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Original Research Article

Low sEng Level in Preeclampsia with *MFTHFR* Gene Polymorphism Suggesting a Protective Factor

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Abstract

Background: Preeclampsia is one of the most serious complications of pregnancy and the leading cause of maternal and fetal mortality. Various studies have shown that Glutathione Peroxidase (GPx) deficiency and increased Soluble endoglin (sEng) level are consistently associated with the incidence of preeclampsia. Several studies also show the role of *MTHFR* A1298C and C677T gene polymorphisms in preeclampsia.

Objective: This study investigated association between blood GPx, sEng levels, *MTHFR* A1298C and C677T gene polymorphisms in Preeclampsia.

Methods: This analytic observational case-control study was conducted on 70 cases of preeclampsia and 70 controls. Blood GPx and sEng levels were measured using Enzyme Linked Immunosorbent Assay (ELISA). *MTHFR* A1298C and C677T gene polymorphism was genotyped using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). The data obtained were analyzed using the Mann-Whitney U test, chi-square test, and independent T-test.

Results: There were no significant differences in GPx levels or MTHFR A1298C/C677T genotype distribution between groups. sEng levels were significantly higher in the preeclampsia group than controls (p=0.001). ROC analysis identified a cut-off of 7.75 ng/mL. Among preeclampsia patients, those with the MTHFR 1298AC/CC genotypes had lower sEng levels than wildtype (p=0.027), suggesting a potential protective effect. No association was found for C677T.

Conclusion: We found no significant difference in GPx level, *MTHFR* A1298C and C677T gene polymorphism between preeclampsia and control group. Soluble endoglin (sEng) level in the preeclampsia group (mean: 11.0±5.22) were significantly different (p=0.001) compared to the control group (mean: 8.1±5.31). Increased level of sEng is associated with incidence of preeclampsia. A key finding in this study is the significantly lower sEng levels observed in preeclampsia patients carrying the *MTHFR* 1298AC and 1298CC alleles compared to the control group (p=0.027). This indicates a protective factor where in preeclampsia with *MTHFR* gene alleles 1298AC and 1298CC sEng levels are lower compared to wildtype.

Keywords: *Glutathione; Peroxidase; MFTHR gene polymorphism; Preeclampsia; Soluble endoglin.*
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INTRODUCTION

Preeclampsia is a pregnancy-specific complication characterized primarily by new-onset high blood pressure (hypertension) and often the presence of high levels of protein in the urine (proteinuria), typically occurring after 20 weeks of gestation. Preeclampsia is one of the most serious complications of pregnancy and the leading cause of maternal and fetal mortality worldwide, with an incidence of 2-8% of all pregnancies.[1]

Recent studies have linked preeclampsia incidence to biochemical abnormalities, including elevated

oxidative stress, increased lipid peroxidation, and decreased levels of antioxidant chemicals.[2] Various studies have shown that GPx deficiency are consistently associated with the incidence of preeclampsia.[3] Decreased antioxidant levels will also cause an increase in the levels of antiangiogenic substances, one of the antiangiogenic substances involved is sEng. Increased sEng levels result in endothelial dysfunction and failure of placental angiogenesis. Increased sEng also impairs vascular vasodilation, causing more damage to blood vessels, including those in the placenta.[4,5]

Previous studies also show the role of genetic factors in the occurrence of preeclampsia. Meta-analysis findings show a significant association between *MTHFR* A1298C gene polymorphisms and preeclampsia incidence.[6] The *MTHFR* A1298C and C677T gene polymorphism affects glutathione peroxidase activity indirectly by reducing *MTHFR* enzyme function, which leads to elevated homocysteine and oxidative stress, and impairs folate-dependent glutathione synthesis. This cascade results in decreased GPx activity and antioxidant defense capacity.[7,8] *MTHFR* A1298C and C677T gene polymorphisms also affect triglyceride levels, lipid peroxidation, and oxidative stress, which may play a role in the pathogenesis of preeclampsia.[9,10]

Further research is needed to clarify direct effects on GPx activity and to measure sEng levels specifically in relation to these *MTHFR* polymorphisms in preeclampsia patients. In the present study, we investigated whether MTHFR A1298C and C677T polymorphisms are associated with GPx and sEng levels in patients diagnosed with preeclampsia. These findings provide important insights for future prevention strategies and the clinical management of preeclampsia patients.

