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Journal of Fertilization: In vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology

Research Article

Serum Asymmetric Dimethylarginine (ADMA) and Nitric Oxide (NO): Their Pathophysiological Role in Patients with Preeclampsia and HELLP Syndrome

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ABSTRACT

Objective: This study aims to investigate the role of serum asymmetric dimethylarginine and nitric oxide levels in the pathogenesis and severity of hemolysis, elevated liver enzymes, and low platelets syndrome, Eclampsia, and Pre-eclampsia.

Methods and methods: A total of 90 patients including hemolysis, elevated liver enzymes, and low platelets syndrome (n=30), Eclampsia (n=30), and Pre-eclampsia (n=30) were included in the study. Pregnancy was calculated according to the last menstrual period and ultrasonographic fetal biometric measurements, and only patients with a 32-week and above pregnancy were included. Similarly, 30 healthy pregnant women in the same age and gestational week who were admitted for pregnancy control were included in the study. Serum asymmetric dimethylarginine, Arginine and nitric oxide levels were measured for all four groups.

Results: There was no statistically significant difference in the age, gravida, parity, gestational week, hemoglobin, fibrinogen, international normalized ratio, and Arginine among the hemolysis, elevated liver enzymes, and low platelets, Eclampsia, Pre-eclampsia and control groups ($p>0.05$). In the hemolysis, elevated liver enzymes, and low platelets group, Eclampsia pregnant group, and late-onset Pre-eclampsia group, systolic blood pressure and diastolic blood pressure, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and asymmetric dimethylarginine levels significantly increased ($p<0.001$). On the other hand, platelet and nitric oxide levels decreased, compared to the control group ($p<0.001$).

Conclusions: Our study results suggest that asymmetric dimethylarginine and nitric oxide levels may be useful for predicting complications such as Eclampsia, Pre-eclampsia, and hemolysis, elevated liver enzymes, and low platelets syndrome and can be helpful in tailoring necessary treatment for each individual patient.

Keywords: PE, Eclampsia, HELLP syndrome, ADMA, NO, Arginine

Abbreviation: ADMA: Serum Asymmetric Dimethylarginine; NO: Nitric Oxide; HELLP: Hemolysis Elevated Liver enzymes and Low Platelets; PE: Pre-eclampsia; INR: International Normalized Ratio; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase

INTRODUCTION

PE is a syndrome which is usually seen after 20-weeks of pregnancy with oxidative stress that seems to be related to endothelial dysfunction in the maternal and feto-placental vascular system [1]. "Eclampsia" is the condition in which PE is accompanied by loss of consciousness and tonic-clonic contractions similar to epileptic seizures. PE is a multisystem disease and, if left untreated, leads to Eclampsia crisis [2].

As one of the leading causes of morbidity and mortality, it is a serious condition which can lead to hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome characterized by severe hepatic involvement and platelet aggregation due to endothelial injury

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Received: June 14, 2021, **Accepted:** July 13, 2021, **Published:** July 20, 2021

Citation: Akçal T, Şahin HG, Uçkan K (2021) Serum Asymmetric Dimethylarginine (ADMA) and Nitric Oxide (NO) : Their Pathophysiological Role in Patients with Preeclampsia and HELLP Syndrome. J Fertil *In vitro* IVF Worldw Reprod Med Genet Stem Cell Biol 9:4. doi: 10.35248/2375-4508.21.9.242.

and microangiopathic hemolytic anemia in untreated patients, in particular. Magann et al., reported an incidence of 0.11% for HELLP syndrome during a 12-year screening study [3]. This rate increases to 20% for severe PE cases. While 10.8 to 32.1 % of the Eclampsia cases develop HELLP syndrome, this rate is about 6 to 52% for Eclampsia risk in the presence of HELLP syndrome [4]. The maternal mortality rate varies between 0 and 4%, and perinatal mortality is mainly related to the gestational age at birth [4].

