



Association between Maternal Serum Uric Acid Levels with Severity and Neonatal Outcome in Preeclampsia / Eclampsia

Freddy W. Wagey¹, Yosep Sutandar^{1*} and Maria F. T. Loho¹

¹Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Sam Ratulangi, Prof. Dr. R. D. Kandou Central General Hospital, Manado, Indonesia.

Authors' contributions

This work was carried out in collaboration among all authors. Author YS designed the study, performed the statistical analysis, wrote the protocol, managed the analyses of the study, managed the literature searches, review and editing and wrote the first draft of the manuscript. Authors FWW and MFTL supervised, reviewed and edited the paper. All authors read and approved the final manuscript.

Article Information

Editor(s):

(1) Dr. Rajbala Singh, Siddhartha Institute of Pharmacy, India.

Reviewers:

(1) Abeer Orabi, King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia.

(2) Santo Grace, SRM University, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/68844>

Original Research Article

Received 20 March 2021

Accepted 25 May 2021

Published 04 June 2021

ABSTRACT

Aims: The objective of the study is to determine the association between maternal serum uric acid levels with the severity and neonatal outcome in preeclampsia/eclampsia.

Study Design: This study was a cross-sectional study with a descriptive-analytic design.

Place and Duration of Study: Department of Obstetrics and Gynecology, Prof. Dr. R. D. Kandou General Central Hospital and affiliated hospitals in Manado, between October 2020 and February 2021.

Methodology: We included 33 normotensive pregnant women and 33 mothers diagnosed with either severe preeclampsia, HELLP syndrome, or eclampsia who delivered at Prof. Dr. R. D. Kandou General Central Hospital and affiliated hospitals in Manado. The serum uric acid of all subjects was examined using the uricase method before delivery.

Results: The mean serum uric acid level in normotensive pregnancy was 4.8 (\pm 0.73) mg/dL and the median value in preeclampsia / eclampsia was 9.2 (5.2-15.1) mg/dL. One-way Anova test showed a significant association between maternal serum uric acid levels with the severity of preeclampsia/eclampsia with a value of $P < .001$ and the degree of hypertension with a value of $P < .001$. At the same time, the Pearson correlation test showed a strong correlation between systolic

*Corresponding author: E-mail: yosep.sutandar@gmail.com;

and diastolic blood pressure with uric acid levels with rho values 0.620 ($P < .001$) and 0.517 ($P = .002$), respectively. We found no significant association between maternal serum uric acid levels and the onset of preeclampsia (P -value = .935); with gestational age at delivery (P -value = 0.431); and with the first minute APGAR score (P -value = 0.209).

Conclusion: There was a significant association between maternal serum uric acid levels and the severity of preeclampsia/ eclampsia. There was no association between maternal serum uric acid levels and neonatal outcome. We recommend investigation of maternal uric acid levels could be used to help determine the prognosis in patients with preeclampsia/eclampsia.

Keywords: Preeclampsia; severity; uric acid; HELLP; eclampsia.

1. INTRODUCTION

The maternal mortality rate (MMR) in Indonesia is still relatively high and a health problem of particular concern to the government. MMR is also an indicator of the quality of health services during pregnancy and the postpartum period. Based on data released by the 2012 Indonesian Health Demographic Survey (IDHS), MMR in Indonesia ranked the highest among Southeast Asian countries, specifically at 359 per 100,000 live births. This figure is still far from the target of Sustainable Development Goals (SDG), in which the MMR in all countries is targeted to as low as 70 per 100,000 live births by 2030 [1].

The cause of maternal death in Indonesia are postpartum hemorrhage (30%), hypertension (25%), and infection (12%). Hypertension in pregnancy affects maternal and neonatal morbidity, and it is estimated that each year there are more than 60,000 maternal deaths worldwide [2]. Preeclampsia results in increased maternal and perinatal morbidity and mortality. In a study involving 442 pregnant women with severe preeclampsia, about 20% of them reported worsening marked by hemolysis, elevated liver enzymes, and thrombocytopenia (HELLP syndrome) even ended in eclampsia [3].