MATERIALS AND METHODS

This was an analytic observational case control study with a total of 140 subjects comprising of 70 preeclampsia subjects and 70 subjects in control group with normotensive pregnancies. Sample size was calculated a priori using power analysis to detect meaningful differences between groups, considering a significance level of 0.05, power of 80%, and effect size estimated from previous literature. All subjects who met the inclusion and exclusion criteria gave their informed consent. They had their blood pressure tested and filled out a questionnaire with demographic and obstetric information. Then, professional health personnel collected venous blood for GPx, sEng level, *MTHFR* A1298C, and C677T gene polymorphism analysis. The analysis was carried out at the Medical Faculty Universitas Diponegoro central laboratory in Indonesia. This research has received approval from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Universitas Diponegoro Semarang (No: 155/EC/KEPK/FK-UNDIP/V/2021).

GPx and sEng level Measurement

Venous blood samples were collected from all patients and controls. Blood was collected into plain tubes and allowed to coagulate in a 37°C water bath, after which blood samples were retrieved by centrifugation at 3000 rpm for 10 minutes, and serum was separated and stored at -20°C until analysis. According to the manufacturer's instructions, the serum GPx and sEng levels were detected using Enzyme Linked Immunosorbent Assay (ELISA) kit.

Genotyping

Venous blood samples from patients and controls were obtained in EDTA tubes. The salting-out method was used to extract genomic DNA from peripheral blood leukocytes. The subjects' genotypes of MTHFR A1298C and C677T gene polymorphisms were determined using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique.

MTHFR A1298C gene polymorphism examination

Primers pairs used for this examination were forward primer 5'-CAAGGAGGAGCTGCTGAAGA-3' and reverse primer 5'-CCACTCCAGCATCACTCACT-3'. The PCR conditions were performed according standard protocol [11] A unique 172 bp amplicon of the *MTHFR* gene was obtained in all assays. The PCR products were digested with a *MboI*I restriction enzyme at 37°C overnight. The digested amplicons were analyzed using electrophoresis in 3% agarose gels. The A/A genotype generated 72 bp product (wild type), the A/C genotype resulted in two bands of 72 bp and 100 bp, and the C/C genotype yielded 100 bp.

MTHFR C677T gene polymorphism examination

The primer pairs used were forward primer 5'-TGAAGGAGAAGGTGTCTGCGGGA-3' and reverse primer 5'-AGGACGGTGCGGTGAGAGTG-3'. PCR was performed according standard protocol.[11] Then 198 bp amplicons of the *MTHFR* gene were obtained. PCR products were digested with *HinfI* restriction enzyme at 37°C overnight. The digested amplicons were analysed using electrophoresis in 3% agarose gel. The genotypes were identified at 198bp band for C/C wild type, 198 and 175bp bands for C/T heterozygote and; 23bp and 175bp bands for T/T homozygote respectively

Statistical analysis

The data were analyzed using the SPSS version 25 for Windows program. Continuous variables were shown as mean and standard deviation (SD), whereas categorical variables were shown as frequency and proportion. The normality of the data distribution was determined using the Shapiro-Wilk test. Since the data were normally distributed, an independent samples T-test was used to compare the two groups. As the data were not normally distributed, a nonparametric Mann-Whitney U test was performed to compare the two groups. Categorical data from the cases and control groups were analyzed using Chi square test.

