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

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ABSTRACT

Objective: This study aims to explore the significance of serum asymmetric dimethylarginine (ADMA) and nitric oxide (NO) levels in the pathogenesis and severity of hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP syndrome), Eclampsia, and Pre-eclampsia.

Methods: Ninety patients, comprising those with HELLP syndrome (n=30), Eclampsia (n=30), Pre-eclampsia (n=30), and 30 healthy pregnant women for comparison, were included. Pregnancy duration was determined by last menstrual period and ultrasonographic fetal biometric measurements, with inclusion criteria set at 32 weeks and above. Serum ADMA, Arginine, and NO levels were assessed for all groups.

Results: No significant differences were observed in age, gravida, parity, gestational week, hemoglobin,

fibrinogen, international normalized ratio, and Arginine levels among the groups ($p>0.05$). In the HELLP syndrome, Eclampsia, and late-onset Pre-eclampsia groups, systolic and diastolic blood pressure, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and ADMA levels were significantly elevated ($p<0.001$). Conversely, platelet and nitric oxide levels were diminished compared to the control group ($p<0.001$).

Conclusions: Serum ADMA and NO levels may serve as predictive markers for complications such as Eclampsia, Pre-eclampsia, and HELLP syndrome, aiding in personalized treatment approaches for affected patients.

Keywords: Pre-eclampsia (PE), Eclampsia, HELLP syndrome, ADMA, NO, Arginine.

ABBREVIATIONS

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

Pre-eclampsia (PE) is a syndrome characterized by oxidative stress and endothelial dysfunction in the maternal and fetoplacental vascular system, typically occurring after 20 weeks of pregnancy [1]. When PE is accompanied by loss of consciousness and seizures resembling epileptic seizures, it is termed "Eclampsia," representing a severe manifestation of the condition [2]. PE can progress to a multisystem disease, leading to the development of hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome if left untreated [2].

HELLP syndrome is a serious complication associated with significant morbidity and mortality, particularly if not diagnosed and managed promptly. It is characterized by severe hepatic involvement, platelet aggregation, and microangiopathic hemolytic anemia due to endothelial injury [3]. The incidence of HELLP syndrome is reported to be 0.11% during a 12-year screening study, with higher rates observed in severe cases of PE [3]. HELLP syndrome may occur earlier in pregnancy compared to PE, and it often affects multiparous women over the age of 25 [4].

Endothelial-derived nitric oxide (NO) plays a crucial role in vascular function regulation and has been implicated in the pathophysiology of PE and related conditions. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, modulates NO synthesis and bioavailability [7]. Reduced NO levels and increased ADMA concentrations have been observed in PE, leading to impaired vasodilation and endothelial dysfunction [8].

NO synthesis from L-arginine amino acid by NO enzyme regulates vascular tone, platelet aggregation, and endothelial function [8]. However, in PE, alterations in NO metabolism contribute to endothelial injury, vasoconstriction, and hypertension [9]. Studies have shown that decreased NO levels are associated with placental hypoperfusion and maternal endothelial injury, contributing to the pathogenesis

of PE [9].

While research on ADMA and NO in vascular diseases has increased, studies specifically investigating their role in PE, HELLP syndrome, and Eclampsia are limited [10,11]. Understanding the relationship between ADMA, Arginine, and NO levels and these pregnancy complications could provide valuable insights into their pathogenesis and aid in diagnosis and treatment.

In this study, we aimed to explore the potential involvement of serum ADMA, Arginine, and NO levels in the pathogenesis of HELLP syndrome, Eclampsia, and PE, shedding light on their diagnostic and therapeutic implications.

MATERIALS AND METHODS

Study Setting and Participants

This prospective study was conducted at Yüzüncü Y?l University Training and Research Hospital, Gynecology and Obstetrics Department, Van, Turkey. Approval for the study protocol was obtained from the institutional Ethics Committee, and all participants provided verbal and written consent by the principles of the Declaration of Helsinki. Women with a gestational age of 24-36 weeks were eligible for inclusion [12].

Study Design and Sample

A total of 90 pregnant women were enrolled in the study, comprising three groups: HELLP syndrome (n=30), Eclampsia (n=30), and Pre-eclampsia (n=30). Additionally, 30 healthy pregnant women from the outpatient clinic were randomly selected as the control group. Gestational age was determined by the last menstrual period and ultrasonographic fetal biometric measurements.

