Correlation between asymmetric dimethylarginine maternal plasma levels and preeclampsia

A. Savvidis, A. Daniilidis, C. Giannoulis, T. Tantanasis, K. Koiou, V. Zournatzi, J. Tzafettas

2nd Department of Obstetrics and Gynecology, Hippokratio General Hospital, Aristotle University of Thessaloniki (Greece)

Summary

Objective: To aim of our study is to support the correlation between blood pressure and asymmetric dimethyl argine (ADMA) concentrations as a possible marker for early diagnosis of the preeclampsia syndrome. *Study design:* We attempted to calculate in 38 pregnant women with preeclampsia (group A) plasma levels of the main inhibitor to nitric oxide synthase (NOS), which is ADMA, and to compare our findings with the levels of ADMA in 36 non preeclamptic pregnant women (group C) and also with the levels in 29 pregnant women who had a history of preeclampsia in previous pregnancies (group B). Maternal venous EDTA plasma samples of 5 ml were collected and analyzed to measure the ADMA concentrations in each subject. Statistical analysis was performed using the Graph Pad Instat Mann-Whitney test, unpaired, non parametric test, two-tail *p* values. *Results:* There was no statistical difference between the three groups regarding maternal and gestational age (24-32 weeks). There was a significant statistical difference between the three groups regarding ADMA levels. The two-tailed *p* value between group A and group C (normal group) was < 0.001, between group A and group B < 0.002 and between group B and group C < 0.002. *Conclusion:* In conclusion we have observed that ADMA probably fulfills many of the criteria to be characterized as a preeclamptic factor and an accurate cut-off point matched to each week of pregnancy should be determined.

Key words: ADMA; Preeclampsia; Pregnancy.

Introduction

Preeclampsia complicates about 3% to 7% of pregnancies worldwide and is considered to be one of the major causes for maternal and fetal demise [1]. Until now several hypotheses and theories about the pathophysiology and etiopathogenesis of preeclampsia have been suggested, such as uteroplacental dysfunction, improper placentation, endothelial dysfunction-oxidative stress and immunologic reactions [2]. The endothelial dysfunction caused by the inhibition of nitric oxide synthase (NOS) seems to play a key role to the development of preeclampsia [3]. It is well known that nitric oxide, which is produced by endothelial cells, is a potent vasodilator which regulates the vascular tone and tissue blood flow thus affecting systemic hemodynamics during pregnancy [4] and it is believed to be closely related to the etiopathogenesis of preeclampsia [5]. In this study we tried to calculate in pregnant women with preeclampsia, the plasma levels of the main inhibitor to NOS, which is the asymmetric dimethyl argine (ADMA), and to compare our findings with the levels of ADMA in non preeclamptic pregnant women and also with the levels in pregnant women who had a history of preeclampsia in previous pregnancies. The aim of the study was to confirm the correlation between blood pressure and ADMA concentrations as a possible marker for early diagnosis of preeclampsia.

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Material and Methods

One hundred and three pregnant women participated in the study. All women were recruited at the time of their admission for prenatal care to the 2nd University Obstetric Clinic of Hippokratio General Hospital of Thessaloniki. The study was approved by the ethical committee of our institution and all participants signed a written informed consent.

The subjects were divided in three groups and were matched for maternal age, ethnic group, and gestational age. All women had a body mass index (BMI) < 25 kg/m^2, were between 24 to 32 weeks of gestation (mean 27 weeks) and were all native North Greek and non smokers. The mean age was 26.6 years old. Group A consisted of 38 women who were diagnosed with preclampsia in their current pregnancy. Group B consisted of 29 women who had no signs of preeclampsia in their current pregnancy but had a positive history of preeclampsia in a previous pregnancy. Group C consisted of 36 primigravida women who had no evidence of preeclampsia in their current pregnancy. The criteria used to include women in group A or B regarding preeclampsia diagnosis were those set by the Royal College of Obstetricians and Gynaecologists [6]. Maternal venous EDTA plasma samples of 5 ml were collected and analyzed with the ADMA enzyme immunoassay test kit (DLD Diagnostica GmbH, Hamburg, Germany) to determine the ADMA concentrations.

Results

There was no statistical difference between the three groups regarding maternal and gestational age. The mean value for ADMA blood concentrations in study group A was 1.374 μmol/l and SD (standard deviation 0.177). The mean values for groups B and C were 1.10 and 0.989 and SD was 0.261 and 0.263, concordantly. The results of our study are summarized in Table 1 and Figure 1. Statistical analysis was performed using the

Table 1. — *Summary of data.*

Group	Patients (No.)	Mean/Median (μmol/l)	SD (μmol/l)	SE of Mean (μmol/l)	Min-Max (μmol/l)	95% CI
A	28	1.374/1.38	0.177	0.33	1.04-1.74	1.305-1.443
B	18	1.101/1.20	0.261	0.61	0.34-1.40	0.970-1.231
C	25	0.989/1.01	0.263	0.53	0.30-1.64	0.878-1.100