Several studies have shown that preeclampsia that progresses to a worsened state is characterized by increased maternal serum uric acid levels [4]. A systematic review of the association between uric acid and pregnancy complications in England found a positive correlation between increased uric acid in preeclampsia and fetal outcome and maternal. The study found that an increase in uric acid levels above 6 mg/dL increased the risk of eclampsia by 2.1 times, and an increase in uric acid levels above 7.5 mg/dL increased the risk of HELLP syndrome by 1.6 times [5].

In the current era of National Health Insurance (JKN), adjustments are needed between

scientific needs and the funds provided. It will improve the outcome of pregnant women [6]. Investigation of uric acid is routinely done and can be adjusted to National Health Insurance funds. This study aims to determine the association between maternal serum uric acid levels with the severity and neonatal outcome in preeclampsia/eclampsia. This study is expected to find out more about the benefits of uric acid investigation in pregnant women with hypertension in pregnancy.

2. MATERIALS AND METHODS

This study was a cross-sectional study with a descriptive-analytic design. The study population were normotensive pregnant women and women diagnosed with either severe preeclampsia, HELLP syndrome or eclampsia who delivered at Prof. Dr. R. D. Kandou General Central Hospital and affiliated hospitals in Manado from October 2020 to February 2021. The subjects in this study were selected by convenience sampling who met the inclusion criteria and had signed informed consent. The total sample size was 33 women with preeclampsia/ eclampsia (severe preeclampsia, HELLP syndrome, or eclampsia) and 33 women with normotensive pregnancies. The Hospital Ethics Committees and Institutional Review Board Approvals for this study were granted.

The inclusion criteria for the subjects of preeclampsia/ eclampsia group were pregnant women who came to the emergency room and/or outpatient clinic in the Department of Obstetrics and Gynecology, Prof. Dr. R. D. Kandou General Central hospital and affiliated hospitals in Manado, live singleton pregnancies, met the diagnostic criteria for Severe Preeclampsia, HELLP Syndrome, or Eclampsia; and willing to participate in the study and signing the Informed Consent. And the inclusion criteria for normotensive women were pregnant women with normal systolic and/ or diastolic blood pressure

without any complication of pregnancy. The exclusion criteria for the subjects of this study were a history of elevated uric acid before pregnancy due to chronic diseases such as gout arthritis and chronic renal dysfunction, congenital abnormalities, metabolic hyperuricemia disease, and unwillingness to participate in the study. The serum uric acid of all subjects was examined using the uricase method before delivery.

The variables in this study were age, occupations, educations, systolic and diastolic blood pressure, the severity of preeclampsia/eclampsia (severe preeclampsia, HELLP syndrome, or eclampsia), the degree of proteinuria, and the onset of preeclampsia. The neonatal outcomes were measure from gestational age when termination of pregnancy occurred, and first minute APGAR score. Continuous variables were described using the mean and standard deviation or median and interquartile ranges. The comparative test was carried out using the t-test or ANOVA test, depending on the variables. A correlation test was performed using the Pearson test. The data were analyzed using SPSS version 23.0 software.

3. RESULTS AND DISCUSSION

3.1 Results

The study population were normotensive pregnant women and women diagnosed with either severe preeclampsia, HELLP syndrome or eclampsia who delivered at Prof. Dr. R. D. Kandou General Central Hospital and affiliated hospitals in Manado from October 2020 to February 2021. The characteristics of all

subjects of this study can be seen below (Table 1).

In this study, three women (9%) were deceased. All of them were in preeclampsia/ eclampsia group with uric acid levels 11.3 mg/dL, 14.7 mg/dL, and 15.1 mg/dL, respectively. The mean uric acid level was 13.7 (± 2.08) mg/dL.

