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RESEARCH ARTICLE **OPEN ACCESS**

The Relationship between Soluble Endoglin Levels, Endothelial Nitric Oxide Synthase Levels, and Thrombocyte Count and the Onset of Preeclampsia

Aladin Aladin[1], Yusrawati Yusrawati[1,*], Hudila Rifa Karmia[1], Reyhan Julio Azwan[1] and Ramya Sausan[1]

[1]*Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Andalas, Padang, West Sumatera, Indonesia*

Abstract:

Background: Early-onset preeclampsia, or EOP, depicts clear placental abnormalities (placental factor), whereas late-onset preeclampsia, or LOP, does not. However, previous studies found varying results on the role of proangiogenic and antiangiogenic factors, including soluble endoglin (sEng), endothelial nitric oxide synthase (eNOS), and thrombocytes in both types of preeclampsia.

Objective: This study aimed to determine the relationship between sEng levels, eNOS levels, and thrombocyte count with the onset of preeclampsia.

Methods: A cross-sectional study was conducted on subjects diagnosed with severe preeclampsia receiving treatment at Dr. M. Djamil Hospital Padang from December, 2023, until March, 2024. After meeting the inclusion and exclusion criteria, maternal plasma concentrations of sEng and eNOS were determined by ELISA, while thrombocytes were measured by a complete blood count.

Results: A total of 40 women with EOP and 40 with LOP participated in this study. This study found no difference between the two groups in eNOS (p = 0.303) and sEng (p = 0.468). However, thrombocyte count differed between early and late-onset PE (p = 0.001). Spearman correlation analysis found a significant correlation between eNOS and sEng (p = 0.033), eNOS and thrombocyte count (p = 0.026), and thrombocyte count and sEng (p = 0.032).

Conclusion: This study found no difference in proangiogenic and antiangiogenic factors between EOP and LOP, which suggests that a subset of patients with LOP also has an imbalance in the concentrations of proangiogenic and antiangiogenic factors in maternal plasma. However, lower thrombocyte counts in EOP reflect a more severe disease course. This study also found a correlation between eNOS and sEng, eNOS and thrombocyte count, and thrombocyte count and sEng in preeclampsia.

Keywords: sEng, eNOS, Thrombocyte, Early onset preeclampsia, Late-onset preeclampsia, Proangiogenic, Antiangiogenic.

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*Address correspondence to this author at the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Andalas, Padang, West Sumatera, Indonesia; E-mail: yusrawati_65@yahoo.co.id