The HELLP syndrome may occur earlier in pregnancy than in PE [5]. About 80% of the cases are seen before the term, and 10% before the 27th week. Approximately one of three cases can be diagnosed for the first time in the postpartum period [4]. As distinct from the classical profile of PE, HELLP syndrome usually occurs in patients with multiparity and Caucasian women over age 25 with poor pregnancy outcomes [6]. Hypertensive pregnancy disorders complicate 4 to 12% of pregnancies with HELLP syndrome [4,6].

Several in vivo studies have shown that endothelial-derived nitric oxide (NO), which is known to protect vascular/endothelial functions, plays a role in the pathophysiology of the disease. Asymmetric dimethyl arginine (ADMA) is an endogenous inhibitor of NO synthase. Many physiological functions of NO alter, when ADMA is replaced by L-arginine in the NO synthase substrate binding site [7].

NO is synthesized from L-arginine amino acid by NO enzyme. This potent free-radical inhibits platelet aggregation and causes vasodilation in the vessels [8]. As a very small lipophilic molecule, NO causes vasodilation through decreased intracellular Ca++ levels. This decrease is due to the guanylyl cyclase activation and increased cyclic guanosine monophosphate (cGMP) concentrations. NO is a gaseous molecular and has a very short half-life (about 4 sec) [8]. Decreased NOS synthesis or half-life causes endovascular invasion of the cytotrophoblasts and impairment in vascular development [9]. NO also interacts with super-oxide anions, which are highly observed in the Pre-eclamptic placenta. Arginase II enzyme activity increases in PE, resulting in a degradation of the NO precursor Arginine and reduction of NO levels [9]. The decrease in the NO levels leads to a decrease in vasodilation and an increase in vasoconstriction. As a result, placental perfusion decreases, which disturbs trophoblast invasion and differentiation by releasing a number of factors. Hypoperfusion, particularly intermittent hypoperfusion, of the placenta causes to generation of free oxygen radicals. Generated radicals pass to maternal blood circulation, which lead to maternal endothelial injury. Increased maternal vascular resistance manifests as hypertension [9].

In the literature, studies related to ADMA have been attempted in recent past [10,11]. The relationship between ADMA and vascular diseases has drawn attention comparatively. Studies towards the marker value of ADMA for diagnosis, monitoring of prognosis and of treatment efficacy assessment of various vascular diseases has been conducted.PE and related complications are one of the major causes of maternal and perinatal morbidity and mortality in developed countries as well as in developing countries. However, the exact etiopathogenesis has not been clearly elucidated and a specific marker is still not currently available for the diagnosis. Currently, although there are studies on the association of ADMA, Arginine, NO levels with PE and other metabolic diseases, there is a limited number of data on HELLP syndrome and Eclampsia.

In the present study, we aimed to investigate the role of serum ADMA, Arginine and NO levels in the pathogenesis of HELLP, Eclampsia, and PE.

MATERIALS AND METHODS

This study was carried out in Yüzüncü Yıl University Training and Research Hospital, Gynecology and Obstetrics department, Van, Turkey. The study protocol was approved by the institutional Ethics Committee. All participants were informed about the study and their verbal and written consents were obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

This study is prospective and women with a gestational age of 24-36 weeks were included in the study.

Patients with gestational ages of 32-week or above were included in this study. Gestational age was calculated by the last menstrual period and ultrasonographic fetal biometric measurements. A total of 90 patients including HELLP syndrome (n=30), Eclampsia (n=30), and Pre-eclampsia (n=30) were included in the study. Thirty healthy pregnant women from the outpatient clinic during the same period were recruited, using random selection method, as the control group. Patients were diagnosed with HELLP in the presence of intravascular hemolysis (H), elevated liver enzymes (EL), and low platelet count (LP). PE diagnosis was made according to the American College of Obstetrics and Gynecology guidelines as ≥140 mmHg systolic and ≥90 mmHg diastolic blood pressure on ≥2 occasions at least 6 hours apart which occurred after the 20th week of gestation in a woman with previously normal blood pressure. Eclampsia cases included in the study were diagnosed in the presence of grand mal convulsions starting from the 20th week of gestation; however other causes of the coma and convulsions were excluded.

