginam or sectio caesarea, apgar score, birth weight, body length was measured.

Univariate analysis was used to observe characteristics of respondents. Bivariate analysis was done using Pearson correlation test if data distribution was normal and Spearman correlation test was used when data distribution was not normal with significance level $p<0.05$. Normality test was assessed using Kolmogorov-Smirnov test (total sample in group$\geq$50).

RESULTS

The maternal and neonatal characteristics were presented in Table 1. Table 2 shown the relationship between MDA and maternal outcome, where MDA-free radical levels had a significant association with elevated systolic blood pressure, diastolic blood pressure and maternal MAP, whereas these three maternal outcome parameters had $p<0.05$. As presented in Table 3, increased levels of MDA-free radicals had positive correlation with infant weight, body length and apgar score of

Table 1: Subject characteristics

Variables	Median (Minimum-Maximum)
Age (years)	33.5 (15-47)
Gestational age (weeks)	35.5 (26-39)
Maternal weight (Kg)	65 (49-98)
Maternal height (cm)	154.5 (145-165)
Systolic blood pressure (mmHg)	177.5 (150-220)
Diastolic blood pressure (mmHg)	110 (80-130)
MAP (mmHg)	132.5 (107-160)
Neonates weight (g)	1700 (600-4900)
Neonates length (cm)	42 (26-50)
Apgar score of the first 1 min	6 (1-8)
Apgar score of the first 5 min	7 (2-9)
MDA (nmol mL^{-1})	4.98 (1.17-26.94)
sFlt1 (ng mL^{-1})	1.755 (0.039-9.368)

Table 2: Relationship between MDA and maternal outcome

	Systolic blood pressure	Diastolic blood pressure	MAP*
MDA	r = 0.587	r = 0.356	r = 0.497
	p<0.001	p = 0.011	p<0.001
	n = 50	n = 50	n = 50

Spear man correlation test and *Pearson correlation test

Table 3: Relationships between MDA and neonatal outcome

	Neonates weight	Neonates length	Apgar Score I	Apgar Score II
MDA	r = 0.393	r = 0.448	r = 0.265	r = 0.328
	p = 0.005	p = 0.001	p = 0.063	p = 0.020
	n = 50	n = 50	n = 50	n = 50

Spear man correlation test

Table 4: Relationship between sFlt1 and maternal outcome

	Systolic blood pressure	Diastolic blood pressure	MAP*
sFlt1	r = 0.003	r = 0.040	r = 0.045
	p = 0.984	p = 0.783	p = 0.758
	n = 50	n = 50	n = 50

Spear man correlation test and *Pearson correlation test

Table 5: Relationship between sFlt1 and neonatal outcome

	Neonates weight	Neonates length	Apgar Score I	Apgar Score II
sFlt1	r = 0.104	r = 0.152	r = 0.068	r = 0.055
	p = 0.471	p = 0.292	p = 0.639	p = 0.707
	n = 50	n = 50	n = 50	n = 50

Spear man correlation test

the first 5 min. While apgar score of the first minute in neonatal outcome was found to have no positive correlation with elevated MDA levels (p>0.05). Table 4 shown increased of sFlt1 compounds were found to be unrelated to elevated systolic blood pressure, diastolic blood pressure and MAP on maternal outcome (p>0.05). From the Table 5 found that the increase in sFlt1 compound had no positive correlation with infant weight, length, apgar score of the first minute and apgar score of the first 5 min in neonatal outcome (p>0.05).

DISCUSSION

Two million women worldwide died each year from pregnancy complications. 10-15% of them were caused by hypertension in pregnancy[7]. Preeclampsia is a part of hypertension in pregnancy with more severe conditions. The incidence of preeclampsia ranged from 15.9% of all maternal deaths in the United States and was the largest cause of perinatal morbidity and mortality[2].

Until now the cause of preeclampsia was still not known certainly. Endothelial dysfunction played an important role in the genesis of multisystem abnormalities that developed in preeclampsia[8]. Oxidative stress due to imbalances of anti-oxidant and free radicals such as MDA was thought to be the underlying mechanism of endothelial dysfunction[4]. sFlt1 was known to have an important role in the pathogenesis of preeclampsia, but the mechanism of effect of sFlt1 was still unknown[9].