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1. INTRODUCTION

Preeclampsia is still the main cause of maternal and perinatal morbidity and mortality worldwide [1, 2] and is the largest contributor to caesarean sections, prolonged hospital stays, and poor neonatal outcomes [3]. Preeclampsia is reported in varying numbers. The prevalence of preeclampsia in Sweden is 2.8%, and in China, it is 2.2%, where 2/3 of cases in Sweden are mild preeclampsia, while 2/3 of cases in China are severe preeclampsia [2]. In a hospital in Ethiopia, preeclampsia was reported as high as 12.4% [4]. Many theories have been developed about preeclampsia; however, the underlying mechanisms are still unknown, so causal management and primary prevention of preeclampsia are still impossible to implement, which results in an increase in morbidity and mortality for both mother and fetus. Preeclampsia affects 5-7% of all pregnant women but is responsible for 70,000 maternal deaths and 500,000 fetal deaths worldwide [5]. The rate of fetal death due to preeclampsia in China is almost 10 times higher than in Sweden [2]. The expression of antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), is increased in preeclamptic patients, whereas the expression of proangiogenic factors, such as vascular endothelial growth factor (VEGF), is decreased, which is manifested as an imbalance in angiogenesis and extensive endothelial damage, resulting in poor placental implantation and impaired glomerular filtration. sEng is a homodimeric membrane glycoprotein that can inhibit the activity of endothelial nitric oxide synthase (eNOS) by binding to transforming growth factor-β (TGF-β), which activates platelets and increases leukocyte adhesion. They subsequently cause extensive endothelial damage that participates in the pathogenesis of preeclampsia [6]. Preeclampsia develops in two stages. In the early stage of the placenta, genetic and maternal factors, placental hypoxia and oxidative stress, as well as pregnancy-induced immunological reactions, lead to abnormal placentation and placental hypoperfusion. In late maternal stages, the hypoperfused and poorly developed placenta releases prothrombotic and proinflammatory factors into the maternal circulation, causing endothelial dysfunction and thrombosis. Platelets are the primary source of placental angiogenic factors and are required to maintain local hemostasis during early placental development (*e.g.*, remodeling of the maternal spiral arteries). The platelet count decreases gradually with increasing gestational age due to hemodilution caused by plasma volume expansion, accelerated sequestration, consumption in the placental circulation, and clearance of activated platelets. Excessive platelet activation and/or an increase in mean platelet volume during early pregnancy predict the incidence of preeclampsia in late pregnancy. Due to platelet activation, preeclamptic patients have high levels of circulating platelet-monocyte aggregates, which induce the expression and release of sFLT-1. Activated platelets also induce inflammatory activation and assembly in trophoblast cells. High platelet volume indicates platelet activation and is negatively correlated with platelet count. Higher platelet activation results in a lower platelet count [7-9]. Based on the onset, preeclampsia is divided into Early Onset Preeclampsia (EOP) and Late-Onset Preeclampsia (LOP). Preeclampsia that appears before 34 weeks is called EOP, and preeclampsia that appears after 34 weeks is called LOP [3, 10-13]. LOP and EOP differ in pathogenesis. EOP depicts clear placental abnormalities (placental factor) [12, 14], while LOP does not (maternal factors are more prominent) [11, 14]. As LOP is not based on placental abnormalities (not based on the failure of trophoblast invasion), it can be assumed that there is no role for sEng, eNOS levels, and thrombocyte counts in the pathogenesis of LOP. However, they play an important role in the pathogenesis of EOP. This assumption could be proven if there are significant differences in soluble endoglin (sEng), endothelial nitric oxide synthase (eNOS), and thrombocyte counts between EOP and LOP. Due to the various hypotheses mentioned above, this study aims to determine the relationship between soluble endoglin (sEng) levels, endothelial nitric oxide synthase (eNOS) levels, and thrombocyte count with the onset of preeclampsia.

2. MATERIALS AND METHODS

This study used the quantitative research method with a cross-sectional design. Pregnant women diagnosed with severe preeclampsia and receiving treatment at Dr. M. Djamil Hospital Padang, who met the inclusion criteria, were included in the study. Inclusion criteria included agreeing to participate, age ≥ 18 years, singleton pregnancy, being diagnosed with preeclampsia at less than 34 weeks of gestation for EOP and after 34 weeks for LOP, and having uncomplicated preeclampsia in which no end organ damage was found. Exclusion criteria included being treated with different management from usual procedures at Dr. Hospital. M. Djamil, died or was discharged against medical advice or was referred to another hospital before data collection was completed, dropped out of the study before data collection was complete, research materials were damaged, could not be assessed, or had incomplete data, and had major fetal morphological abnormalities discovered through examination. Data were analyzed using the SPSS application, and bivariate analysis was performed using Mann-Whitney and Spearman correlation. This study involved patients' medical records, and all medical matters relating to this research were kept confidential. The ethical implications of this study followed the provisions of the Declaration of Helsinki and were approved by the research ethics committee of medical faculty at Andalas University in order to protect human rights and the welfare of medical/health research subjects (approval number: 508/UN.16.2/KEP-FK/2023). The participants approved and signed the informed consent.

3. RESULTS

A total of 80 pregnant women diagnosed with preeclampsia and receiving treatment at Dr. M. Djamil Padang Hospital participated in this study. Table **1** shows the characteristics of respondents.

