



## ANALYZING URIC ACID CONCENTRATION AS A TOOL TO DIAGNOSE PREECLAMPSIA

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ABSTRACT	Keywords
<p>Preeclampsia is a hypertensive disorder that occurs during pregnancy. So far, uric acid levels have been used as a guide to diagnose preeclampsia. Uric acid is a by-product of metabolism and its levels in the blood can be influenced by various factors, including kidney function and eating habits. This research is an observational study with a prospective approach. In this study, 258 pregnant women were involved at the Wonoasih Community Health Center and Jorongan Community Health Center from March to June 2023. Laboratory examinations were carried out to measure the serum uric acid levels of the research subjects. statistical tests of differences were carried out using SPSS. In pregnant women who suffered from preeclampsia before 34 weeks of gestation and after 37 weeks of gestation with a fetus that was not developing, a significant increase in uric acid levels was found with a Phi coefficient of 0.090 and a contingency test of 0.087. The cut-off point for the uric acid ratio (UAr) test is 1.5, where pregnant women who have been diagnosed with preeclampsia in the 1st trimester of pregnancy have a higher UAr value. The results of the data analysis p value were 0.918 [95% confidence interval (CI): 0.858–0.979) in the group of pregnant women with preeclampsia; This means that uric acid can be a tool for diagnosing preeclampsia in pregnant women.</p>	<p><i>Uric Acid levels, Diagnosis, Preeclamsia</i></p>

### INTRODUCTION

Preeclampsia is a pregnancy specific multisystem disease whose cause is unclear. With a very varied clinical picture, this disease reached 1,066 cases of hypertension reported as part of the causes of maternal and neonatal deaths in Indonesia (Kemenkes R1, 2020). And is the first cause of maternal death in 2021 (Dinkes Prov Jatim, 2022).

The effects of this syndrome extend beyond pregnancy and can cause long-term vascular and metabolic problems, as well as a heightened risk of cardiovascular disease in both mother and fetus (Benagiano et al., 2021). Pregnancy problems and their long term effects can be minimized by early

discovery and referral to a high-complexity center, even though this condition is incurable. Unfortunately, preeclamptic women are currently not recognized until after the development of clinical symptoms, which significantly complicates patient care (Mutlara Putri & Ismiyatun, 2020; Peck Palmer & Das, 2020).

It is still difficult to identify which women are at risk of getting preeclampsia due to the severe repercussions of this illness. There are now a number of interesting biomarkers that have been found that may be utilized to diagnose a patient early. Biomarkers are used as indicators of the biological response to exposure and are

used to predict, diagnose, and monitor disease (Daniel et al., 2018). Pro-angiogenic factors like placenta growth factor (PlGF) and vascular endothelial growth factor (VEGF) as well as anti-angiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) have shown some utility in the diagnosis and prediction of preeclampsia (Andalas & Harahap, 2017; Sello, 2019; Zulkarnain, 2018). Even though the choice of biomarkers as markers has been proven to be reliable in its role in showing the pathophysiology of disease, in terms of the costs that must be incurred by a client, the cost benefit is not appropriate. Therefore, uric acid levels are an indicator of preeclampsia in addition to high blood pressure and organ damage (Mark et al., 2018).

Increases in uric acid levels and blood pressure have long been recognized as indicators of preeclampsia, including indicating the severity of preeclampsia (Ganie et al., 2021; Sello, 2019). In uncomplicated pregnancies, serum uric acid levels decrease 25 to 35% due to hypervolemia, increased renal blood flow, glomerular filtration rate, and the uricosuric effects of estrogen (Abbas et al., 2020; Haribaik et al., 2022), which, at 35 weeks of gestation, will slowly increase to close to  $5.1 \pm 1.2$  mg/dl until the end of the pregnancy period (Laughon et al., 2011; Amini et al., 2014).