Diagnostic Criteria

HELLP syndrome was diagnosed based on the presence of intravascular hemolysis, elevated liver enzymes, and low platelet count. Pre-eclampsia was diagnosed according to the American College of Obstetrics and Gynecology guidelines, with systolic blood pressure ?140 mmHg and diastolic blood pressure ?90 mmHg on ?2 occasions after the 20th week of gestation [13-19]. Eclampsia cases were diagnosed based on the presence of grand mal convulsions after the 20th week of gestation, excluding other causes of coma and convulsions.

Exclusion Criteria

Exclusion criteria included maternal diabetes, renal diseases, fetal anomalies, cardiovascular diseases, intrauterine fetal demise, use of medications, and hematological or autoimmune diseases.

Data Collection

Data including demographic characteristics, gestational age, blood pressure, hemoglobin levels, platelet count, liver function test results (AST, ALT, LDH, INR), serum ADMA, Arginine, and NO levels were

recorded for all groups. Ultrasonographic evaluations were performed using a General Electric Voluson 730 Expert 3D color Doppler Ultrasonography Device.

Serum Sampling and Analysis

Serum samples were obtained from the antecubital veins, centrifuged, and stored at -80 °C. Serum ADMA, Arginine, and NO levels were measured using quantitative sandwich enzyme immunoassays. Kits used for measurements were Nitrate/Nitrite Colorimetric Assay Kit (Cayman Chemical, Michigan, USA), Human Arginine ELISA Kit (Adipo Bioscience, CA, USA), and Human asymmetric dimethylarginine (ADMA) ELISA Kit (Adipo Bioscience, CA, USA). Measurements were performed using a CA2000 model ELISA-reader (CIOM Medical Co. Ltd China).

Statistical Analysis

Categorical variables were compared using the chi-square test, and the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Parametric and non-parametric tests (one-way ANOVA, Kruskall wallis test) were used to compare measured values. Post hoc Tamhane test was applied to determine significant differences between groups. The relationship between variables was analyzed using Spearman correlation test. Statistical significance was set at $p<0.05$ using SPSS (ver: 13).

RESULTS

The clinical and biochemical characteristics of the study groups are summarized. There were no statistically significant differences observed in the mean age, gravida, parity, gestational age, hemoglobin, fibrinogen, international normalized ratio (INR), and Arginine levels among the HELLP, Eclampsia, Pre-eclampsia, and control groups ($p>0.05$).

However, compared to the control group, significant increases were noted in systolic and diastolic blood pressure, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and asymmetric dimethylarginine (ADMA) levels in the HELLP group, Eclampsia group, and Pre-eclampsia group ($p<0.05$).

Conversely, platelet and nitric oxide (NO) levels were found to be decreased in the HELLP group, Eclampsia group, and Pre-eclampsia group compared to the control group ($p<0.05$) (Figure 1).

The mean serum asymmetric dimethylarginine (ADMA) levels were 44.432 ± 7600 ng/mL in the HELLP group and 44.597 ± 8700 ng/mL in the Eclamptic group. In comparison, the mean serum ADMA levels were 24.310 ± 1210 ng/L in the Pre-eclampsia (PE) group and 11528 ± 1150 ng/L in the healthy control group, indicating a statistically significant difference among the four groups ($p<0.001$).

Furthermore, the ADMA levels were notably higher in the HELLP group compared to either healthy controls or the Pre-eclampsia group ($p<0.001$). Similarly, the ADMA levels were significantly higher in the Eclamptic group compared to either healthy controls or the PE group ($p<0.001$). However, no significant differences in ADMA levels were observed between the HELLP group and the Eclamptic group (Figure 2). The mean serum levels of nitric oxide (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, whereas in the healthy pregnant group, they were 180.9 ± 13.4 mmol/L (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 compared to the eclampsia group [20-25].

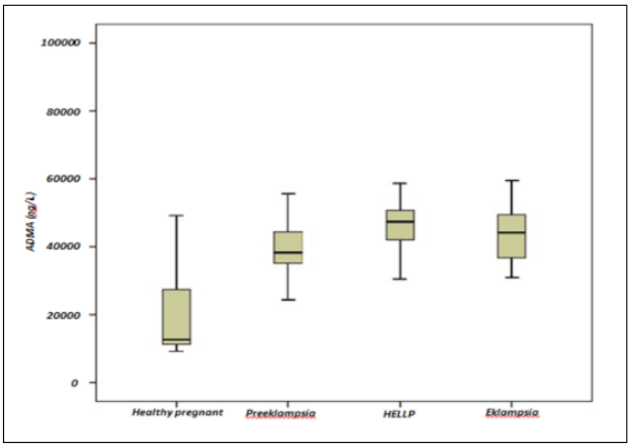

Figure 1: Maternal serum ADMA levels of each group ($p<0.001$).

