Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Johan Frangky Selanno, Deviana Soraya Riu, Telly Tessy, Maisuri Tajuddin Chalid, Nugraha Utama Pelupessy & Eddy Hartono (2020): Maternal serum levels of asymmetric dimethylarginine in normal and preeclamptic pregnancies, Gynecological Endocrinology, DOI: 10.1080/09513590.2019.1707793

To link to this article: https://doi.org/10.1080/09513590.2019.1707793

Published online: 04 Mar 2020.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2019.1707793

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ORIGINAL ARTICLE

Maternal serum levels of asymmetric dimethylarginine in normal and preeclamptic pregnancies

Johan Frangky Selanno, Deviana Soraya Riu, Telly Tessy, Maisuri Tajuddin Chalid, Nugraha Utama Pelupessy and Eddy Hartono

Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

ABSTRACT

The study aims to investigate maternal serum levels of asymmetric dimethylarginine (ADMA) in preeclampsia. Serum samples were collected from 57 women with preeclamptic pregnancies and 30 women with normal pregnancies during the third trimester. ADMA levels were measured with the ELISA method. ADMA levels in preeclamptic pregnancies were significantly higher when compared with normal pregnancies (2.35 ± 3.20 nmol/l versus 0.35 ± 0.10 nmol/l; $p < .05$). ADMA levels show a significant positive correlation with systolic and diastolic pressure, urea, and creatinine but a negative correlation with proteinuria. ADMA levels have a significant strong correlation with PE. ADMA levels are significantly higher in preeclamptic pregnancy compared with normal pregnancy.

ARTICLE HISTORY
Received 28 June 2019
Revised 28 November 2019
Accepted 18 December 2019
Published online 4 March 2020

KEYWORDS
Asymmetric dimethylarginine (ADMA); preeclampsia; pregnancy

Introduction

Preeclampsia (PE) occurs in ≥20 weeks of gestational age with the onset of hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) and proteinuria (protein ≥300 mg for 24 h). PE causes maternal and fetal mortality, acute and long-term morbidity, preterm birth and intrauterine growth restriction (IUGR) [1]. PE increases the risk of eclampsia, which develops into HELLP syndrome [2,3].

Asymmetric dimethylarginine (ADMA) is a marker for endothelial dysfunction in renal disease/disorder, cardiovascular system, hypertension, and ischemic stroke [4–6]. ADMA act as an endogenous enzyme inhibitor of NO. ADMA that was synthesized from post-translational modification of arginine residues present in specific proteins occurred in the most cell nucleus. The arginine residue methylation process is catalyzed by arginine N-methyltransferase (PRMT) protein type 1 and free methylarginine that were released from proteolysis [7]. ADMA plasma levels in normal pregnancy decrease but increase with age gestation [8] whereas ADMA levels in preeclampsia show conflicting results [9–11]. Our study aimed to investigate the maternal plasma levels of asymmetric dimethylarginine (ADMA) levels between normal pregnancy and preeclamptic pregnancy.

Materials and methods

Subjects

A cross-sectional study was conducted on 57 pregnant women with preeclampsia in the third-semester, live singleton, exact last menstrual period, and without a history of hypertension, renal, cardiac, or vascular disorders. Preeclamptic patients were admitted to the Wahidin Sudirohusodo General Hospital, and affiliated hospitals of the Department of Obstetrics and Gynecology Medicine Faculty of Hasanuddin University in Makassar because of the symptoms of the disease but without signs of labor from August 2016 until February 2017.

Thirty normotensive pregnant women with singleton uncomplicated third-trimester pregnancy, without a history of hypertension, renal, cardiac, or vascular disorders and normal laboratory test were included in the control group. Patients with multiple gestations were excluded from this study. This study approval was given by the Medical Research Ethics Committee of Hasanuddin University/Dr Wahidin Sudirohusodo General Hospital.

Clinical and laboratory assessment

Preeclampsia was confirmed by an increased blood pressure o>140 mmHg systolic and >90 mmHg diastolic in women who were normotensive before 20 weeks of gestation accompanied by proteinuria, defined as the urinary excretion of >0.3 g protein in a 24-h specimen. The blood pressure from all the participants was measured at rest. The body mass index (BMI) was calculated as kg/m^2.

Five milliliters of blood was collected by venipuncture and placed in the sterile tubes immediately after the diagnosis and before administering any medication. The blood was allowed to clot and centrifuged at 1500×*g*. The serum samples were stored at −20 °C until assayed. ADMA levels were measured using the Human Asymmetrical dimethylarginine (ADMA) enzyme-linked immunosorbent assay (ELISA) kit according to the instructions from the manufacturer (Korain Biotech Co., Ltd., Shanghai, China).

Statistical analyses

Data were presented as mean ± SD. Sample characteristics and difference ADMA levels between study groups were tested using a *t* test and the Mann–Whitney test. To determine the

CONTACT Johan Frangky Selanno johanfrangkys@gmail.com Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar 90245, Indonesia

correlation between the clinical parameters of pregnant women and ADMA levels, the Spearman correlation test was used.

Results

Age, parity, and gestational age were not significantly different between the study groups (Table 1). ADMA levels in preeclamptic pregnancies were higher compared with normal (2.35 ± 3.20 nmol/l versus 0.35 ± 0.10 nmol/l). ADMA levels show significantly different between preeclamptic and normal pregnancies (Figure 1).

Further analysis with Spearman's correlation test between ADMA levels and clinical parameters (Table 2) shows a statistically significant positive correlation among systolic pressure ($r = 0.689$; $p < .01$), diastolic pressure ($r = 0.714$; $p < .01$), urea ($r = 0.493$; $p < .01$), and creatinine ($r = 0.306$; $p < .022$) but ADMA levels were not significant negative correlation with proteinuria ($r = 0.306$; $p < .022$). Our study found that ADMA levels have a significant strong correlation with PE ($r = 0.826$; $p < .01$).