Exclusion criteria were as follows: maternal diabetes, renal diseases, fetal anomalies, cardiovascular diseases, intrauterine ex fetus, the use of medications, hematological or autoimmune diseases.

Data including age, gravida, gestational age, blood pressure, hemoglobin, platelet count, liver function test results, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), international normalized ratio (INR), serum ADMA during pregnancy, Arginine, and NO of the patient and control groups were recorded in the study forms.

Ultrasonographic evaluations of the eclamptic (n=30), pre-eclamptic (n=30), HELLP (n=30), and healthy control (n=30) groups were performed using General Electric Voluson 730 Expert 3D color Doppler Ultrasonography Device.

Serum samples obtained from the antecubital veins were centrifuged at 4,000 rpm for 10 min (Nuve NF 800R, Ankara, Turkey) and collected in the Eppendorf tubes and stored at -80 °C away from the light. After all samples were collected, serum ADMA, arginine, and NO were measured by the quantitative sandwich enzyme immunoassay. The kits used were; Serum NO levels: Nitrate/Nitrite Colorimetric Assay Kit: (Cayman Chemical, Michigan- USA, Catalog No: 780001); Assay Range 40-600 pg/mL, Human Arginine ELISA Kit: (Adipo Bioscience, CA-USA, Catalog no: SK00114-01) ; Assay Range 1-400 ng/mL, Human asymmetric dimethylarginine, ADMA ELISA Kit: (Adipo Bioscience, CA-USA, Catalog no: SK00122-01); Assay Range 200-60.000 ng/L. The kits were used according to the manufacturer's recommendations and measurements were performed using CA2000 model ELISA-reader (CIOM Medical Co. Ltd China). During the washing process, a CIOM/CA200 ELISA microplate washer was used.

Statistical Analysis

Chi-square test was used to compare categorical variables. Whether the distributions of continuous variables were normal was determined by the Kolmogorov-Smirnov test. One-way ANOVA test was used when parametric test conditions were met to compare the measured values. In addition, Kruskall wallis test was used when parametric test conditions were not met. Post hoc Tamhane test was used to determine the significant difference between the groups. The relationship between the variables was analyzed using Spearman correlation test. Statistical significance level was taken as $p<0.05$ in the calculations and SPSS (ver: 13) package program was used for the calculations.

RESULTS

Clinical and biochemical values of the groups are shown in Table 1.

There were no statistically significant differences in the mean age, gravida, parity, gestational age, hemoglobin, fibrinogen, INR, and Arginine among the HELLP, eclampsia, pre-eclampsia, and control groups ($p>0.05$). Compared to the control group, however, systolic and diastolic blood pressure, AST, ALT, LDH and ADMA levels significantly increased in the HELLP group, Eclamptic pregnant group and PE group ($p<0.05$). On the other hand, platelet and NO levels decreased in the HELLP group, Eclamptic pregnant group, and PE group compared to the control group ($p<0.05$) (Figure 1).

The mean serum ADMA levels were 44.432 ± 7600 ng/mL in the HELLP group and 44.597 ± 8700 ng/mL in the Eclamptic group. The mean serum ADMA levels were 24.310 ± 1210 ng/L in the PE group and 11528 ± 1150 ng/L in the healthy control group, indicating a statistically significant difference among the four groups ($p<0.001$). In addition, the ADMA levels were significantly higher in the HELLP group, compared to either healthy controls or Pre-eclampsia group ($p<0.001$). The ADMA levels were also significantly higher in the Eclamptic group, compared to either healthy controls or PE group ($p<0.001$). However, there were no significant differences in the ADMA levels between the HELLP group and Eclamptic group (Figure 2).

The mean serum levels of NO were 113.5 ± 6.8 mmol/L in the HELLP group and 97.3 ± 4.9 mmol/L in the eclamptic group. In the pre-eclamptic group, the mean serum levels of NO were 125.0 ± 13.08 mmol/L and 180.9 ± 13.4 mmol/L in the healthy pregnant group (Figure 3).