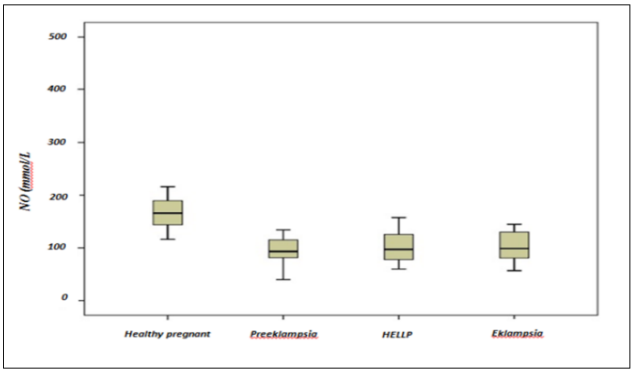

Figure 2: Maternal serum NO levels of each group ($p<0.001$).

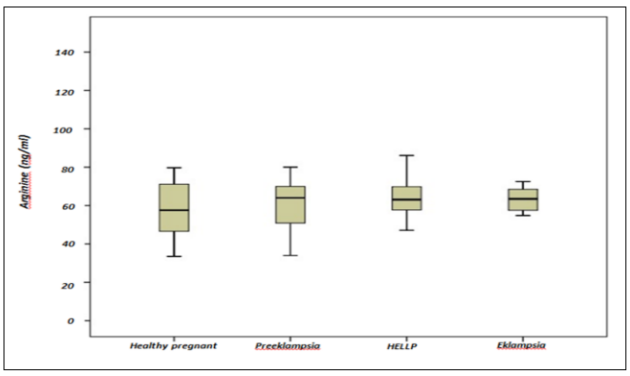

Figure 3: Maternal serum Arginine levels of each group ($p>0.05$).

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 in the healthy controls, they were 64.1 ± 28.6 ng/mL. 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. In our study, a positive correlation was observed between ADMA, AST, ALT, LDH, SBP, and DBP, while a negative correlation was observed between ADMA, PLT, and NO. Additionally, a positive correlation was observed between Nitric Oxide, PLT, Arginine, and a negative correlation was observed between SBP, DBP, AST, and ADMA. Positive correlations were observed between AST, ALT, and ADMA with LDH, while negative correlations were observed with PLT.

DISCUSSIONS

Despite numerous studies, the etiology and pathogenesis of PE remain incompletely understood. Reduced placental blood flow due to abnormal cytotrophoblast invasion and widespread endothelial injury are considered key factors in PE pathophysiology. Endothelial dysfunction triggers hemostatic and inflammatory systems, leading to abnormal placentation and subsequent placental ischemia and hypoxia, which release factors responsible for endothelial dysfunction.

Nitric oxide (NO) is a crucial mediator in the cardiovascular system, regulating vascular tone and tissue blood flow, inhibiting platelet aggregation, and modulating leukocyte adhesion. Endothelial dysfunction in PE leads to reduce NO levels, contributing to increased systemic vascular resistance and blood pressure.

Our study compared NO levels in PE, Eclampsia, and HELLP syndrome patients, highlighting significantly lower NO levels in all patient groups compared to healthy controls. However, there were no significant differences between the patient groups themselves [26-33]. Additionally, no significant differences were observed in serum arginine levels among the groups.

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, has been implicated in endothelial dysfunction. Our study found significantly higher ADMA levels in HELLP syndrome and Eclampsia patients compared to healthy controls and PE patients. However, there were no significant differences between the HELLP and Eclampsia groups. Positive correlations were observed between ADMA levels and blood pressure parameters, while negative correlations were observed between ADMA and NO levels.

The increase in ADMA levels in HELLP syndrome and Eclampsia suggests exacerbated endothelial dysfunction in these patients. Higher ADMA levels have been associated with cardiovascular diseases, indicating potential cardiovascular effects in patients with HELLP syndrome and Eclampsia.

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 help tailor necessary treatment for each 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 enzyme levels in anabolism and catabolism of the ADMA, the role of ADMA in HELLP syndrome and Eclampsia can be further clarified.

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