

## Research Article

## A Significant Increase in Maternal Blood Uric Acid Levels Accompanies the Severity of Hypertensive Disorders in Pregnancy

### *Peningkatan Signifikan Kadar Asam Urat Darah Ibu menyertai Keparahan Gangguan Hipertensi pada Kehamilan*

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#### Abstract

**Objective:** To assess the relationship between maternal serum uric acid level and severity of hypertensive disorders in pregnancy and perinatal outcomes.

**Methods:** A cross sectional study was conducted at Persahabatan Hospital from January 2014 to December 2018. Subject were pregnant women with hypertensive disorder. Serum uric acid levels were taken from a venous blood sample at the time the patient came for delivery. The severity of hypertensive disorders in pregnancy were grouped into chronic hypertension, gestational hypertension, preeclampsia without severe feature, preeclampsia with severe feature, and preeclampsia with severe feature and organ involvement. The perinatal outcomes were the gestational age at birth, birth weight, and the first minute APGAR score. The relationship between maternal serum uric acid level and severity of hypertensive disorders in pregnancy and perinatal outcomes were analyzed using Mann Whitney and Kruskal Wallis test.

**Result:** A total of 704 out of 880 pregnant women with hypertensive disorder have met the criteria as research subjects. Maternal uric acid levels were found to increase significantly ( $p < 0.001$ ) with increasing severity of hypertensive disorders in pregnancy. Maternal who experienced preterm delivery had significantly higher blood uric acid levels ( $p < 0.001$ ) than those who experienced a term delivery. Maternal blood uric acid levels of infants with small birth weight for gestational age and first minute Apgar score  $< 7$  were slightly higher but not significant compared to maternal blood uric acid levels of normal birth weight infants and first minute Apgar score  $> 7$ .

**Conclusions:** Maternal blood uric acid levels increased significantly accompanying the severity of hypertensive disorders in pregnancy. Blood uric acid levels tend to be higher in maternal who have poor perinatal outcomes.

**Keywords:** APGAR score, hypertensive disorders in pregnancy, preeclampsia, uric acid.

#### Abstrak

**Tujuan:** Untuk menilai hubungan antara kadar asam urat serum ibu dan keparahan gangguan hipertensi pada kehamilan dan luaran perinatal.

**Metode:** Studi potong lintang dilakukan Rumah Sakit Persahabatan periode Januari 2014 sampai Desember 2018. Subjek penelitian adalah ibu hamil dengan gangguan hipertensi. Kadar asam urat darah diambil dari sampel darah vena pada saat ibu hamil datang untuk melahirkan. Tingkat keparahan gangguan hipertensi pada kehamilan dikelompokkan menjadi hipertensi kronik, hipertensi gestasional, preeklamsia tanpa gejala berat, preeklamsia dengan gejala berat, dan preeklamsia dengan gejala berat dan keterlibatan organ. Luarannya perinatal adalah usia kehamilan saat lahir, berat badan bayi lahir, dan skor APGAR menit pertama. Hubungan antara kadar asam urat darah ibu dan tingkat keparahan gangguan hipertensi pada kehamilan dan luaran perinatal dianalisis menggunakan uji Mann Whitney atau uji Kruskal Wallis.

**Hasil:** Sebanyak 704 dari 880 ibu hamil penderita hipertensi telah memenuhi kriteria sebagai subjek penelitian. Kadar asam urat darah ibu meningkat secara signifikan ( $p < 0,001$ ) dengan meningkatnya keparahan gangguan hipertensi pada kehamilan. Ibu yang melahirkan preterm memiliki kadar asam urat darah yang lebih tinggi secara bermakna ( $p < 0,001$ ) dibandingkan ibu yang melahirkan aterm. Kadar asam urat darah ibu dari bayi dengan berat lahir kecil untuk usia kehamilan dan skor Apgar menit pertama  $< 7$ , sedikit lebih tinggi tetapi tidak signifikan, dibandingkan kadar asam urat darah ibu dari bayi berat lahir normal dan skor Apgar menit pertama  $> 7$ .

**Kesimpulan:** Kadar asam urat darah ibu meningkat secara signifikan menyertai beratnya gangguan hipertensi pada kehamilan. Kadar asam urat darah cenderung lebih tinggi pada ibu yang memiliki luaran perinatal kurang baik.