NO levels were lower in all patient groups, indicating a significant difference between the control group and all patient groups ($p<0.001$). However, there was no statistically significant difference between the Pre-eclampsia and HELLP groups and compared to eclampsia group. The mean serum levels of arginine were 73.1 ± 35 ng/mL in the HELLP group and 62.9 ± 16.4 ng/mL in the Eclamptic group. In the Pre-eclamptic group, the mean serum Arginine levels were 80.0 ± 53 ng/mL and 64.1 ± 28.6 ng/mL in the healthy controls. There were no significant differences in the mean serum arginine levels among the groups ($p>0.05$).

The correlation among serum NO, ADMA and Arginine levels and the clinical analyses of women with PE, Eclampsia and HELLP syndrome are shown in Table 2. In our study, positive correlation between ADMA, AST, ALT, LDH, SBP and DBP was observed, while negative correlation between ADMA, PLT and NO was observed. In our study, while negative correlation between ADMA, PLT and NO was observed, a positive correlation was observed between ADMA and AST, ALT, LDH, SBP, DBP. A positive correlation was observed between Nitric Oxide, PLT, Arginine,

Table 1: Clinical and biochemical values of the groups.

	Healthy Pregnant Group (n=30)	Pre-eclamptic Group (PE) (n=30)	HELLP Group (n=30)	Eclamptic Group (n=30)	P values
Gestational age (week)	33.8 ± 3.00	33.0 ± 3.22	33.0 ± 2.74	33.0 ± 3.23	0.467
Gravida	3.47 ± 1.79	2.90 ± 1.32	3.07 ± 2.05	2.8 ± 1.34	0.466
Age (years)	27.50 ± 7.03	28.2 ± 8.50	31.2 ± 4.97	28.6 ± 6.52	0.181
Parity	2.10 ± 1.42	1.53 ± 1.10	1.70 ± 1.81	1.60 ± 1.32	0.361
Hemoglobin (g/dL)	11.1 ± 1.42	11.4 ± 1.85	10.9 ± 1.45	11.3 ± 1.62	0.409
Platelet (10^3/uL)	328.83 ± 30.86	208.96 ± 66.68[f]	74.83 ± 12.0[a,b,c]	196.13 ± 74.57[e]	0.001
ADMA (ng/L)	11528 ± 1150	24.310 ± 1210[f]	44432 ± 7600[a,b]	44597 ± 8700[d,e]	0.001
NO (mmol/L)	180.9 ± 13.4	125.0 ± 13.08[f]	113.5 ± 6.8[a]	97.3 ± 4.9[e]	0.001
Arginine (ng/mL)	64.1 ± 28.6	80.0 ± 53	73.1 ± 35	62.9 ± 16.4	0.650
Systolic Blood Pressure (mmHg)	121.5 ± 8.21	165.6 ± 15.8[f]	175 ± 15.0[a,b]	182.5 ± 8.21[e,d]	0.001
Diastolic Blood Pressure (mmHg)	73.1 ± 7.93	97.5 ± 6.98[f]	105.3 ± 7.73[a,b]	110.8 ± 6.2[d,e]	0.001
AST (U/L)	15.3 ± 5.3	31.0 ± 30.0[f]	177.3 ± 130[a,b]	155.1 ± 72[d,e]	0.001
ALT (U/L)	10.9 ± 3.9	21.2 ± 27.3[f]	92.6 ± 47.5[a,b]	79.2 ± 52[d,e]	0.001
LDH (U/L)	359.8 ± 25	443 ± 121[f]	995 ± 62[a,b]	801 ± 75[d,e]	0.001
Fibrinogen (mg/dl)	212.8 ± 15.3	265.2 ± 23.9	341.3 ± 34.2	236.7 ± 34.2	0.350

ADMA: Serum Asymmetric Dimethylarginine; NO: Nitric Oxide; AST: Aspartate Aminotransferase; ALT:Alanine Aminotransferase; LDH: Lactate Dehydrogenase

Data was present: mean ± standard deviation (SD) or median (min-max)
a: HELLP group *vs.* Healthy group($p < 0.05$)
b: HELLP group *vs.* PE group ($p < 0.05$)
c: HELLP group *vs.* Eclampsia group ($p < 0.05$)
d: Eclampsia group *vs.*PE group ($p < 0.05$)
e: Eclampsia group *vs.* Healthy group ($p < 0.05$)
f: PE group *vs.* Healthy group ($p < 0.05$)