EOP and LOP have almost the same mean age, 31.80 ± 5.57 years and 30.47 ± 6.73 years, respectively. Both groups were overweight, with a mean BMI of 26.28 ± 4.85 kg/m^2 in EOP and 27.23 ± 5.88 kg/m^2 in LOP. EOP had a mean gestational age of 29.42 ± 3.41 weeks, while LOP had a mean gestational age of 36 ± 2.07 weeks. Moreover, 62.5% of EOP patients were primiparous, and 37.5% were multiparous, while a majority of patients had LOP, which was primiparous, *i.e.*, 77.5% and 22.5% were multiparous.

Table 1. Characteristics of subjects.

Characteristics	EOP		LOP	
	Mean ± SD	Min - Max	Mean ± SD	Min - Max
Age (years)	31.80 ± 5.57	21- 42	30.47 ± 6.73	15 - 43
BMI (kg/m^2)	26.28 ± 4.85	18.36 – 39.6	27.23 ± 5.88	20 – 40.15
Gestational age (weeks)	29.42 ± 3.41	20 – 33	36 ± 2.07	30 – 40
Parity **Primiparous (%)** **Multiparous (%)**	25 (62,5) 15 (37,5)		31 (77,5) 9 (22,5)	

3.1. Differences of eNOS, sEng, and Thrombocyte between EOP and LOP

The mean eNOS value in the EOP group was almost similar to LOP, which was 59.65 ± 32.65 pg/mL *vs.* 68.95 ± 44.10 pg/mL. Based on the Mann-Whitney U test (Table **2**), the *p*-value was 0.303. Therefore, it was concluded that there was no significant difference between the eNOS levels in both groups.

Table 2. eNOS, sEng levels, and thrombocyte count in early-onset preeclampsia and late-onset preeclampsia.

Variable	EOP	LOP	*P*-value
eNOS	59.65±32.65	68.95 44.10	[a]0.303
sEng	0.09±0.09	0.11±0.09	[a]0.468
Thrombocyte	168,30±84,72	244,87±92,45	**[a]0.002**

Note: [a]Mann-Whitney.

The table also shows that the mean levels of sEng in EOP were lower than LOP (0.09 ± 0.09 pg/mL *vs.* 0.11 ± 0.09 pg/mL). However, the Mann-Whitney U test obtained $p = 0.468$, indicating no significant difference between the levels of sEng in both groups.

The mean thrombocyte count in the EOP group was lower than in the LOP group (168.300±85.725/mm^3*vs.* 244.875±92.458/mm^3). Based on the results of the Mann-Whitney U test, the *p*-value was 0.002, so it was concluded that there was a significant difference between thrombocyte counts in both groups.

3.2. Correlation between eNOS and sEng, eNOS and Thrombocyte Count, sEng and Thrombocyte Count in Preeclampsia

Table **3** shows a correlation between eNOS levels and sEng levels in preeclampsia, where the *p*-value was 0.033. The Spearman correlation value was 0.238, which included the low correlation.

Tabel 3. Correlation of eNOS and sEng, eNOS and thrombocyte count, sEng and thrombocyte count in preeclampsia.

Variables	Spearman Correlation	*P*-value
eNOS **sEng**	0.238	**[b]0.033**
eNOS **Thrombocyte**	0.249	**[b]0.026**
sEng **Thrombocyte**	0.240	**[b]0.032**

Note: [b]*Spearman correlation.*

The results of the correlation test between eNOS levels and thrombocyte count in preeclampsia also demonstrated a significant correlation ($p = 0.026$). The Spearman correlation value was 0.249, which indicated a low correlation.

The correlation test between sEng levels and thrombocyte count in preeclampsia demonstrated a significant relationship, where the *p*-value = 0.032 and the Spearman correlation value was 0.240.

