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Original Article

Increased Uric Acid Levels in Pregnant Women with Preeclampsia and Normal Pregnant Women

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ABSTRACT

Background: Preeclampsia is an acute complication of pregnancy characterized by hypertension, proteinuria, and other organ disorders occurring after 20 weeks of gestation. Early detection of preeclampsia is crucial to avoid complications and poor prognosis. The association between increased uric acid concentration and preeclampsia has been recognized since the early 1900s. The classic interpretation of elevated uric acid levels suggests that the vasoconstriction mechanism of blood vessels due to hypertension can reduce kidney clearance. This study aims to analyze the differences in blood uric acid levels in pregnant women with preeclampsia and normal pregnant women.
Methods: The research method used is a case-control design, with 10 blood samples from normal pregnant women as the control population and 10 blood samples from pregnant women with preeclampsia as the case population. Preeclampsia data were obtained from patients' medical records, whereas uric acid level data were obtained from laboratory tests. Bivariate analysis was performed using T-test.
Results: The results of this study show that the case group has a higher uric acid level (68.1%) compared to the control group (31.9%).
Conclusions: Based on bivariate analysis, the p-value is <0.05, indicating a significant difference in uric acid levels between pregnant women with preeclampsia and normal pregnant women.

Key Words: *Uric acid; pregnancy; preeclampsia*

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INTRODUCTION

In 2020, it is estimated that around 800 pregnant women had died each day [1]. Maternal mortality resulting from bleeding stands at 28%, while infection is attributed to anemia and chronic energy deficiency (CED) of the mother [2]. Apart from bleeding, hypertension in pregnancy is one of the main causes of maternal morbidity and mortality to date [3].

Most guidelines worldwide had agreed in defining hypertension in pregnancy as Blood Pressure (BP) ≥140/90 mmHg [4]. Hypertension in pregnancy is divided into four categories, namely gestational hypertension, which is elevated blood pressure in pregnant women ≥ 140/90 mmHg after 20 weeks of gestation, chronic hypertension, which is hypertension existing before pregnancy or before 20 weeks of gestation, then preeclampsia/eclampsia, which is an increase in blood pressure accompanied by edema (swelling) and proteinuria, and preeclampsia accompanied by chronic hypertension [5].

Hypertension in pregnancy can be chronic (pre-existing hypertension before pregnancy) or de novo (as in preeclampsia or gestational hypertension). Globally, preeclampsia is responsible for >500,000 fetal and neonatal deaths, as well as >70,000 maternal deaths each year. This condition can deteriorate rapidly and without warning [6]. Epidemiologically, it is estimated that preeclampsia occurs in 2-8% of pregnant women worldwide [7].

The exact cause of preeclampsia cannot be definitively identified until now. There is a popular theory stating that the cause of preeclampsia is placental ischemia, but this theory cannot fully explain everything about the disease or its specific relationship to the occurrence of preeclampsia. From this, it can be concluded that there is more than one factor involved in triggering the occurrence of preeclampsia and eclampsia. Risk factors for preeclampsia are not only related to maternal factors but also connected to external factors. Maternal risk factors include age, gestational age, parity, type of

pregnancy (single or multiple), low socioeconomic status, body mass index, history of previous preeclampsia, family history of diabetes, and history of hypertension [8].

Uric acid is the end product of the metabolism of endogenous and exogenous nucleic acid and purine. This metabolic process is catalyzed by the enzyme xanthine oxidase, converting excess or unused purines into uric acid in the human liver. This enzyme transforms excessive or unused purines into uric acid to be transported in the bloodstream to the kidneys. In the purine metabolism process, reactive oxygen species (ROS), including superoxide, are produced simultaneously with uric acid production [9].

Uric acid is one of the most frequently conducted laboratory examinations in preeclampsia patients, this examination is often found to be higher in preeclampsia compared to patients with normal blood pressure. The reason proving the increase in uric acid levels in preeclampsia is the vasoconstriction mechanism which is associated with decreased renal uric acid secretion, reduced renal blood flow, and decreased glomerular filtration, followed by uric acid clearance or excretion [10]. On the other hand, because uric acid interacts with proinflammatory cytokines, the increase in plasma uric acid levels in preeclampsia patients can directly indicate the pathophysiology of this syndrome, as it can trigger inflammation [11].