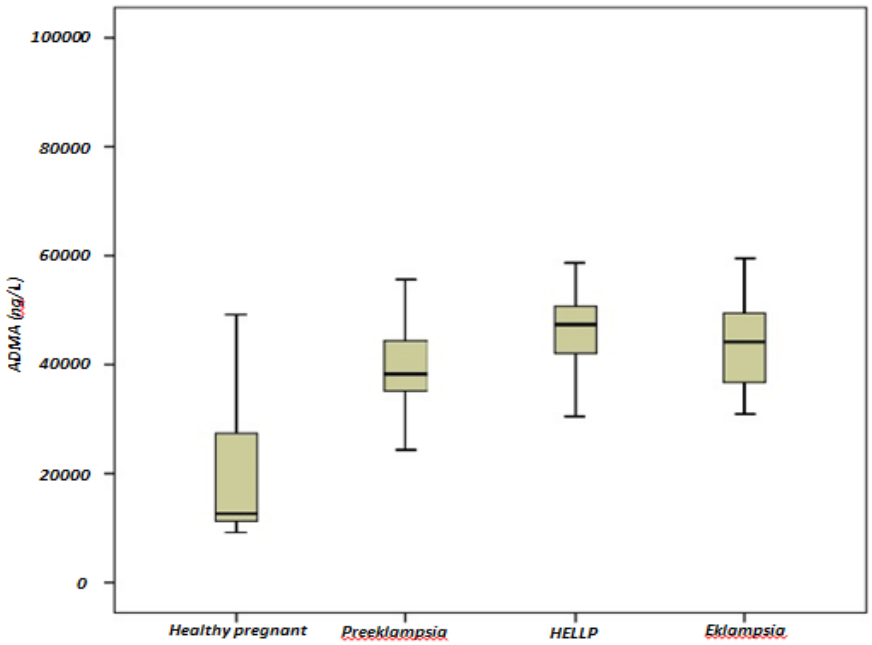

Figure 1: Maternal serum ADMA levels of each group (p<0.001).

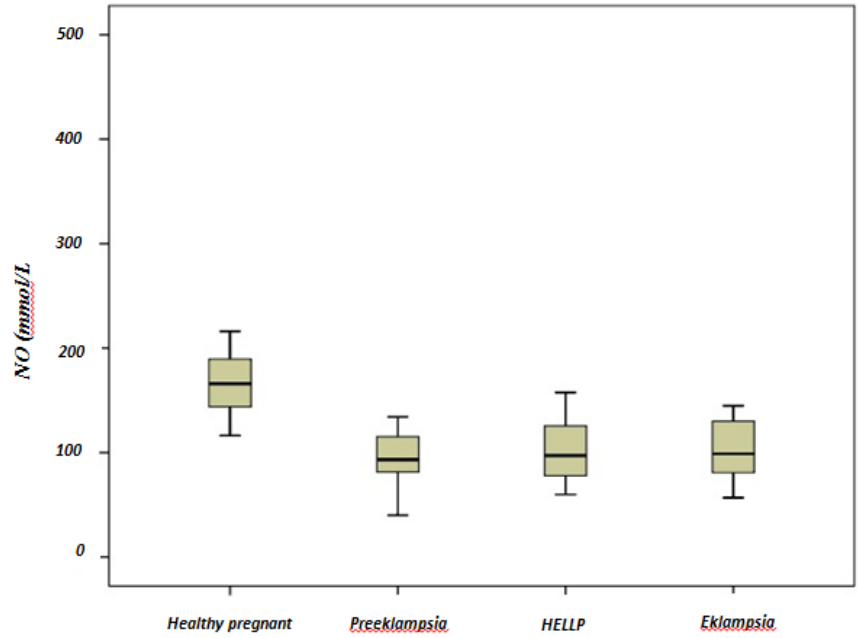

Figure 2: Maternal serum NO levels of each group (p<0.001).