**Kata kunci:** APGAR, asam urat, hipertensi dalam kehamilan, preeklamsia.

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## INTRODUCTION

Maternal mortality rate (MMR) is one of major health problems in Indonesia. In 2015, maternal mortality rate in Indonesia ranks among the highest among Southeast Asian countries at 305 per 100,000 live births.<sup>1,2</sup> This figure is still far from the Sustainable Development Goals target (SDG), which in 2030 expected that MMR in all countries will drop to under 70 per 100,000 live births.<sup>3,4</sup> The three main causes of maternal death are bleeding (30%), hypertension (25%), and infections (12%).<sup>5</sup> Among those three main causes, hypertension is one of the most difficult problems to undertake in pregnancy, causing maternal and neonatal morbidity. In fact, there are more than 60,000 maternal deaths worldwide each year due to hypertensive disorder in pregnancy.<sup>6</sup>

Based on guidelines from The American Congress of Obstetricians and Gynecologists (ACOG) in 2019, hypertensive disorders in pregnancy can be classified into; Hypertension in pregnancy; chronic hypertension, preeclampsia without severe disorders (preeclampsia without severe features), and preeclampsia with severe disorders (severe preeclampsia feature).<sup>7</sup> Preeclampsia appears at 20 weeks after gestation, characterized by hypertension accompanied by proteinuria.<sup>8,9</sup> There are many risk factors of hypertension in pregnancy, one of which is maternal serum uric acid level.<sup>9</sup>

Uric acid is a purine degradation product that is catalyzed by the enzyme xanthine dehydrogenase / xanthinoxidase (XDH / XO).<sup>10</sup> Previous studies reported a significant increase in uric acid levels in 16% of patients with hypertension in pregnancy and 75% of patients with preeclampsia.<sup>11,12</sup> Previous theory mentioned that elevated uric acid levels in the condition of preeclampsia is a secondary change caused by worsening of kidney function.<sup>13</sup> However, other studies have shown that worsening in preeclampsia is characterized by an increase in maternal uric acid blood levels.<sup>14,15</sup> Blood uric acid plays a role in the pathophysiology of preeclampsia through the process of inhibition of endothelial cell proliferation, trophoblast invasion, and inhibiting the release of nitric oxide (NO).<sup>16</sup> This results in blood vessels with large diameters that do not respond to smooth muscle thereby making inadequate oxygen and nutrient transport. Other studies have even shown that increased uric acid in patients with preeclampsia can be seen since the 10th week of gestation,

much earlier than the initial clinical symptoms shown by patients.<sup>14</sup> However, there has not been any study analyzing the outcome of mothers with hypertensive disorders having elevated uric acid level in Indonesia.

This study aims to assess the relationship between maternal serum uric acid level and severity of hypertensive disorders in pregnancy and perinatal outcomes.

## METHODS

This is a cross sectional study determined to assess the relationship between maternal serum uric acid level and various maternal and perinatal complications. This study was performed in January 2011 to December 2018, at Persahabatan General Hospital, Jakarta, Indonesia. Subjects were all pregnant mothers with hypertensive disorders having delivery during the course of the study. Mothers with history of serum uric acid level elevation before pregnancy due to chronic diseases such as arthritis gout or renal disease were excluded from the study. The samples were recruited using total sampling method.

This study use 5% error bound and 95% confidence interval limit, power of the test considered to be 90%. The study was approved by the Research Ethics Committee, Faculty of Medicine, Universitas Indonesia with protocol number 17-03-0208 and Persahabatan General Hospital with ethical clearance number 09/KEPK-RSUPP/02/2018. All patients who were included in this study had given their informed consent prior to their inclusion in the study.

Collected data were then analyzed using SPSS for Macintosh ver. 20. Characteristics of patients in the form of sociodemographic and clinicopathologically are analyzed descriptively. Serum uric acid levels were taken from a venous blood sample at the time the patient came for delivery. The maternal outcome in this study was the degree of hypertension and grade of hypertension. Severity of hypertensive disorder was grouped into chronic hypertension, gestational hypertension, preeclampsia without severe feature, preeclampsia with severe feature, and preeclampsia with severe feature and organ involvement. Chronic hypertension was defined as hypertensive disorder history prior to pregnancy. Gestational hypertension was defined as blood pressure of more than 140/90 mmHg after 20 weeks of pregnancy without proteinuria or severe feature of preeclampsia. Preeclampsia without

severe feature was defined as blood pressure between 140/90 mmHg and 160/110 mmHg with proteinuria. Preeclampsia with severe feature was defined as blood pressure of more than 160/110 mmHg with proteinuria while preeclampsia with severe feature and organ involvement was defined as preeclampsia with or without proteinuria with either thrombocytopenia, liver dysfunction, renal insufficiency, pulmonary edema, new onset headache unresponsive to medication, or new onset visual disturbance. The infant outcomes in this study were gestational age at birth, infant

birth weight according to the Lubchenco Curve and first minute APGAR score. The relationship between uric acid levels and various outcomes was questioned using the Kruskal Willis and Mann Whitney test.