4. DISCUSSION

4.1. Characteristics of the Respondent

In this study, it was found that the mean age of the EOP and LOP groups was almost the same, above 30 years. Risk factors for preeclampsia include race, advanced maternal age, obesity, nulliparity, multiple pregnancies, and other comorbidities [15]. You *et al.* stated that old age tends to be a risk factor for EOP [16]. The placenta of older women has pathological characteristics of premature aging from the early stages of pregnancy, which is associated with higher rates of delayed villous maturation, fetal vascular malperfusion, and maternal vascular lesions [17]. This contributes to the incidence of EOP.

Both groups had an overweight BMI, indicating that overweight/obesity is a risk factor for both types of preeclampsia. Motedayen *et al.* also reported a relationship between BMI and the incidence of preeclampsia [18]. Increased weight during pregnancy or before pregnancy is associated with hyperinsulinism, insulin resistance, and maternal systemic inflammation that triggers endothelial dysfunction, hypertension, proteinuria, and thrombotic responses, thereby contributing to preeclampsia [19].

The mean gestational age was found to be lower in EOP than in LOP. This may be influenced by the definition

of EOP and LOP itself, where LOP is diagnosed after 34 weeks of gestation, while EOP is diagnosed before 34 weeks of gestation [20].

Most of the patients in both groups were primiparas, and there was no difference in parity between the EOP and LOP groups. A study by You *et al.* on pregnant women in Taiwan from 2001 to 2014 found that primiparity was related to the incidence of preeclampsia, both in early and late-onset. However, correlation analysis showed that the strongest relationship was obtained in LOP (r = 0.71). In this study, no correlation analysis was carried out regarding parity, so it is not known which group was most influenced by primiparity [16]. Lin *et al.* also conducted a study on 15 hospitals in Beijing and found that nulliparity affected the incidence of LOP (OR 2.00; $p< 0.001$) [21]. Based on percentages, there were also more primiparas in LOP than EOP in this study, which was similar to previous studies.

Primiparity was associated with a threefold increase in risk of preeclampsia. It is suspected that one of the mechanisms for the emergence of preeclampsia is immune maladaptation and maternal alloimmune reactions triggered by the rejection of paternal antigens in the fetal allograft. This response is greatest in the first pregnancy; therefore, primiparous mothers are more likely to experience preeclampsia, whereas multiparous mothers are protective and reduce the risk of preeclampsia. This protective effect is lost when subsequent pregnancies involve exposure to new paternally inherited antigens. Several studies have reported that primiparas is a risk factor for LOP because it is believed that LOP occurs due to maternal factors, including the mother's immune system [22].

4.2. Differences in eNOS, sEng Level, and Thrombocyte Count between EOP and LOP

In this study, no differences were found in eNOS levels between the EOP and LOP groups, indicating that both groups had decreased eNOS levels. Similar results were found in previous studies. In 2023, Kaihara *et al.* conducted a study on 417 PE subjects, consisting of 43 non-pregnant women, 156 healthy pregnant women, 122 pregnant women with gestational hypertension, and 96 PE pregnant women. The study found lower plasma eNOS concentrations in the EOP group, but it was not statistically significant ($p > 0.05$), which was similar to this study [23].

Laskowska *et al.* also found no difference in eNOS levels based on the onset of preeclampsia. They found higher eNOS levels, which were 154,327 ± 155,308 U/ml in EOP and 156,247 ± 127,019 U/ml in LOP. However, the results of the bivariate test found a *p*-value of 0.64, so it was concluded that there was no significant difference in eNOS levels based on the onset of preeclampsia [24].

A study by Shaheen *et al.* on 600 women consisting of 188 PE patients, 112 PE patients with severe symptoms, and 300 normotensive pregnant women found that NO concentrations decreased in all PE groups. In addition, it was found that the mutation in the Glu298Asp protein caused destabilization of the protein molecule and reduced the stability of all eNOS proteins, leading to a decrease in NO concentration. In this study, there was no difference between EOP and LOP, with the mean gestational age in PE at the time of the study being 33.12 ± 0.15 weeks, indicating that in both EOP and LOP, there was the same decrease in eNOS, which had an impact on reducing NO concentrations [25].