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RESULTS

Table 1. The genotype distribution of *MTHFR* A1298C and C677T in the case and control groups

Genotype	Case Group n (%)	Control Group n (%)
MTHFR A1298C - AA	39 (55.71%)	41 (58.57%)
MTHFR A1298C - Polymorphism (AC, CC)	31 (44.29%)	29 (41.43%)
MTHFR C677T - CC	43 (61.43%)	50 (71.43%)
MTHFR C677T - Polymorphism (CT, TT)	27 (38.57%)	20 (28.57%)

Table 2. Statistical analysis of GPx, sEng, and *MTHFR* Gene Polymorphisms in Case and Control Groups

No	Variable	Case (n=70)	Control (n=70)	*p*
1	Glutathione peroxidase (GPx) - Mean ± SD - Median (min - max)	 87.5±47.55 76.45(46.7-309.6)	 82.2±30.7 78.45(8.5-190.6)	0.782
2	Soluble endoglin (sEng) - Mean ± SD - Median (min - max)	 11.0 ± 5.22 10.70 (2.5-23.9)	 8.1± 5.31 7 (1.3-25)	0.001
3	*MTHFR* C677T Gene - Polimorfisme (CT,TT) - *Wildtype* (CC)	 27 (38.57%) 43 (61.43%)	 20 (28.57%) 50 (71.43%)	0.283
4	*MTHFR* A1298C Gene - Polimorfisme (AC,CC) - *Wildtype* (AA)	 31 (44.29%) 39 (55.71%)	 29 (41.43%) 41 (58.57%)	0.864

The age distribution of research subjects in the preeclampsia group had a mean of 31.67 ± 6.98 years, while in the control group, the mean age was 27.96 ± 6.03 years. The age variable showed a significant difference between the ages of the preeclampsia group (p=0.001) compared to the controls. Mean systolic blood pressure in preeclampsia group was 159.41 + 17.12 mmHg and diastolic 99.20 + 11.44 mmHg, while in the control group the mean systolic was 118.21 + 9.57 mmHg and diastolic 75.93 + 7.01 mmHg.

The genotype distribution of *MTHFR* A1298C and C677T in the case and control groups is presented in Table 1. Table 2 shows the results of the statistical test between the Preeclampsia group and the control group, the results obtained p>0.05 on the variables of GPx level, *MTHFR* A1298C and C677T gene polymorphism, which indicate that there is no significant difference between the Preeclampsia and control groups. Meanwhile, sEng levels in the preeclampsia group (mean: 11.0±5.22) were also significantly different (p=0.001) compared to the control (mean: 8.1±5.31).

The analysis results between the *MTHFR* A1298C gene polymorphism with GPx and sEng levels in preeclampsia can be seen in table 3. This study showed no significant differences in GPx level between preeclampsia patients with the *MTHFR* A1298C gene polymorphism and wild type. Soluble endoglin levels in the preeclampsia patients with the *MTHFR* A1298C gene polymorphism (mean:9.3±5.11) were also significantly different (p=0.013) compared to the wildtype (mean: 12.4±4.95). Table 4 shows the statistical test between the *MTHFR* C677T gene polymorphism with GPx and sEng levels in preeclampsia. The result showed no significant differences in GPx and sEng levels between preeclampsia patients with the *MTHFR* C677T gene polymorphism and wild type.

The result of the Receiver Operator Characteristics (ROC) test to determine the cut-off for sEng level in the blood as a predictor of preeclampsia showed an area under the curve (AUC) = 0.668, the cut-off for sEng level in the blood was 7.75 ng/ml, with a sensitivity = 70 and specificity=57.1 (see figure 1).