Our findings showed a significant association between uric acid levels between normotensive pregnant women and preeclampsia/ eclampsia with a P -value $< .001$. We also found a significant association between maternal serum uric acid levels and the severity of preeclampsia/eclampsia with a P -value of $< .001$ (Fig. 1). There was also a significant association between maternal serum uric acid levels and the degree of hypertension with a P -value $< .001$. From the correlation Pearson test, the results showed a strong correlation between systolic and diastolic blood pressure and uric acid levels with an r -value of 0.620 ($P < 0.001$) and 0.517 ($P = 0.002$), respectively (Table 3 & Fig. 2).

Our comparative tests showed a significant association between maternal serum uric acid levels with preeclampsia/eclampsia and the degree of proteinuria with a P -value = .006 (Table 2 & Fig. 3). However, we found no significant association between maternal serum uric acid levels and the onset of preeclampsia, P -value = .935; between maternal serum uric acid levels in the preeclampsia/eclampsia group and gestational age at delivery with a P -value = 0.431; and between maternal serum uric acid levels and preeclampsia/eclampsia with the first minute APGAR score with P -value = 0.209 (Table 2).

Table 1. Characteristics of the subjects

Characteristics	Normotensive Pregnancy		Preeclampsia/ Eclampsia	
	n	%	n	%
Age				
<20 years old	4	12.1	2	6.1
20 - 35 years old	22	66.7	23	69.7
≥ 35 years old	7	21.2	8	24.2
Education				
Uneducated	0	0	3	9
Primary school	0	0	7	21.2
Middle School	7	21.2	8	24.2
High school	22	66.7	12	36.6
Undergraduate	4	12.1	3	9
Occupation				
Housewife	24	72.7	29	87.8
Private Sector	5	15.2	2	6.1
Employee	4	12.1	2	6.1

Table 2. Association between maternal serum uric acid levels and categories of hypertension in pregnancy and neonatal outcomes

Categories	n (%)	Uric Acid Levels (mg/dL)	P-value
All group			
Normotensive pregnancy	33 (50%)	4.8 (± 0.73)	<0.001
Preeclampsia/ Eclampsia	33 (50%)	9.2 (5.2-15.1)	
Severity			
Normotensive Pregnancy	33 (50%)	4.8 (± 0.73)	<0.001
Severe Preeclampsia	11 (16.7%)	6.7 (±0.81)	
HELLP Syndrome	11 (16.7%)	9.2 (5.2-11.3)	
Eclampsia	11 (16.7%)	11.3 (9.8-15.1)	
Classification of Hypertension			
Normotension	33 (50%)	4.8 (± 0.73)	<0.001
Stage II hypertension	17 (26%)	7.0 (±1.58)	
Hypertensive Crisis	16 (24%)	11.1 (±1.91)	
Degrees of Proteinuria			
Positive 1	6 (9%)	6.1 (±0.63)	0.006
Positive 2	4 (6%)	7.8 (±2.17)	
Positive 3	4 (6%)	7.9 (±1.72)	
Positive 4	19 (29%)	10.4 (±2.49)	
Onset of Preeclampsia			
Early-onset preeclampsia	15 (45%)	10.0 (±2.65)	0.965
Late-onset preeclampsia	18 (55%)	8.5 (±2.54)	
Gestational Age			
Extreme preterm	1 (3%)	9.8	0.431
Very Preterm	7 (21%)	10.3 (±2.30)	
Preterm	7 (21%)	9.8 (±3.29)	
Aterm	18 (55%)	8.5 (±2.54)	
First Minute APGAR Score			
< 7	29 (88%)	9.4 (±2.75)	0.209
≥ 7	4 (12%)	7.78 (±1.54)	