Preeclampsia is also characterized by mild invasion of trophoblasts and exacerbated by hypoxia (insufficient oxygen levels in the blood), Reactive Oxygen Species (ROS), and oxidative stress. Uric acid secretion is inhibited due to the hypoxic condition that stimulates the production of lactic acid. Additionally, an increase in uric acid enhances sympathetic activity, which decreases the activity of the angiotensin system and further elevates blood pressure in preeclampsia. Serum uric acid concentrations significantly increase in hypertensive pregnancies compared to normal pregnancies [10].

The correlation between increased uric acid concentration and preeclampsia has been identified since the early 1900s. The classical interpretation of elevated uric acid concentration in the blood suggests that the vasoconstriction mechanism of blood vessels due to hypertension can reduce renal clearance. Despite showing a significant increase, the clinical benefits of elevated uric acid levels as an indication of disease severity are still debated to this day [12].

Other relevant studies have concluded that uric acid levels in pregnancies with preeclampsia are indeed higher compared to normal pregnancies without preeclampsia. This indicates a significant relationship between uric acid levels and the likelihood of developing preeclampsia [13].

METHODS

This study used the observational analysis method with a case-control study design. This research method is applied to understand and compare the profile of uric acid levels in normal pregnant women and pregnant women with preeclampsia.

This study utilized a population consisting of pregnant women with a gestational age > 20 weeks and normal blood pressure, as well as pregnant women with preeclampsia, totaling 20 individuals. The sample size in this research was calculated using the Lemeshow formula. Subsequently, the participants were grouped into 10 samples in the control group and 10 samples in the case group. The sampling technique employed in this study was random sampling.

The respondents will be screened again according to the research inclusion criteria, as follows: (1) multigravida, (2) pregnancy with single fetal, (3) mild preclampsia, severe preeclampsia, cronic hypertension superimposed preeclampsia, (4) complete medical record documents. Next, data recapitulation was carried out, including: name, age, height, weight, Body Mass Index (BMI), education, systolic blood pressure, diastolic blood pressure, and uric acid levels.

Before proceeding to the procedures, informed concent was given to the participants regarding the purpose, procedures, potential risks, as well the as benefits of this research. After obtaining signed informed consent, venous blood samples are collected from pregnant women with normal pregnancies and those with preeclampsia, with gestational age above 20 weeks, both in inpatient and outpatient settings. This is done to examine the uric acid levels in the blood.

Univariate analysis techniques are employed to determine the frequency of each variable under investigation. The variables in this study include the elevation of uric acid levels and the occurrence of preeclampsia. Bivariate analysis is conducted on two variables suspected to be related using a T-Test with a confidence level of 95% ($\alpha = 0.05$) to conclude the presence of a significant difference between the two variables in the study.

RESULTS

This research was carried out at a Regional General Hospital in Surabaya, Indonesia. The primary data used were 10 blood samples from normal pregnant women as the control group and 10 blood samples from pregnant women with preeclampsia as the case group. From this study, descriptive statistical results were obtained, indicating that the average values of characteristics such as age, systolic blood pressure, diastolic blood pressure, weight, height, and BMI in the case group (pregnant women with preeclampsia) were recorded to be higher compared to the control group (normal pregnant women) This study indicates that the average value in the normal pregnant women group is recorded to be lower (2.11) compared to the group of pregnant women with preeclampsia (4.0) (Table 1).

The normality test used in this study is the Shapiro-Wilk test. This is because the sample size used in the research is less than 50 data (a total of 20 samples). The decision on normality testing can be determined based on the significance value, where the Shapiro-Wilk test indicates a normal distribution if $p > 0.05$. The significance values obtained in this study are 0.142 for the normal group and 0.064 for the preeclampsia group (>0.05). Therefore, the data obtained can be categorized as normally distributed. Consequently, the subsequent test to be conducted is a parametric statistical test (Table 2).

After obtaining the results from the normality test of the data, the next step involves a parametric statistical test, namely the independent samples t-test. The purpose of this test is to determine whether there is a significant difference between two groups of data that have a normal distribution.

