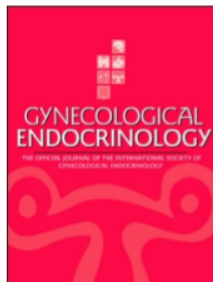


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## Maternal serum <sup>2</sup> levels of asymmetric dimethylarginine in normal and preeclamptic pregnancies

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## Maternal serum levels of asymmetric dimethylarginine in normal and preeclamptic pregnancies

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### 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 ( $2.35 \pm 3.20$  nmol/l versus  $0.35 \pm 0.10$  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

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### KEYWORDS

Asymmetric dimethylarginine (ADMA); preeclampsia; pregnancy

### Introduction

Preeclampsia (PE) occurs in  $\geq 20$  weeks of gestational age with the onset of hypertension (systolic  $\geq 140$  mmHg and/or diastolic  $\geq 90$  mmHg) and proteinuria (protein  $\geq 300$  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 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  $> 140$  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  $\text{kg/m}^2$ .

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  $1500 \times g$ . The serum samples were stored at  $-20^\circ\text{C}$  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  $\pm$  SD. Sample characteristics and difference ADMA levels between study groups were tested using a *t* test and the Mann–Whitney test. To determine the

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 ( $2.35 \pm 3.20$  nmol/l versus  $0.35 \pm 0.10$  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) was 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 [15]. 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

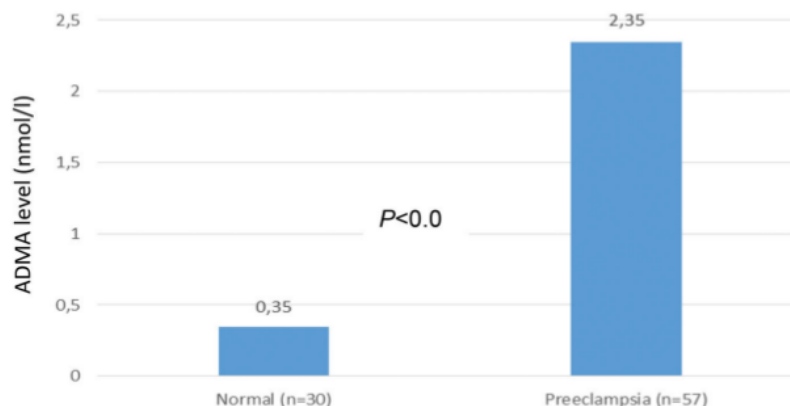


Figure 1. ADMA levels between normal and preeclamptic pregnancies.

which regulated ADMA synthesis [24]. A <sup>14</sup> positive correlation between ADMA levels and p<sup>29</sup>roteinuria 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

<sup>6</sup>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.

## <sup>26</sup>Disclosure statement

The authors report no conflict of interest.