Discussion

Our study found higher ADMA levels during the third trimester of pregnancy with preeclampsia compared with normal pregnancy. A meta-analysis by Yuan et al. shows that ADMA levels were increased before the onset of the disease in women with a history of preeclampsia [12]. Another study of preeclamptic pregnancies with the similar gestational age shows higher ADMA levels in preeclampsia compared with normal pregnancies [13,14]. Rizos et al.'s study in the second-trimester pregnancy shows a significant increase in ADMA levels which developed into preeclampsia [15]. However, a decrease in blood pressure early in normotensive pregnancy followed a significant decrease in plasma ADMA levels did not occur in preeclampsia [16]. The present study might indicate that ADMA plays a role in blood pressure changes both in normal and preeclamptic pregnancies. However, our findings differed from Siroen et al.'s study which found no difference in ADMA levels between normal and preeclamptic pregnancies [17] and Sandrim's study also found no association between ADMA and nitrite in normal and preeclamptic pregnancies [18].

Discrepancies in ADMA levels might be due to ADMA level measurement performed on different pregnancy trimester and onset of preeclampsia. The first trimester of ADMA levels in preeclampsia in the study by Bian was similar to ADMA levels in our study, although the correlation is weak [19]. In the present study, ADMA levels during the third trimester of preeclamptic pregnancy were higher compared with ADMA levels in the Petterson study [13]. Nevertheless, both studies show higher levels of ADMA in preeclampsia compared with normal pregnancy during the similar trimester. The Ehsanipoor study at the similar gestational age with preeclampsia but smaller sample size (20 samples) than our study found that ADMA levels were significantly higher compared with normal pregnancies [20]. In contrast, a study by Maeda shows no difference in ADMA levels between the first and third trimesters [21]. ADMA levels show no difference between the early onset and the late onset of PE [9,21]. Increased ADMA levels because of the increasing trimester of pregnancy might be due to a physiological influence of the uterine muscle preparation for higher contractility. This contraction is required during labor processes that act antagonistically with NO as an inducer of uterine relaxation [22].

Our study also found that ADMA levels were correlated with blood pressure in term pregnancy with preeclampsia. Our study findings are consistent with the Holden study that ADMA levels increase with gestational age [16]. Other findings were found that ADMA levels had weak correlated with urea and creatinine levels and negatively correlated with proteinuria. The previous study by Arcos et al. shows that proteinuria is associated with endothelial dysfunction and inhibition of NO [23]. A study by Kaidah et al. further demonstrates proteinuria leads to ADMA accumulation through increased expression of PRMT proteins

Table 1. Patients characteristics.

Characteristics	Normal ($n = 30$)	Preeclampsia ($n = 57$)	p
Age (years)	28.77 ± 5.10	31.28 ± 5.89	.051*
Parity	1.40 ± 1.04	1.91 ± 1.21	.062**
Gestational age (weeks)	37.83 ± 0.65	37.89 ± 0.65	.672**

*t test; **Mann–Whitney test.

Table 2. Correlation between clinical parameters and ADMA levels in preeclamptic pregnancies.

ADMA levels	r	p
Systolic blood pressure (mmHg)	0.689	<.01
Diastolic blood pressure (mmHg)	0.714	<.01
Urea	0.493	<.01
Creatinine	0.306	.022
Proteinuria	−0.14	.114
Preeclampsia	0.826	<.01

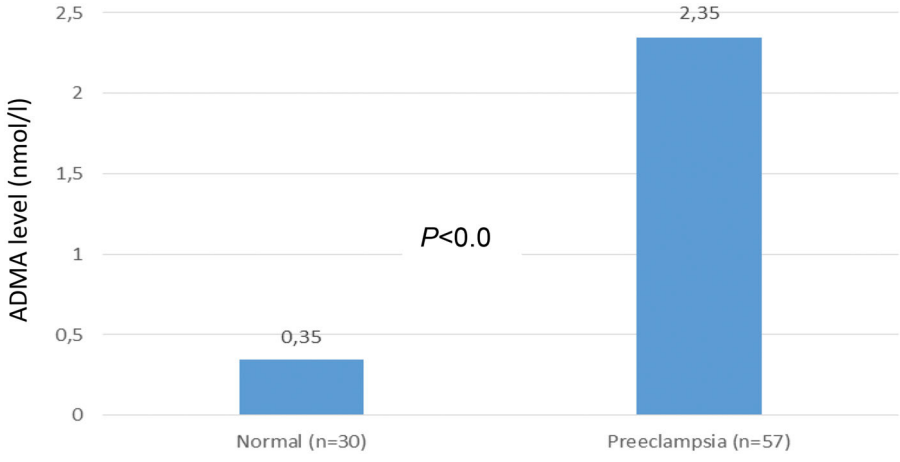

Figure 1. ADMA levels between normal and preeclamptic pregnancies.

which regulated ADMA synthesis [24]. A positive correlation between ADMA levels and proteinuria shows failure in chronic kidney patients [25]. Higher ADMA levels were also shown in hypertensive patients compared with non-hypertensive [26].

Proteinuria is not correlated with severe preeclampsia but when detected, proteinuria is associated with the severity of preeclampsia and pregnancy outcomes [27]. The correlation between elevated ADMA levels and preeclampsia might be affected by medical history, arginine metabolism, body mass index, nutritional intake, and comorbidities [10,28–30].

Conclusion

ADMA levels are significantly higher in preeclamptic pregnancy compared with normal pregnancy. Our findings may have the implication for pathogenesis and therapeutic approaches of preeclampsia.

Disclosure statement

The authors report no conflict of interest.

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