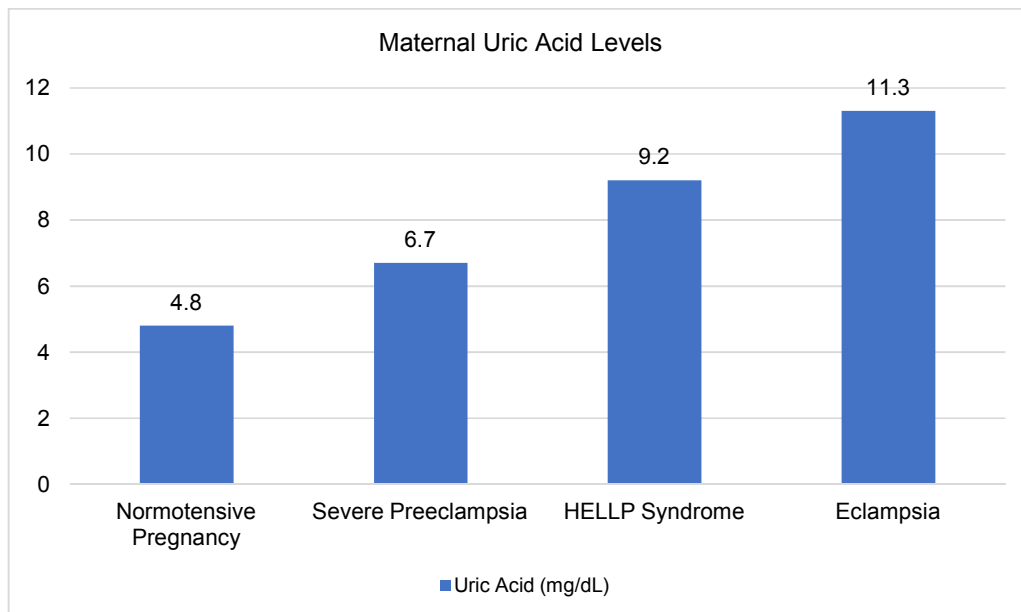


Fig. 1. Maternal uric acid levels were significantly increased following the severity of preeclampsia/ eclampsia