The mechanism of PE remains unclear but may involve abnormal placentation characterized by impaired trophoblast invasion of the spiral arteries, which increases ROS production, triggering oxidative stress, hypoxia, and decreased placental perfusion and endothelial dysfunction. The main cause of abnormal placentation and endothelial dysfunction in PE is reduced nitric oxide (NO) bioavailability [26].

eNOS is an important regulator of vascular tone and contributes to the reduction in uteroplacental resistance seen in normal pregnancy through the production of Nitric Oxide (NO) with the reduction of L-arginine to L-citruline [25, 26]. The main consequence of decreasing eNOS levels is that it impairs NO production, which is critical for PE and the development of hypertension in pregnancy. During pregnancy, if impaired NO production creates an environment susceptible to endothelial dysfunction, this may affect feto-placental blood flow and embryonic development. The placenta relies on a balance of NO to provide vascular adaptation and maintenance, which is the reason why the placenta may be a focal point for research on hypertension in pregnancy. eNOS levels have been explored in vascular disorders. Decreased plasma eNOS levels were found in slow coronary flow and were associated with endothelial dysfunction, which was consistent with the finding of reduced eNOS levels in preeclampsia [23].

Although the basic pathophysiology of EOP and LOP is different, with EOP being associated with a defect in the placenta and LOP being associated with the interaction of the placenta and maternal genetic predisposition, it appears that decreased plasma eNOS concentrations are associated with the occurrence of both types of preeclampsia. In EOP, a decrease in eNOS levels causes a decrease in NO bioavailability, resulting in endothelial dysfunction that ends in abnormal placentation. In EOP, maternal factors that accompany its pathogenesis, such as obesity, hypertension, glucose intolerance, and dyslipidemia, also cause an increase in ROS through an increase in pro-inflammatory adipokines and NADPH oxidase and a decrease in SOD. The increase in ROS in metabolic syndrome, which is related to LOP pathogenesis, will ultimately also reduce eNOS production in LOP. This supports the findings in this study, where there was no difference between eNOS levels in the EOP and LOP groups [27].

Although an imbalance of pro-angiogenic and anti-angiogenic factors is more likely to occur in EOP, in this study, there was no difference in levels of sEng, which has an antiangiogenic effect, in the EOP and LOP groups. This indicates that some LOP patients are also affected by an

imbalance of angiogenic/anti-angiogenic factors in the maternal circulation. This was proven by a previous study by Soto *et al.* in 2012. In this study, placental underperfusion was found in 47% of LOP patients, which was higher than healthy controls (7.8%), and this finding was in line with the lower PlGF values, PlGF/sEng ratio, and PlGF/sVEGFR-1 ratio found in this study. They also found elevated sEng levels in LOP, similar to the general finding in EOP [27].

Soluble Eng (sEng) resulting from the release of Eng from the surface of endothelial cells into the maternal circulation has antiangiogenic effects in preeclampsia through its binding to circulating TGF-β1, thereby preventing TGF-β1 signaling on endothelial cells (*i.e.*, proangiogenic and vasodilator effects on the endothelium normal) [5, 28].

Some studies have proposed that EOP and LOP may have different pathophysiologies, and these two phenotypes should be studied separately. Although the magnitude of the imbalance between the concentrations of angiogenic and antiangiogenic factors in maternal blood is greater in EOP compared with LOP, and the presence of placental lesions, such as decidual arteriolopathy, infarction, and villous hypermaturity (which may be related to reduced uteroplacental blood flow) is more common in EOP than LOP, some patients with LOP are also influenced by an imbalance of proangiogenic and antiangiogenic factors in the maternal circulation. Non-placental sources of angiogenic/antiangiogenic factors are activated monocytes, platelets, and endothelial cells, which may be responsible for the increase in anti-angiogenic factors in this subgroup of patients. This interpretation would be consistent with the hypothesis that other factors (*i.e.*, maternal systemic inflammation), rather than unique placental factors, may play an important role in the pathogenesis of LOP [27]. Aneman *et al.* also stated that the increase in innate immune B1 cells in both conditions of preeclampsia, which produce AT1-AAs, stimulates the release of anti-angiogenic molecules, sFtl-1 and sEng [29].