Table 2: Correlation between NO, ADMA, Arginine and clinical parameters in women with PE, Eclampsia and HELLP syndrome.

	AST (U/L)r	ALT (U/L)r	PLT (10^3/uL)r	NO (mmol/L)r	ADMA (ng/L)r	ARJ (ng/ml)r	FİBRİNOGEN (mg/dl)r	LDH (U/L)r	SBP (mmHg)r	DBP (mmHg)
AST (U/L)	-	0.843**	-0.543**	-0.443**	0.685**	0.102	0.453**	0.333**	0.221	0.141
ALT (U/L)	0.843**	-	-0.385**	0.185*	0.552**	0.067	0.315**	0.246**	0.99	0.232
PLT (10^3/uL)	-0.543**	-0.385**	-	0.526**	-0.526**	0.003	-0.326**	-0.405*	0.423	0.111
NO (mmol/L)	-0.443**	0.185*	0.526**	-	-0.458**	0.282**	0.098	0.048	-0.332**	-0.245**
ADMA (ng/L)	0.685**	0.552**	-0.526**	-0.458**	-	0.131	0.118	0.455**	0.621**	0.424**
ARJ (ng/ml)	0.102	0.067	0.003	0.282**	0.131	-	0.007	0.116	0.32	0.12
FİBRİNOGEN (mg/dl)	0.453**	0.315**	-0.326**	0.098	0.518**	0.007	-	0.269**	0.223	0.34
SBP (mmHg)	0.221*	0.99	-0.123	-0.332**	0.621**	0.32	0.223	0.244	-	0.235*
DBP (mmHg)	0.141	0.232	0.111	-0.245**	0.424**	1.12	034	0.324	0.235*	-
LDH (U/L)	0.333**	0.246**	-0.405**	0.048	0.455**	0.116	0.269**	-	0.244	0.324

*p<0.05; **p<0.01

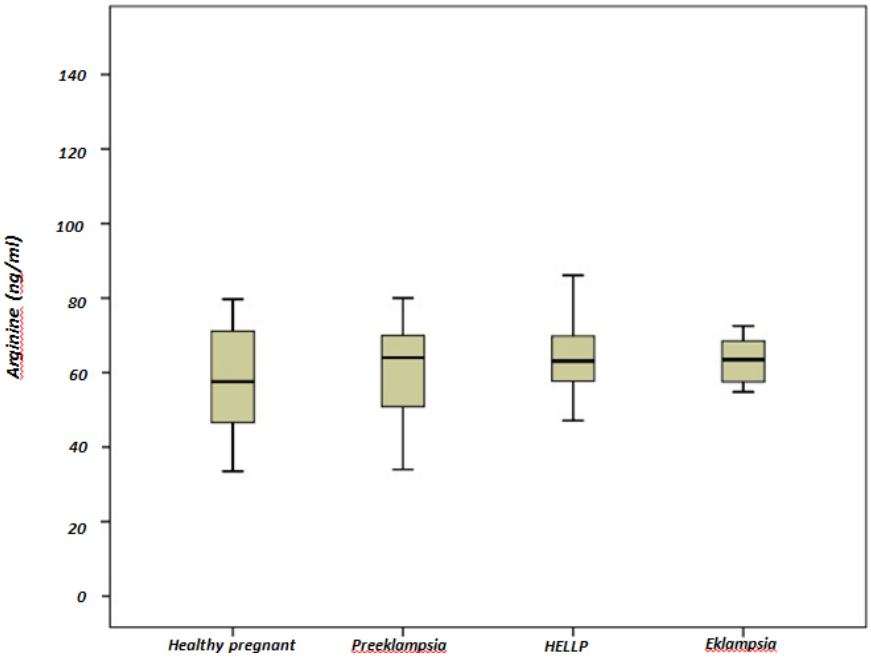

Figure 3: Maternal serum Arginine levels of each group (p>0.05).

and a negative correlation was observed between SBP, DBP, AST, and ADMA. There was a positive correlation between AST, ALT and ADMA with LDH, while there was a negative correlation with PLT.