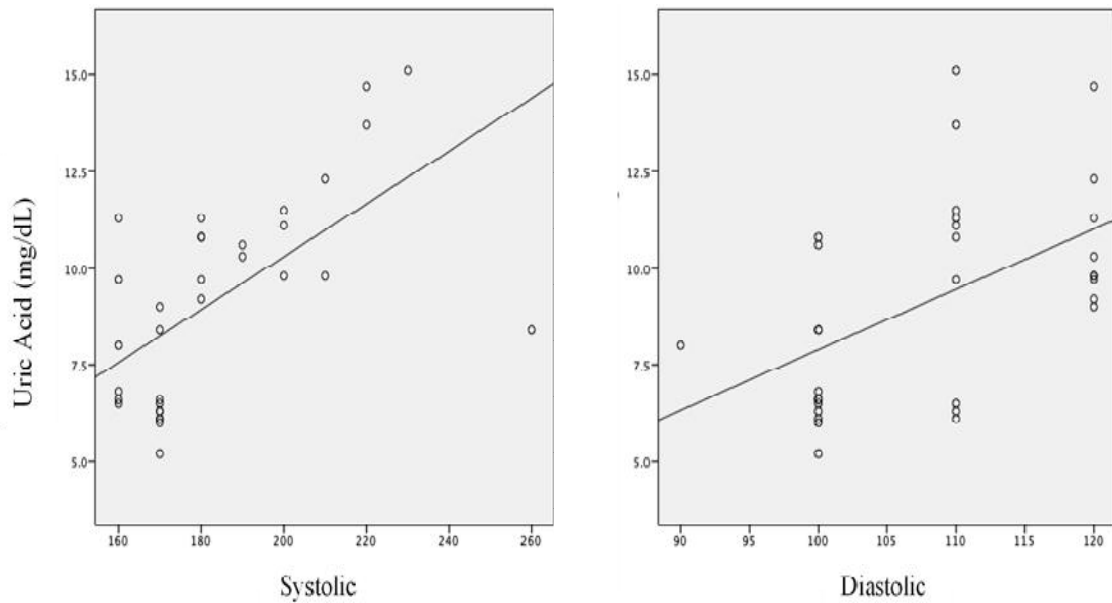


Fig. 2. A scatter plot shows correlation between uric acid with blood pressure

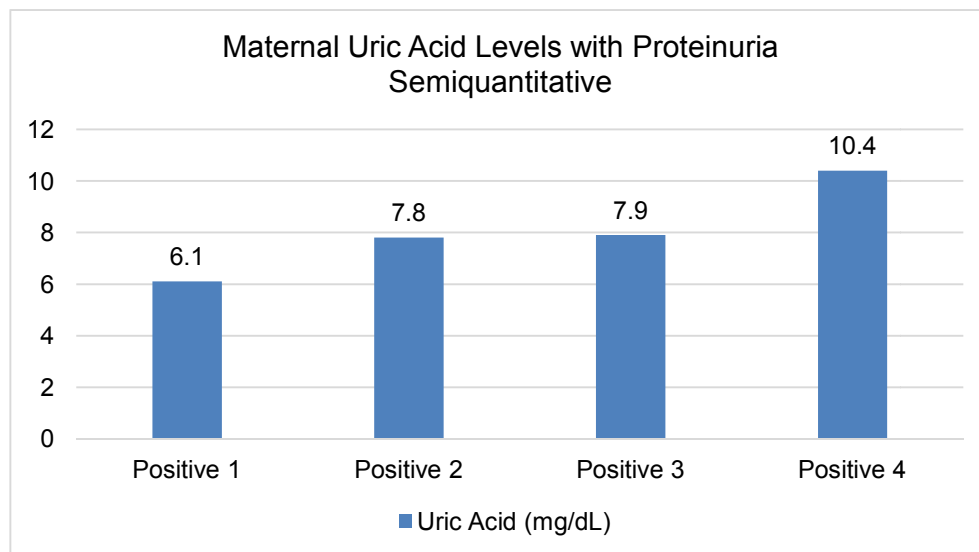


Fig. 3. Maternal uric acid levels were significantly and progressively increased following the degree of proteinuria semiquantitative

Table 3. Correlation between maternal serum uric acid levels and systolic and/or diastolic blood pressure in preeclampsia/eclampsia

Variables	Uric Acid Levels (mg/dL)	
	Correlation coefficient (r)	p-value
Systolic blood pressure	0.620	<0.001
Diastolic blood pressure	0.517	0.002

3.2 Discussion

Our study found a significant difference between uric acid levels between the normotensive and preeclampsia/eclampsia groups with a *P*-value of <0.001. These results are consistent with other studies in which they found that maternal serum uric acid levels in women with preeclampsia/eclampsia were increased compared to normotensive pregnancies and could be used to predict poor maternal and neonatal outcomes [7-10]. The increase in maternal serum uric acid levels in the preeclampsia/eclampsia group is probably not only the result of decreased glomerular filtration rate but also because of increased uric acid production due to placental ischemia and increased trophoblast shedding. These events lead to increased uric acid levels and play a significant role in the pathophysiology of preeclampsia/eclampsia [11-15]. Our study suggests that maternal uric acid levels should be routinely assessed in patients with hypertension in pregnancy [4].

Our findings are similar to the study by Bellos et al., which is uric acid levels are linked to the severity of preeclampsia/ eclampsia. They significantly and progressively increase from severe preeclampsia, HELLP syndrome, to eclampsia [8]. This is probably because of abnormal placentation that causes an imbalance between oxidant and antioxidant activity [16]. Placental ischemia and oxidative stress will increase the expression of xanthine dehydrogenase/xanthine oxidase holoenzyme produced by cytotrophoblasts. This will cause an increase in serum uric acid. In addition, increased uric acid levels can be caused by a decrease in Nitric Oxide levels, thereby reducing the vasodilation ability of blood vessels and increasing vascular tone, especially placental vascularization, as well as increasing levels of vasopressors such as endothelin and thromboxane [17].