## RESULTS

A total of 704 subjects met the inclusion criteria and had been further analyzed. Clinical variables were analyzed for its distribution and presented accordingly. (Table 1)

**Table 1.** Clinical Characteristics of Subjects

Hypertensive Disorder	n (%)	Serum uric acid (mg/dL)
Chronic hypertension#	13 (1.8)	3.35 + 0.63
Gestational hypertension*	133 (18.9)	4.9 (3.2 – 8.0)
Preeclampsia without severe feature#	82 (11.6)	5.18 + 1.54
Preeclampsia with severe feature*	360 (51.1)	5.3 (2.2 – 9.8)
Preeclampsia with severe feature and organ involvement*	116 (16.5)	7.6 (2.7 – 16.0)

#mean ± std deviation; \*median (min – max)

In order to determine the relationship between hypertensive disorder and serum uric acid level, hypertensive disorder categories suffered by patient was transformed into 3 different categories, namely 1) chronic hypertension

and gestational hypertension, 2) preeclampsia without severe feature, and 3) preeclampsia with severe feature with/without organ involvement. The result can be found on Table 2

**Table 2.** Relationship between Hypertensive Disorder and Serum Uric Acid Level

Hypertensive Disorder	n (%)	Serum uric acid (mg/dL)	P-value
Chronic hypertension and gestational hypertension*	146 (20.7%)	4.8 (2.2 – 8.0)	< 0.001+
Preeclampsia without severe feature #	82 (11.6%)	5.18 + 1.54	
Preeclampsia with severe feature with/without organ involvement*	476 (67.7%)	5.7 (2.2 – 16.0)	

\*Mean ± std deviation; \*median (min – max), \*Kruskall Wallis test

In order to determine the relationship between maternal serum uric acid level and perinatal outcome, Kruskal Willis analysis was

done between preterm birth, birth weight, and APGAR score with maternal serum uric acid level. (Table 3)

**Table 2.** Relationship between Hypertensive Disorder and Serum Uric Acid Level

Category	n (%)	Maternal Serum Uric Acid (mg/dL)	P-value
<b>Preterm Birth</b>			
Aterm*	465 (66.01)	5.0 (2.2 – 9.8)	< 0.001#
Preterm*	239 (34.09)	6.3 (2.7 – 16)	
<b>Birth Weight</b>			
Normal*	619 (87.9)	5.4 (2.2 – 14.5)	0.169#
Small for Gestational Age*	85 (12.1)	5.6 (2.7 – 16.0)	
<b>APGAR score</b>			
> 7*	630 (89.5)	5.35 (2.2 – 14.5)	0.06#
< 7*	74 (10.5)#	6.0 (2.8 – 16.0)	

\*median (min – max), #Mann Whitney U test

Based on the analysis done, it was known that preterm birth babies tend to be born by mother with higher level of serum uric acid ( $p < 0.001$ ). There was no relationship between maternal serum uric acid with birth weight and first minute APGAR Score ( $p > 0.05$ ).

## DISCUSSION

According to ACOG 2013 and 2019, hypertension disorders in pregnancy are divided into 4 groups, namely chronic hypertension, hypertension in pregnancy, preeclampsia without severe symptoms, and preeclampsia with severe symptoms.<sup>7</sup> In this study, it was found that there was significant difference between groups ( $p < 0.001$ ). Studies have reported that increased maternal and perinatal complications were associated with higher maternal blood uric acid levels  $> 6$  mg / dL in preeclampsia patients.<sup>10,11</sup>

There are several studies assessing the pathophysiology behind increased severity of hypertensive disorders in pregnancy due to higher maternal uric acid level, namely endothelial dysfunction due to high oxidative stress, decreased NO levels suppressing the ability of vasodilation of blood vessels and increase vascular tone, especially placental vascularization, as well as increased vasopressor levels such as endothelin and thromboxane. One study has shown that administration of allopurinol in women with hypertensive disorders in pregnancy can reduce the incidence of endothelial dysfunction and improve vascular vasodilation.<sup>13</sup> Previous studies reported that condition of hypertension accompanied by hyperuricemia had the same risk of having preeclampsia compared to pregnant women with hypertension accompanied by proteinuria. In this study, it was not explained about the degree of hypertension in patients.<sup>17</sup>

Based on the analysis conducted in this study, maternal having preterm birth had higher level of serum uric acid ( $p < 0.001$ ). Previous studies suggested that hyperuricemia condition increases incidence of preterm birth, especially in patients with preeclampsia. However, the study also showed that patients with hyperuricemia without preeclampsia were more likely to have preterm births than patients with normal uric acid levels.<sup>13</sup> Previous study also reported that increased maternal blood uric acid levels are associated with stunted fetal development and low birth weight babies.<sup>18</sup> Other studies in India

show that 100% of patients with blood uric acid levels  $> 5.5$  mg/dL during the last trimester of pregnancy have term infants with birth weights below 2500 grams.<sup>19</sup> However, it was known from this study that there was no relationship between serum uric acid level and birth weight or APGAR score.

## CONCLUSIONS

Maternal blood uric acid levels increased significantly accompanying the severity of hypertensive disorders in pregnancy. Blood uric acid levels tend to be higher in maternal who have poor perinatal outcomes.

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## CONFLICT OF INTEREST

There is no conflict of interest in this study.

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