## References

- [1] Lindheimer MD, Taler SJ, Cunningham FG. American Society of Hypertension. ASH position paper: hypertension in pregnancy. *J Clin Hypertens (Greenwich)*. 2009;11(4):214–225.
- [2] Dusse LM, Rios DR, Pinheiro MB, et al. Pre-eclampsia: relationship between coagulation, fibrinolysis and inflammation. *Clin Chim Acta*. 2011;412(1–2):17–21.
- [3] Brennan LJ, Morton JS, Davidge ST. Vascular dysfunction in preeclampsia. *Microcirculation*. 2014;21(1):4–14.
- [4] Franceschelli S, Ferrone A, Pesce M, et al. Biological functional relevance of asymmetric dimethylarginine (ADMA) in cardiovascular disease. *IJMS*. 2013;14(12):24412–24421.
- [5] Chen S, Li N, Deb-Chatterji M, et al. Asymmetric dimethylarginine as marker and mediator in ischemic stroke. *IJMS*. 2012;13(12):15983–16004.
- [6] Lyall F, Jablonka-Shariff A, Johnson RD, et al. Gene expression of nitric oxide synthase in cultured term placental trophoblast during in vitro differentiation. *Placenta*. 1998;19(4):253–260.
- [7] Cooke JP. Asymmetrical dimethylarginine: the Uber marker? *Circulation*. 2004;109(15):1813–1819.
- [8] Huang LT, Hsieh CS, Chang KA, et al. Roles of nitric oxide and asymmetric dimethylarginine in pregnancy and fetal programming. *IJMS*. 2012;13(12):14606–14622.
- [9] Power RW, Speer PD, Frank MP, et al. Elevated asymmetric dimethylarginine concentrations precede clinical preeclampsia but not pregnancies with small for gestational age infants. *Am J Obstet Gynecol*. 2008;198(1):112.e1–7.
- [10] Alpoim PN, Godoi LC, Freitas LG, et al. Assessment of L-arginine asymmetric 1 dimethyl (ADMA) in early-onset and late-onset (severe) preeclampsia. *Nitric Oxide*. 2013;33:81–82.
- [11] Lawskowska M, Lawskowska K, Terbosh M, et al. A comparison of maternal serum levels of endothelial nitric oxide synthase, asymmetric dimethylarginine, and homocysteine in normal and preeclamptic pregnancies. *Med Sci Monit*. 2013;19:430–437.
- [12] Yuan J, Wang X, Xie Y, et al. Circulating asymmetric dimethylarginine and the risk of preeclampsia: a meta-analysis based on 1338 participants. *Oncotarget*. 2017;8(27):43944–43952.
- [13] Pettersson A, Hedner T, Milsom I. Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in pre-eclampsia. *Acta Obstet Gynecol Scand*. 1998;77(8):808–813.
- [14] Mao D, Che J, Li K, et al. Association of homocysteine, asymmetric dimethylarginine, and nitric oxide with preeclampsia. *Arch Gynecol Obstet*. 2010;282(4):371–375.
- [15] Rizos D, Eleftheriades M, Batakis E, et al. Levels of asymmetric dimethylarginine throughout normal pregnancy and in pregnancies complicated with preeclampsia or had a small for gestational age baby. *J Matern Fetal Neonatal Med*. 2012;25(8):1311–1315.
- [16] Holden DP, Fickling SA, Whitley GS, et al. Plasma concentrations of asymmetric dimethylarginine, a natural inhibitor of nitric oxide synthase, in normal pregnancy and preeclampsia. *Am J Obstet Gynecol*. 1998;178(3):551–556.
- [17] Siroen MP, Teerlink T, Bolte AC, et al. No compensatory upregulation of placental dimethylarginine dimethylaminohydrolase activity in preeclampsia. *Gynecol Obstet Invest*. 2006;62(1):7–13.
- [18] Sandrim VC, Palei AC, Metzger IF, et al. Interethnic differences in ADMA concentrations and negative association with nitric oxide formation in preeclampsia. *Clin Chim Acta*. 2010;411(19–20):1457–1460.
- [19] Bian Z, Shixia C, Duan T. First-trimester maternal serum levels of sFLT1, PGF and ADMA predict preeclampsia. *PLoS One*. 2015;10(4):e0124684.
- [20] Ehsanipoor RM, Fortson W, Fitzmaurice LE, et al. Nitric oxide and carbon monoxide production and metabolism in preeclampsia. *Reprod Sci*. 2013;20(5):542–548.
- [21] Maeda T, Yoshimura T, Okamura H. Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, in maternal and fetal circulation. *J Soc Gynecol Investig*. 2003;10(1):2–4.
- [22] Khalil AA, Tsikas D, Akolekar R, et al. Asymmetric dimethylarginine, arginine and homoarginine at 11–13 weeks' gestation and preeclampsia: a case-control study. *J Hum Hypertens*. 2013;27(1):38–43.
- [23] Böger RH, Diemert A, Schwedhelm E, et al. The role of nitric oxide synthase inhibition by asymmetric dimethylarginine in the pathophysiology of preeclampsia. *Gynecol Obstet Invest*. 2010;69(1):1–13.
- [24] Arcos MI, Fujihara CK, Sesso A, et al. Mechanisms of albuminuria in the chronic nitric oxide inhibition model. *Am J Physiol Renal Physiol*. 2000;279(6):1060–1066.
- [25] Kaida Y, Ueda S, Yamagishi S, et al. Proteinuria elevates asymmetric dimethylarginine levels via protein arginine methyltransferase-1 overexpression in a rat model of nephrotic syndrome. *Life Sci*. 2012;91(9–10):301–305.
- [26] Caglar K, Yilmaz MI, Sonmez A, et al. ADMA, proteinuria, and insulin resistance in non-diabetic stage I chronic kidney disease. *Kidney Int*. 2006;70(4):781–787.
- [27] Sonmez A, Celebi G, Erdem G, et al. Plasma apelin and ADMA Levels in patients with essential hypertension. *Clin Exp Hypertens*. 2010;32(3):179–183.
- [28] Dong X, Gou W, Li C, et al. Proteinuria in preeclampsia: not essential to diagnosis but related to disease severity and fetal outcomes. *Pregnancy Hypertens*. 2017;8:60–64.
- [29] Baylis C. Nitric oxide synthase derangements and hypertension in kidney disease. *Curr Opin Nephrol Hypertens*. 2012;21(1):1–6.
- [30] Briet M, Burns KD. Chronic kidney disease and vascular remodelling: molecular mechanisms and clinical implications. *Clin Sci (Lond)*. 2012;123(7):399–416.

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---
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---
- 3** B. Demir, S. Demir, S. Pasa, S. Guven, Y. Atamer, A. Atamer, Y. Kocyigit. "The role of homocysteine, asymmetric dimethylarginine and nitric oxide in pre-eclampsia", *Journal of Obstetrics and Gynaecology*, 2012  
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---
- 4** Femke Slaghekke, Gus Dekker, Bill Jeffries. "Endogenous inhibitors of nitric oxide and **%1**

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- 10 [iai.asm.org](http://iai.asm.org) % 1  
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- 11 R BOGER. "The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk % 1

factor", Cardiovascular Research, 10/2003

Publication

---

12

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---

13

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Student Paper

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14

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---

15

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Publication

---

16

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---

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---

22 Charitidou, C.. "The administration of estrogens, combined with anti-androgens, has beneficial effects on the hormonal features and asymmetric dimethyl-arginine levels, in women with the polycystic ovary syndrome", *Atherosclerosis*, 200802  
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---

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experimentally induced-preeclampsia in rats: Targeting the role of peroxisome proliferator-activated receptors gamma expression & asymmetric dimethylarginine", Archives of Biochemistry and Biophysics, 2019

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---

26

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---

27

H. Fujii, S. Takiuchi, Y. Kawano, M. Fukagawa. "Putative Role of Asymmetric Dimethylarginine in Microvascular Disease of Kidney and Heart in Hypertensive Patients", American Journal of Hypertension, 2008

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---

28

Sertório, J T, R Lacchini, L M Amaral, A C T Palei, R C Cavalli, V C Sandrim, G Duarte, and J E Tanus-Santos. "Haptoglobin polymorphism affects nitric oxide bioavailability in preeclampsia", Journal of Human Hypertension, 2012.

Publication

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---

29

SEIJI UEDA. "Asymmetric dimethylarginine may be a missing link between cardiovascular disease and chronic kidney disease", Nephrology, 8/20/2007

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---

30

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---

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---

31

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