Our findings suggest that uric acid can affect blood pressure in pregnant women. This finding is consistent with the research conducted by Lee et al. [18] and Niraula et al. [19], where the severity of increased blood pressure was associated with increased levels of serum uric acid. It is associated with endothelial injury and dysfunction due to crystal-independent pathways leading to RAAS activation, blockade of nitric oxide production, and superoxide generation [20].

Uric acid levels in pregnant women can also affect the degree of proteinuria. We found that there was a significant association between maternal serum uric acid levels with preeclampsia/eclampsia and the degree of proteinuria with a *P*-value = .006. Paula et al. concluded that the combination of high maternal serum uric acid levels and high degrees of proteinuria was strongly associated with the development of an eclamptic crisis [21].

Although there was no significant association in the onset of preeclampsia/eclampsia, we found a clinical difference between uric acid levels in the early-onset preeclampsia compared to late-onset preeclampsia with 1.5 mg/dL uric acid levels higher in the early-onset preeclampsia group. The higher maternal serum uric acid levels in early-onset preeclampsia are due to early placental ischemia and/or hypoxia. This activates the systemic maternal vascular endothelium and increases the formation of superoxide and reactive oxygen species, which in turn causes earlier oxidative stress. This is supported by the research by Kimura et al., where more severe placental hypoxia and oxidative damage were found in early-onset preeclampsia [22]. Furthermore, these results are supported by a study conducted by Fukushima et al., in which 8-hydroxy-2-deoxyguanosine (8OHdG) immunohistochemical staining was performed on the placenta of preeclampsia/eclampsia patients to determine the degree of tissue damage due to oxidative and reactive oxygen species and at the same time associated with maternal uric acid levels. The study demonstrated a stronger positive immunohistochemical staining in early-onset preeclampsia and patients with higher uric acid levels [17].

Systematic review and meta-analysis conducted by Pecoraro and Trenti concluded that there is no strong evidence to support that serum uric acid levels are useful in predicting perinatal outcomes, including prematurity [9]. Research conducted by ISSHP [4], Hawkins et al. [10], and Livingston et al. [7] demonstrated that increased maternal uric acid levels are associated with poor maternal, fetal, and neonatal outcomes. The poor perinatal outcome is associated with the disruption of placental processes. This condition causes disruption in oxygen transport, placental amino acid transport, trophoblast invasion, and endothelial incorporation of trophoblasts in fetuses conceived by mothers with preeclampsia/eclampsia.

4. CONCLUSION

Maternal serum uric acid levels in the preeclampsia/eclampsia group were significantly higher than in the normotensive group. Specifically, maternal serum uric acid levels increased progressively and significantly in severe preeclampsia, HELLP syndrome, and the highest in eclampsia. We concluded that assessment of maternal uric acid levels could be used to help determine the prognosis and severity of preeclampsia / eclampsia. Unfortunately, there was no association between maternal serum uric acid levels and neonatal outcome. Our study recommends that maternal uric acid levels should be routinely assessed in patients with hypertension in pregnancy.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this research.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The Hospital Ethics Committees approved this study.