DISCUSSION

Despite the studies to date, the etiology and pathogenesis of PE have not been fully understood, yet. The main problem is considered to be reduced placental blood flow due to abnormal cytotrophoblast invasion and widespread endothelial injury [12]. The endothelial cell dysfunction has been considered crucial to PE pathophysiology, since it may trigger hemostatic and inflammatory systems and results in abnormal placentation. The abnormal placentation which is considered as a starting point for the PE development leads to placental ischemia and hypoxia: it results in the release of factors responsible for the endothelial dysfunction [13].

Several studies using different inflammation markers would provide a better understanding of these pathologies, and may help to resolve disease-related discussions. One of these markers is NO. It plays multiple roles in the cardiovascular system. It is a potent vasoactive mediator that is released in response to stress and is important in maintaining endothelial homeostasis [14]. Apart from inducing vasodilatation to regulate vascular tone and tissue blood flow, endothelial NO also inhibits platelet aggregation, inhibits adhesion of leukocytes and monocytes to the endothelium and inhibits smooth muscle cell proliferation [15].

Mao et al., investigated ADMA, NO, and homocysteine levels in PE and normotensive control groups, and found a significant increase in the ADMA and homocysteine levels and a decrease in the NO level in the PE group, compared to the controls [16]. In another study, inducible NOS (iNOS) and endothelial NOS (eNOS) levels were evaluated in patients with HELLP syndrome (n=15) and control group (n=30), and a significant decrease in the iNOS and eNOS was observed in the HELLP group, compared to healthy normotensive pregnant [17]. This decline was attributed to the fact that both played a role in endothelial dysfunction in HELLP syndrome, leading to severe placental dysfunction. Tranquilli et al., conducted another study to investigate the possible relationship between the placental NOS expression and umbilical/uterine artery wave forms in pregnant women [18]. The authors reported a significant decrease in the iNOS levels in the patients with HELLP syndrome, and concluded that these abnormal iNOS levels could accompany endothelial dysfunction and placental insufficiency in HELLP syndrome. Currently, studies on NO and its metabolism, which are known to play a role in endothelial dysfunction, are still ongoing [19,20]. Azizi et al. stated that the deterioration in endothelial dysfunction increased with decreasing Enos factor and this situation progressed the course of the disease towards PE and Eclampsia [21].

In our study, as different from literature studies, NO-levels were compared between simultaneously PE patients, Eclampsia patients and HELLP group pregnant women with the highest mortality. In our study, NO values were significantly higher in the HELLP syndrome, PE, and Eclampsia pregnant groups, compared to healthy controls. There were no statistically significant differences between the Eclampsia, PE and the HELLP groups.

It is also known that low NO levels increase systemic vascular resistance and blood pressure [22]. In this study, a negative correlation was found between NO and SBP, DBP and ADMA. It was observed that NO level decreased further in the course of HELLP and Eclampsia compared to PE. On the contrary of this, the blood pressure values increased. Noris et al., have reported decreased levels of L-arginine in umbilical cord blood and villous tissues of pre-eclamptic patients and they suggested that, L-arginine reduction may alter oxidant species through NOS [23]. Pettersson et al., measured both plasma ADMA and plasma Arginine concentrations in PE and normotensive pregnants. They observed no difference between PE women and normotensive control group for Arginine levels, but the plasma Arginine/ADMA ratio was lower in PE group [24]. Similar to the literature, Arginine levels were not significantly different in all four groups. Arginase II enzyme activity, which plays roles in Arginine catabolism, also increases PE [23]. Since Arginine is the precursor of NO, increase in Arginase II enzyme activity causes a decrease in the NO levels. In our study, the enzyme activities that play a role in anabolism and catabolism have

not been examined. We believe that, one possible explanation of the indifferent Arginine levels between groups could be an increase in catabolic enzyme activity.