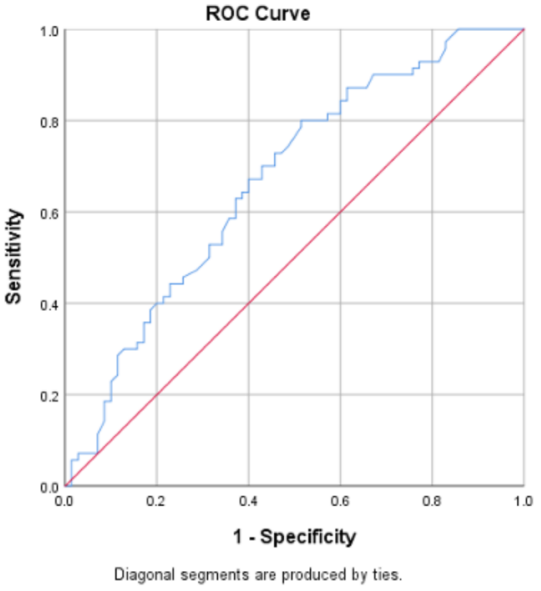

Figure 1. ROC curve for determining cut-off levels of sEng as predictor of preeclampsia

Table 5 shows a significant difference in the level of sEng in the preeclampsia group with the *MTHFR* A1298C gene polymorphism compared to normal (p=0.027; OR=0.266; RR=0.520). The likelihood of high sEng levels in preeclampsia with the *MTHFR* gene alleles 1298AC and 1298CC is 0.266 times compared to normal. This indicates a protective factor, whereby preeclampsia with the *MTHFR* gene alleles 1298AC and 1298CC has a 1.92 times likelihood of having lower sEng levels compared to wildtype.

consistent with previous study that showed no significant differences between GPx level in PE pregnant groups and the normal pregnancy group.[12] Antioxidant systems are not sufficiently active in preeclampsia, hence the buffer systems are unable to keep the equilibrium. Whether antioxidant levels in preeclamptic women increase, decrease or remain unchanged is still controversial.[13]

The results of the analysis showed that the *MTHFR* C677T gene polymorphism, GPx, and sEng levels did not significantly correlate. Meanwhile, there was a

Table 3. Association analysis between GPx and sEng levels with *MFTHFR* A1298C gene polymorphism in preeclampsia

No	Variable	***MTHFR* A1298C gene**		***p***
		Polymorphism (AC,CC) n=31	**Normal (AA) n=39**	
1	Glutathione peroxidase (GPx)			
	- Mean ± SD	89.8±55.85	85.7±40.43	0.887
	- Median (min - max)	76.60(46.7-309.6)	76.30(49.9-286.7)	
2	Soluble endoglin (sEng)			
	- Mean ± SD	9.3 ± 5.11	12.4± 4.95	0.013
	- Median (min - max)	8 (2.5-17.5)	12 (2.8-23.9)	

Table 4. Association analysis between GPx and sEng levels with *MTHFR* C677T genepolymorphism in preeclampsia

No	Variable	**MTHFR C677T gene**		***p***
		Polymorphism (CT,TT) n=27	**Normal (CC) n=43**	
1	Glutathione peroxidase (GPx)			
	- Mean ± SD	88.6±42.61	86.8±50,88	0.136
	- Median (min - max)	82.3(49.9-286.7)	74.3(46.7-309.6)	
2	Soluble endoglin (sEng)			
	- Mean ± SD	11.7 ± 5.47	10.6± 5.07	0.399
	- Median (min - max)	11 (2.8-23.8)	10.2 (2.5-23.9)	

Table 5. Chi-square test of sEng level with *MTHFR* A1298C gene polymorphism in preeclampsia

No	Variable	***MTHFR* A1298C Gene**		***p***
		Polymorphism (n=31)	**Normal (n=39)**	
1	Soluble endoglin (sEng)			
	- High (≥7.75)	17 (54.8%)	32 (82.1%)	0.027 (OR:0.266; RR:0.520)
	- Low (<7.75)	14 (45.2%)	7 (17.9%)	

DISCUSSION

In this study, there was a significant difference in sEng levels between the preeclampsia and control group. This is consistent with research by Leaños-Miranda which found that pregnant patients with normotension had considerably lower sEng levels than those with preeclampsia. The study also indicates that the rate of complications from preeclampsia rises with greater sEng levels. Because of its antiangiogenic properties, sEng levels can be used to predict damage to the blood vessel endothelium. Soluble endoglin has the potential to be a biomarker for diagnosing preeclampsia conditions in pregnant women and for predicting the prognosis of preeclampsia patients' adverse effects.[14]