Different results were obtained by Akbar *et al.* in 2017, who conducted studies at RSUD with Dr. Soetomo, Airlangga University Hospital, and Dr. M. Soewandhi Surabaya. The study included 39 pregnant women, consisting of EOP, LOP, and normal pregnant women. From this study, sEng concentrations were found to be significantly higher in EOP compared with LOP and normal pregnancies (47.65 ± 40.17 *vs.* 13.46 ± 9.48 *vs.* 6.11 ± 1.45 ng /mL; $p = 0.000$) [30].

Nafratilova *et al.* also conducted a study at Dr. M. Djamil Hospital on 13 EOP and 13 LOP patients. In this study, it was found that the mean sEng value was higher in the EOP group, *i.e.*, 1.44 ± 0.06 ng/mL compared to 1.35 ± 0.14 ng/mL in the LOP group [31].

These results may be related to the pathophysiology of EOP, which is based on an imbalance between the concentration of proangiogenic and antiangiogenic factors, which is greater in EOP, causing placental abnormalities. However, in both studies, the sample size was smaller, so it is possible that patients with LOP who also experienced increased sEng and placental underperfusion, as stated in a study by Soto *et al.*, were not represented in the study, which caused the mean sEng levels obtained to not increase significantly [27].

We found that the thrombocyte count was lower in EOP than in LOP. A previous study by Nuraini *et al.* also found a significant difference between the platelet counts of EOP and LOP patients [26]. This is caused by the greater number of activated platelets in EOP compared to LOP. The mechanism of platelet activation includes local vascular stasis or turbulence that contributes to fibrinoid formation. In addition, the oxidative stress found in preeclamptic patients activates platelets and makes them procoagulant. Plasma levels of the adhesive ligand VWF also increase significantly during pregnancy and increase further in preeclamptic patients. Low platelet reduction in EOP indicates a more severe disease where inflammation is greater and organ damage is more common [32-34].

During normal pregnancy, platelet count falls physiologically due to hemodilution, increased platelet consumption in peripheral tissues, and increased platelet aggregation due to increased thromboxane A2 levels. This pregnancy-induced thrombocytopenia is mild and does not cause negative consequences for the mother or fetus; however, significant thrombocytopenia is associated with medical conditions and can have serious maternal-fetal consequences. In PE, changes in the coagulation system lead to a decrease in platelets, which is an early sign of the disease. Moreover, the progression of PE to a severe stage leads to increased platelet turnover and increased platelet consumption due to an abnormal coagulation system and platelet activation. In preeclamptic women, plasma platelet activation markers, such as β-thrombomodulin and PLT factor-4, were significantly increased. Increased plasma platelet activation markers, such as β-thrombomodulin and platelet factor-4, and expression of activation markers on the platelet surface confirmed platelet activation. It was found that platelet activation causes platelet consumption [35].

Impaired endothelial synthesis of prostacyclin and nitric oxide has been associated with PE. In this study, we found lower eNOS in the EOP group; although this difference was not significant, lower eNOS could contribute to the lower thrombocyte count found in the EOP group. Prostacyclin and nitric oxide relax blood vessels and inhibit platelet activation. Impaired synthesis of these molecules in PE can lead to the narrowing of blood vessels and platelet activation, and consumption causes a lower thrombocyte count [35, 36].