The significance level of the T-Test is $\alpha = 0.05$. The results of the parametric test show a Sig. (2-tailed) value greater than the significance level, which is $0.003 > \alpha = 0.05$. Therefore, it can be stated that in this study, a significant difference was found between the uric acid levels of pregnant women with preeclampsia and normal pregnant women (Table 3).

DISCUSSION

The average systolic blood pressure obtained from this study is 102.1 mmHg in the control group and higher in the case group, at 156.1 mmHg. Previous research investigating a similar matter found a rapid increase in systolic blood pressure in 54 studied patients with preeclampsia, with 96% of those cases even exceeding 160 mmHg [14].

The average value of diastolic blood pressure in the control group is 66.3 mmHg, and 99.2 mmHg in the case group. Another study had compared 81 cases of preeclampsia and 81 cases of normal pregnancy using logistic regression on diastolic blood pressure ($p=0.000$; OR=85.957; 95%CI=17.655-418.496), indicates that diastolic blood pressure exceeding 80 mmHg has an 85.95 times higher risk of preeclampsia compared to pregnant women with lower diastolic blood pressure [15].

In addition to blood pressure, age is a dominant risk factor for the occurrence of preeclampsia [15]. In this study, the mean score in preeclampsia group is 32.6 y.o. which is higher than the normal group (28.3 y.o.). The mean score of the body weight (81.3 kg) and height (158.7 cm) in preeclampsia was also found to be higher than that of the control group (52.95 kg and 151.47 cm respectively).

This results in the difference between the body mass index of the two groups. The Body Mass Index (BMI) in the control group is 23.122, while in the case group, it indicates a higher figure, specifically 32.4. These results align with a systematic review and meta-analysis done in 2019, involving 5,946 samples from 16 different case studies, showing a significant difference between the two groups [16]. Therefore, measuring BMI can be an effective way to help diagnose preeclampsia.

The average uric acid levels in pregnant women with preeclampsia in this study were recorded to be higher (4.5 mg/dL) compared to the uric acid levels in normal pregnant women (2.1 mg/dL). Until now, there are many biomarkers that can be used for the early diagnosis of preeclampsia. However, the selection of biomarkers cannot only be linked to biological characteristics in the pathogenesis of the disease but also to their feasibility as screening tools.

A previous study has used uric acid as a biomarker to predict the occurrence of preeclampsia in Argentina, showing a significant increase compared to normal pregnancies [17]. The role of uric acid in early diagnosis of preeclampsia is also supported by other relevant studies in the previous years, especially since the research results indicate a significant increase in uric acid levels in the preeclampsia group ($p<0.05$) [13, 18].

Despite the research results in various studies indicating a significant increase, the clinical benefits of elevated uricacid levels as an indication of disease severity are still debated and have not been used as a definitive predictor up to this date [12].

CONCLUSIONS

This study shows a significant increase in uric acid levels between pregnant women with preeclampsia and normal pregnant women.

DECLARATIONS

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Conflict of interest: No conflict of interest to be disclosed

Ethical approval: This research has obtained a permit from the National Unity and Politics Agency (Badan Kesatuan Bangsa dan Politik) with approval number 070/7145/209/2023. All procedures involving research subjects were conducted following the guidelines specified in the ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine Ciputra University (Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Ciputra), approval number 054/EC/KEPK-FKUC/VII/2023. All participants provided written consent before participating in this study.

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Table 1: Demographic Characteristics

Variable	**Preeclampsia (N = 10)**	**Normal (N = 10)**
Age	32.6 ± 4.142	28.3 ± 4.739
Systolic BP	156.1 ± 16.482	102.1 ± 10.754
Diastolic BP	99.2 ± 5.903	66.3 ± 8.097
Weight	81.3 ± 7.1188	52.96 ± 6.9069
Height	158.7 ± 6.6508	151.470 ± 6.1678
BMI	32.4 ± 3.76445	23.122 ± 2.66038
Uric acid	4.5 ± 1.8306	2.11 ± 0.8465

Table 2: Saphiro-Wilk Normality Test

	Preeclampsia (N = 10)	**Normal (N = 10)**
Statistic	0.142	0.883
Sig.	0.064	0.854

Table 3: T-Test

	Equal variances assumed	**Equal variances not assumed**
T-Test	-3.747	-3.747
Sig. (2-tailed)	0.001	0.03