Our study found no significant differences in GPx level between PE group and control. This result is

significant difference (p=0.013) between sEng levels (9.31±5.11) in preeclampsia patients with *MTHFR* A1298C gene polymorphism compared to preeclampsia patients with wildtype/normal *MTHFR* A1298C gene (12.39±4.95). The *MTHFR* A1298C gene polymorphism can be a risk factor for blood vessel damage to preeclampsia.[15,16] Damage to blood vessels can also be caused by increased levels of sEng where sEng has an antiangiogenic effect in the maternal circulation system by binding to TGF-b1. As a result of this, the proangiogenic and vasodilator properties of TGF-b1 are inhibited. This causes blood vessels to become more likely to experience vasoconstriction and cannot repair cell damage that occurs in the endothelium.[14] This suggests that the condition of the *MTHFR* A1298C gene polymorphism which plays a role in the genetic susceptibility of blood vessel damage

can affect the increase in sEng levels in preeclampsia patients.

sEng contributes to preeclampsia by disrupting the balance between angiogenic and anti-angiogenic factors due to placental ischemia. Increased endoglin expression from hypoxia and oxidative stress raises sEng levels, leading to endothelial dysfunction in the maternal circulation.[4] Oxidative stress, also increases the expression of membrane endoglin in the placenta. Reduced endogenous antioxidants in placental trophoblast tissue in preeclampsia such as hemeoxygenase, superoxide dismutase and glutathione peroxidase, play a role in the increased expression of membrane endoglin and sEng.[17,18]

This study also found that pregnant women with high sEng levels (≥7.75 ng/mL) were 3.11 times more likely to experience preeclampsia than pregnant women with sEng levels less than 7.75 ng/mL. This result is in accordance with a case control study which showed that sEng as a diagnostic and prognostic marker for predicting the severity of preeclampsia.[19] A meta-analysis study showed that sEng levels were higher in preeclampsia than normotension.[4]

One new finding in this study is that the preeclampsia group with *MTHFR* gene alleles 1298AC and 1298CC had significantly lower levels of soluble endoglin (sEng) than the normal group (p=0.027). This indicates a protective factor whereby in preeclampsia with *MTHFR* gene alleles 1298AC and 1298CC sEng levels are lower compared to wildtype. Low sEng levels reduce the risk of preeclampsia. This is in accordance with a case control study in Punjab Pakistan with a sample of 40 preeclampsia cases and 40 control groups which showed that the *MTHFR* A1298C gene polymorphism reduced the risk of preeclampsia.[15] A case control study (2019) conducted in Pakistan with a sample size of 125 preeclampsia groups and 125 control groups also showed that the A1298C polymorphism was a protective factor for preeclampsia.[20]

This study investigated only two MTHFR gene polymorphisms, additional research is necessary to explore the association of other gene polymorphisms, potentially within other folate or angiogenesis-related genes and the risk of preeclampsia. The sample size in this study was limited to a single center. Future studies with larger, multi-center cohorts are recommended to confirm and strengthen the validity of these findings.

CONCLUSION

Increased level of sEng is associated with incidence of preeclampsia. Pregnant women with high sEng levels (≥7.75 ng/mL) were 3.11 times more likely to experience preeclampsia than pregnant women with sEng levels less than 7.75 ng/mL. Preeclampsia group with *MTHFR* gene alleles 1298AC and 1298CC had significantly lower levels of soluble endoglin (sEng) than the normal group. This finding demonstrates an association that may indicate a protective effect, as sEng levels are lower in preeclampsia with the *MTHFR* 1298AC and 1298CC alleles than in the wildtype. However, there is no association in GPx level, *MTHFR* A1298C and C677T gene polymorphism with incidence of preeclampsia. The findings of this study provide a foundation for future research into the pathophysiology of preeclampsia and guides the development of more effective prevention and treatment strategies.

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