The activities of enzymes involved in the synthesis and degradation of ADMA have been found altered in various diseases. In some diseases, ADMA levels increase through increasing PRMT1 activity and ADMA synthesis, while the levels increase through decreasing ADMA catabolism in the others. The number of the studies examining the close relationship between the oxidant/antioxidant system and ADMA has been also gradually increasing. Currently, there is a number of evidence relating to the effects of oxidative stress on both anabolic and catabolic enzymatic activity of ADMA [25,26].

It is known that endothelial dysfunction is the main mechanism in the general inflammation response in Pre-eclampsia-Eclampsia, which involves coagulation system, complement system, platelet aggregation, leukocyte adhesion, oxidative stress. In patients with HELLP syndrome and Eclampsia, further endothelial injury and related oxidative stress may occur, and which can activate the coagulation system further. NOS inhibition of ADMA is likely to lead to hemodynamic changes before the clinical manifestations of Pre-eclampsia/Eclampsia and HELLP syndrome [27]. For a better understanding of whether this increase is due to an elevated anabolic activity or increase in construction or an attenuated in catabolic activity, enzymes levels in anabolism and catabolism should be measured. The association between ADMA and PE has been shown by Fickling et al., for the first time. They also observed higher concentrations of ADMA in pre-eclampsia patients, compared to healthy pregnant [28].

Laskowska et al., investigated serum ADMA and homocysteine levels in early onset (n=65) and late onset (n=53) PE patients, as well as 65 healthy pregnancies and found higher serum ADMA levels in PE patients [29]. In another study which evaluated uterine artery Doppler ultrasound and ADMA levels showed that increased ADMA concentrations could be observed before the clinical signs of PE [30]. In addition, these results indicated a correlation between abnormal uterine artery Doppler ultrasound and ADMA. It is known that abnormal uterine artery resistance and placental perfusion impairment may cause intrauterine growth retardation. Similarly, Laskowska et al. reported a relationship between high ADMA levels and intrauterine growth retardation in PE patients [31].

Later, Siroen et al., conducted a study in which they investigated ADMA levels in 27 non-pregnant healthy women, 15 normotensive pregnant women, 16 pre-eclamptic women, and 7 HELLP syndrome patients. The authors found no significant difference in the fetomaternal gradient of ADMA, placental DDAH activity and placental ADMA content between normotensive and Pre-eclamptic pregnancy groups. However, they reported a significant difference between the HELLP group and PE and control group [32]. However, the authors of the recently published meta-analysis have concluded that the concentrations of ADMA, the remarkable marker of the endothelial dysfunction, are significantly higher in PE, mainly early-onset PE, than in healthy pregnant patients. They are of the opinion that ADMA may play a major role in the PE development [33].

Consistent with the literature, we observed a statistically significant difference in the mean serum ADMA levels among the four groups ($p<0.001$). The ADMA levels were significantly higher in HELLP and Eclampsia groups, compared to either healthy controls or PE groups. However, there were no significant differences between the HELLP group and Eclamptic group.

The fact that ADMA values are significantly higher in patients with HELLP and Eclampsia than in other groups suggests that endothelial dysfunction is exacerbated in these patients. High levels of ADMA have been observed in people with cardiovascular diseases including atherosclerosis, hypertension and hypercholesterolemia and chronic renal failure [16]. In the correlation study, a positive correlation was found between increasing ADMA values and SBP, DBP, but a negative correlation was found between NO values. Since ADMA values are known to have a stimulating effect on cardiovascular diseases, it can also be stimulating about cardiovascular effects in patients with HELLP and Eclampsia too.

In conclusion, our study results showed a statistically significant increase in the ADMA levels in the patients with HELLP syndrome. Therefore, ADMA and NO levels may be useful for predicting complications such as Eclampsia, PE and HELLP syndrome and can be helpful in tailoring necessary treatment for each individual patient. However, the role of ADMA in the placental vascularization in tissue-level, and its possible role in abnormal uterine placentation and trophoblast invasion should be investigated further. In larger-scale studies using enzymes levels in anabolism and catabolism of the ADMA, the role of ADMA in HELLP syndrome and Eclampsia can be further clarified.

COMPLIANCE WITH ETHICAL REQUIREMENTS

Disclosure of potential conflicts of interests

The authors declare that they have no conflict of interest

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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