DATA AVAILABILITY

The authors declare that data supporting the findings of this study are available within the article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lee BX, Kjaerulf F, Turner S, Cohen L, Donnelly PD, Muggah R, et al. Transforming Our World: Implementing the 2030 agenda through sustainable development goal indicators. *J public health policy* [Internet]. 2016;1–21. Available: https://www.who.int/violenceprevention/project_groups/2_JPHP_VPA_Special_Issue_Lee_et_al.pdf
2. National population and family planning board, ministry of health republic of Indonesia. Indonesia Demographic and Health Survey; 2012. Available: <https://dhsprogram.com/pubs/pdf/FR275/FR275.pdf>
3. Kınay T, Küçük C, Kayıkçıoğlu F, Karakaya J. Severe preeclampsia versus HELLP syndrome: Maternal and perinatal outcomes at <34 and ≥34 weeks' gestation. *Balkan Med J*. 2015;32(4):359–63.
4. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018;13:291–310.
5. Thangaratinam S, Ismail KMK, Sharp S, Coomarasamy A, Khan KS. Accuracy of serum uric acid in predicting complications of pre-eclampsia: A systematic review. *BJOG*. 2006;113(4):369–78.
6. Kementerian kesehatan republik Indonesia. Buku pegangan sosialisasi jaminan kesehatan nasional (JKN) dalam Sistem Jaminan Sosial Nasional (SJSN). kementerian kesehatan republik Indonesia, editor. Jakarta: Kementerian Kesehatan Republik Indonesia; 2013.
7. Livingston JR, Payne B, Brown M, Roberts JM, Cote A-M, Magee LA, et al. Uric acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia. *J Obstet Gynaecol Can*. 2014;36(10):870–7.
8. Bellos I, Pergialiotis V, Loutradis D, Daskalakis G. The prognostic role of serum uric acid levels in preeclampsia: A meta-analysis. *J Clin Hypertens (Greenwich)*. 2020;22(5):826–34.
9. Pecoraro V, Trenti T. Predictive value of serum uric acid levels for adverse maternal and perinatal outcomes in pregnant women with high blood pressure. A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:447–54.
10. Hawkins TL-A, Roberts JM, Mangos GJ, Davis GK, Roberts LM, Brown MA. Plasma uric acid remains a marker of poor outcome in hypertensive pregnancy: a retrospective cohort study. *BJOG*. 2012; 119(4):484–92.

11. Maynard SE, Thadhani R. Pregnancy and the kidney. *J Am Soc Nephrol*. 2009;20(1): 14–22.
12. Vazquez-Rodriguez JG, Rico-Trejo EI. Role of uric acid in preeclampsia-eclampsia. *Ginecol Obstet Mex*. 2011; 79(5):292–7.
13. Lam C, Lim K-H, Kang D-H, Karumanchi SA. Uric acid and preeclampsia. *Semin Nephrol*. 2005;25(1):56–60.
14. Wantania JJ, Homenta C, Kepel BJ. Association of Heme Oxygenase-1 (HO-1) level with onset and severity in normotensive pregnancy and severe preeclampsia. *Bali Med J*. 2016;5(1):118.
15. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: role of oxidative stress. *Front Physiol*. 2014;5:372.
16. Schoots MH, Gordijn SJ, Scherjon SA, van Goor H, Hillebrands J-L. Oxidative stress in placental pathology. *Placenta*. 2018;69: 153–61.
17. Fukushima K, Murata M, Tsukimori K, Eisuke K, Wake N. 8-Hydroxy-2-deoxyguanosine staining in placenta is associated with maternal serum uric acid levels and gestational age at diagnosis in pre-eclampsia. *Am J Hypertens*. 2011; 24(7):829–34.
18. Lee JJ, Ahn J, Hwang J, Han SW, Lee KN, Kim JB, et al. Association between uric acid and blood pressure in different age groups. *Clin Hypertens*. 2015;21:14.
19. Niraula A, Lamsal M, Majhi S, Khan SA, Basnet P. Significance of serum uric Acid in pregnancy induced hypertension. *J Natl Med Assoc*. 2017;109(3):198–202.
20. Lanaspá MA, Andrés-Hernando A, Kuwabara M. Uric acid and hypertension. *Hypertens Res [Internet]*. 2020;43(8): 832–4. Available: <https://doi.org/10.1038/s41440-020-0481-6>
21. Paula LG, Pinheiro da Costa BE, Hentschke MR, Antonello IC, Luz JH, da Cunha Filho E V, et al. Increased proteinuria and uric acid levels are associated with eclamptic crisis. *Pregnancy Hypertens*. 2019;15:93–7.
22. Kimura C, Watanabe K, Iwasaki A, Mori T, Matsushita H, Shinohara K, et al. The severity of hypoxic changes and oxidative DNA damage in the placenta of early-onset preeclamptic women and fetal growth restriction. *J Matern Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet*. 2013;26(5):491–6.

© 2021 Wagey et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/68844>