Given the relationship between MDA and sFlt1 as a marker of preeclampsia that would cause poor outcomes in neonates, we were interested in studying the association between MDA and sFlt1 with neonatal and maternal outcomes in preeclampsia.

Based on the baseline characteristics in this study, it was found that the age of the subjects with preeclampsia was from the early adolescent age group to the early elderly with median gestational age at termination which indicated late onset of preeclampsia. For neonatal outcome we found that in general, infants born were low birth weight infants. The median value of Apgar score classifies infants into mild asphyxia groups.

MDA-free radical levels were found to have a significant effect on maternal outcomes in the form of systolic blood pressure, diastolic blood pressure and maternal MAP. MDA also had a positive correlation with neonatal outcome i.e., infant weight, length and apgar score of the first 5 min (p<0.05). However, for the apgar score for the first 1 min there was no significant relationship (p>0.05).

This study was almost in line with the results of Surya's study comparing MDA levels in preeclampsia and normal pregnant women. It was concluded that there was a significant difference between mean MDA levels in preeclampsia and normal pregnancy (p<0.05). In addition, it was found that the relative risk of preeclampsia with elevated MDA levels was 7 times higher than for normal pregnancy (RO = 1.27, IK 95% = 2.58-20.16, p = 0.001)[10].

Besides, Jammalamadaga found a significant increase of MDA, TNF-α and sFlt1 levels in women with preeclampsia and

eclampsia. When compared further it was found that elevated levels of MDA, TNF-α and sFlt1 in eclampsia were higher than preeclampsia[8].

Spearman correlation test for increased sFlt1 compound was known not to have positive correlation with increase of systolic blood pressure and diastolic blood pressure in maternal outcome ($p>0.05$) and also with infants weight, length, apgar score of the first minute and apgar score of the first 5 min in neonatal outcome ($p>0.05$). Pearson correlation test on the increased sFlt1 compound for MAP was also known to have no positive correlation ($p>0.05$).

Lee, *et al*. evaluated and measured sFlt1 concentrations in preeclampsia and normotensive pregnant women. From this study found that there was a positive correlation of total sFlt-1 concentration with systolic and diastolic blood pressure[11].

Reddy, *et al*. showed that sFlt-1 levels increased significantly at labor in women with preeclampsia compared with normal pregnant women and then declined after 24 h. Placental oxygen concentration was associated with sFlt-1[12].

Jiang, *et al*. found that there were significant differences in sFlt1, systolic blood pressure, diastolic blood pressure, proteinuria and infant birth weight in pregnant women with preeclampsia and normotensive pregnant women. From the test performed on mouse, it was found that there was a significant correlation between sFlt1, systolic blood pressure, MAP and ratio of urinary albumin: Creatinine to preeclampsia, whereas diastolic blood pressure was found to have no effect on preeclampsia. Jiang concluded that sFlt-1 appeared to play a role in oxidative stress that promoted trophoblastic apoptosis. This process may be an important mechanism in the development of preeclampsia[9].

It was difficult to determine the cause of the variation in the results of several other studies and also the results of this study. Differences in the study design, gestational age at the time of sampling, the characteristics of the subjects, the number of study populations, as well as examination methods technique done by other researchers may yield different results compared with results in this study.

CONCLUSION

Through this study, concluded that there is a relationship between MDA with maternal and neonatal outcomes in preeclampsia woman in Indonesia who have different characteristics than other woman around the world. However, sFlt-1 has not been shown to be associated with maternal and neonatal outcomes.

SIGNIFICANCE STATEMENT

From this study we found that preeclampsia leads to an increase of free radicals resulting in elevated maternal serum MDA levels that affect maternal and neonatal outcomes. However, although sFlt1 has been known to be a potent antagonist of VEGF and PIGF, we found no significant effect on maternal and neonatal outcomes. Moreover, we found that measurement of maternal serum MDA levels could serve as one of the preventive and early diagnostic points of preeclampsia and effects that can be caused to the neonatal. The results we have found are expected to be a reference for further research, especially in proving factors affecting the outcomes of MDA and sFlt1.

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