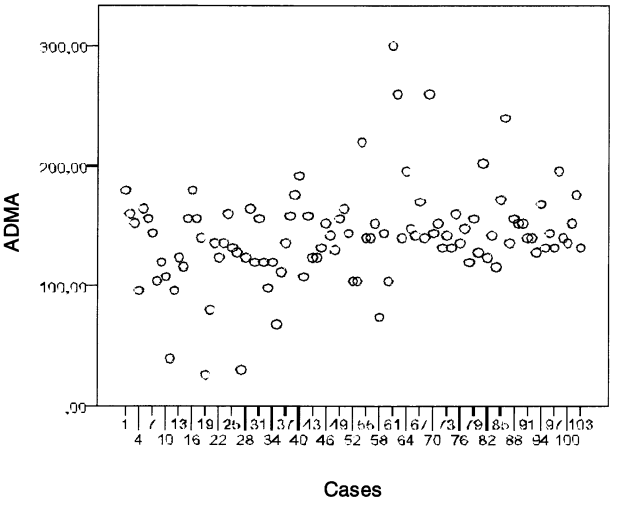

Figure 1. — Scatter plot of maternal mean plasma ADMA values in all three groups.

GraphPad InStat Mann-Whitney test, unpaired/non parametric test with two-tail p values. The two-tailed p value between group A (preeclampsia group) and group C (normal group) was statistically significant ($p < 0.001$). The two-tailed p value between group A and group B (history of preeclampsia) was $p < 0.002$, which was extremely significant as was the two-tailed p value between group B and group C ($p < 0.002$).

Discussion

Since the exact pathogenetic mechanism of preeclampsia is still poorly understood the development of a reliable predictive test is still under investigation. Preeclampsia is a unique human pregnancy multisystemic disorder, in which endothelial dysfunction and enhanced endothelial cell permeability and platelet aggregation are the commonest clinical manifestations [6]. It has already been demonstrated that inhibition or reduced production of nitric oxide plays a key role in mediating systemic hemodynamics during pregnancy and in the development of vasospasm and hypertension [7]. It is already known that ADMA concentrations in maternal plasma are raised significantly in preeclamptic women [8, 9] and this could be a reason for the reduced placental NOS production [10]. Even in mild preeclampsia ADMA levels are significantly elevated in comparison to normotensive pregnancies [11]. The origin of the elevated ADMA levels in preeclampsia cases is yet to be determined. There is much speculation about the possible causative mechanisms, like placental ischemia and reperfusion with oxidative stress [12]. During preeclampsia the increased oxidative stress could enhance the breakdown of methylated proteins leading to high levels of ADMA [13]. Angiogenesis is negatively affected by ADMA concentrations in pregnancy. Savvidou *et al.* demonstrated that although all women with preeclampsia had significantly increased ADMA levels in the peripheral circulation, not all women with increased ADMA levels developed preeclampsia [10]. In our study all women with preeclampsia had not significantly higher levels of ADMA in comparison with normotensive women with or without a history of previous preeclampsia ($p < 0.1$). The mean value for ADMA in our preclamptic group was 1.374 μmol/l, thus in Savvidou *et al's* study it was significantly higher (2.4 μmol/l) [10]. One limitation of our study was perhaps that we lacked Doppler data of the uterine arteries of our subjects thus not allowing a comparison of the two studies. We did not include any data about birth weight outcome in our study groups, since it is already well known that preeclampsia is accompanied with fetal intrauterine restriction. The finding that ADMA levels are still significantly elevated in women with previous preeclampsia even if they are normotensive in their current pregnancies is very interesting, but the exact mechanism as to why is not clear. Perhaps, during the manifestation of preeclampsia syndrome ADMA levels increase as a protective mechanism to the fetus, which increases maternal systemic blood pressure in order to enhance perfusion pressure and to overcome the inadequate placental supply [14]. Maybe in these women with a history of preeclampsia a less potent mechanism of increased ADMA production still remains for an undetermined duration of time. Unfortunately we did not perform a statistical analysis of the time interval between previous preeclampsia and current normotensive pregnancies, which is another limitation of our study.

In conclusion we observed that ADMA probably fulfills many of the criteria to be characterized as a preeclamptic factor and an accurate cut off level matched to each week of pregnancy should be determined. Indeed the proposed role of elevated ADMA levels in the pathophysiology of preeclampsia syndrome is still a subject of speculation and further investigations regarding the role of ADMA as a predictive value for early diagnosis of preeclampsia is required. Probably the combination of uterine artery Doppler studies and measurement of ADMA levels in maternal circulation used in a unified statistical model could be in the future a reliable test with high sensitivity and specificity, something like nuchal translucency and PAPP-A studies used for prenatal diagnosis.

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Address reprint requests to:
A. DANIILIDIS, M.D., Ph.D.
9 Smirnis, 56224, Evosmos
Thessaloniki (Greece)
e-mail: angedan@hotmail.com