4.3. Relationship between eNOS and sEng Levels, sEng and Thrombocyte Count, and eNOS and Thrombocyte Count in Preeclampsia

In this study, a correlation was found between eNOS and sEng in preeclampsia patients. Endoglin is a coreceptor for transforming growth factor-β1 (TGF-β) isoforms, TGF-β1 and TGF-β3, which are highly expressed

in endothelial cells and syncytiotrophoblasts, and modulates the actions of TGF-β1 and TGF-β3. Endoglin is a molecule with proangiogenic activity that prevents apoptosis in hypoxic endothelial cells and is important for the activation of eNOS and, subsequently, the regulation of local vascular tone. Soluble endoglin (sEng) has antiangiogenic activity because it prevents the binding of transforming growth factor-β1 to its receptor on endothelial cells, interfering with eNOS activation and NO production [37]. By inhibiting TGF-β1 binding and signaling in endothelial cells, blocking TGF-β1-mediated eNOS activation and inhibiting NOS-dependent vasodilation suggest the involvement of endoglin in cardiovascular development and vascular homeostasis [6].

Thrombocytopenia is a characteristic worsening of preeclampsia because it indicates platelet activation and aggregation as well as microangiopathic hemolysis. sEng is a homodimeric membrane glycoprotein that can inhibit the activity of eNOS, activate platelets, and increase leukocyte adhesion, subsequently causing extensive endothelial damage and participating in the pathogenesis of preeclampsia. Platelet activation from sEng causes low thrombocyte count [26]. This supports the reason why our study did find a correlation between sEng levels and platelet counts in preeclampsia.

In this study, we also found a correlation between eNOS and thrombocyte count. eNOS activities are increased during normal pregnancy and decreased in PE, leading to vasoconstriction and an altered capillary permeability that is partly responsible for oedema and hypertension. Meanwhile, atherosclerotic lesions were detected in the spiral arteries of PE patients, together with platelet activation, as evidenced by the presence of TXA2, fibrin and complement deposits, and foam cells [26].

Nitric Oxide (NO) is synthesized by endothelial Nitric Oxide Synthase (eNOS) in both vascular tissues and platelets. It plays an important role as a protective mediator in the cardiovascular system. It modulates blood pressure, vasodilation, and thrombosis. Nitric oxide relaxes blood vessels and inhibits platelet activation, demonstrating a correlation between eNOS and platelet activation. [35, 26].

This study had some limitations. First, this study only evaluated plasma levels of eNOS, sEng, and thrombocyte count in women with preeclampsia and did not include women with normal pregnancies. Second, this study only included pregnant women in the third trimester of pregnancy, and it is important to analyze these parameters at other gestational ages. Third, this study did not assess the molecular expression of sEng and eNOS, whereas several studies found that genetic mutations in the genes coding for these proteins also contributed to preeclampsia. In addition, this study did not calculate mean platelet volume as a better marker of platelet activation.

CONCLUSION

There was no significant difference between the levels of sEng and eNOS between early and late-onset PE, indicating that a subset of patients with late-onset PE also had an imbalance of proangiogenic and antiangiogenic factors in maternal plasma. However, this study found that thrombocyte count was lower in EOP, reflecting more severe disease in EOP. Moreover, a correlation was found between eNOS and sEng, eNOS and thrombocyte count, and sEng and thrombocyte count in preeclampsia.

A study at the molecular level needs to be carried out to assess the expression of sEng and eNOS in the incidence of EOP and LOP. In addition, mean platelet volume also needs to be assessed to evaluate platelet activation in PE. Further studies need to assess the comparison between preeclampsia women and healthy controls. Moreover, further studies are needed on different gestational ages to assess this parameter.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

VEGF	=	Vascular Endothelial Growth Factor
eNOS	=	endothelial nitric oxide synthase
TGF-β	=	Transforming growth factor-β
sEng	=	soluble endoglin
NO	=	Nitric Oxide

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The name of the institute or committee that provided the ethical approval are the research ethics committee of medical faculty at Andalas University, Indonesia (approval number: 508/UN.16.2/KEP-FK/2023).

HUMAN AND ANIMAL RIGHTS

All procedures were performed according to the ethical standards of the institutional and/or research committee and the 1975 Declaration of Helsinki.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available by correspondencing with author [Y.Y].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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