The level of uric acid concentration that is considered to influence the activity of the renin-angiotensin system, which leads to an increase in blood pressure, is still a matter of debate (Mule et al., 2016; McMullan et al., 2017; Scheepers et al., 2017). Serum uric acid levels are important for monitoring high blood pressure in pregnancy, but they're not very reliable or predictive (Chen et al., 2016; Pecoraro & Trenti, 2020a). Some studies also suggest that proteinuria alone may not be a good predictor of the health outcome of preeclampsia (Dong et al., 2017; Henderson et al., 2017; Garovic et al., 2022). Because it is possible that there are other variables that could confound the conclusions of the results of checking uric acid levels, such as maternal age, gestational age, BMI, kidney disease/disorder (Norden et al., 2000;

Haribaik et al., 2022; Hong C et al., 2022; Colmenares-Mejia et al., 2023).

In recent times, there have been suggestions that the hyperuricemia linked to preeclampsia could also be attributed to elevated oxidative stress and reactive oxygen species production (Kumari, 2021; Niyongabo Niyonzima et al., 2021). However, because uric acid interacts with proinflammatory cytokines, elevated uric acid levels in preeclamptic patients' plasma may suggest that the acid directly contributes to the pathophysiology of this disease by inducing inflammation (Dakhil et al., 2023; Zha X et al., 2022). However, in clinical practice, to date, at both primary and tertiary health care levels, the majority of patients with gestational hypertension will be diagnosed with preeclampsia based on the presence of proteinuria.

The description above shows that there is still a diagnostic dilemma because proteinuria can reflect other conditions of pregnant women such as chronic hypertension, kidney disorders or diseases, or whether it is pure preeclampsia. The aim of this study was to examine the increase in uric acid levels during pregnancy, its predictive value in identifying the possibility of preeclampsia in pregnant women with IUGR and pregnant women in terms of age, gestational age, BMI, and maternal blood pressure.

## METHOD

A prospective observational study was conducted to investigate the behavior of serum uric acid levels during pregnancy and determine their predictive utility in predicting the development of preeclampsia. This approach was chosen because the researcher will only observe without providing intervention, and the data obtained will have to go through an observation process from time to time. The study involved 258 pregnant women by using quota sampling technique. Women with chronic hypertension, comorbid diseases and multiple pregnancies were not included in this study. All subjects provided written informed consent. This research was carried out at the Wonoasih and Jorongan

Community Health Centers from March to June 2023.

Uric acid levels in pregnant women without comorbidities will change after the gestational age enters the second and third trimesters of pregnancy, namely around more than 20 weeks of gestation (Ayu & Isaac, 2019). To examine the rise in uric acid levels throughout pregnancy, we divided pregnant women based on maternal age, gestational age, BMI, increase in blood pressure. In addition, pregnant women will be grouped based on the onset of preeclampsia.

Each pregnant woman's serum samples were collected during pregnancy and kept at 20-25°C for analysis (Intantri & Alivameita, 2023; Palupi, 2021). Gestational hypertension and Preeclampsia were defined on the basis of the following criteria Hypertension in Pregnancy Clinical Guideline – Women's Health and ACOG (ACOG, 2019; Women's Health, 2018).

Pregnant women who initially had normal blood pressure but after 20 weeks of gestation experienced persistent high diastolic blood pressure increases of 140 mmHg and/or 90 mmHg on two separate occasions (at least 6 hours apart after the 20th week of pregnancy) without proteinuria. Preeclampsia was defined as systolic blood pressure (140 mmHg) or diastolic blood pressure (90 mmHg) with proteinuria ( $\geq 0.3$  g/d) or 2 ++ (on urine dipstick test) after 20 weeks of pregnancy previously without hypertension.

Serum uric acid was measured using an enzymatic diagnostic kit and urine dipstick test, according to the manufacturer's protocol. The reference value for women is 2.4–5.6 mg/dL Changes in uric acid according to standard uric acid levels in pregnant women without complications (Ghanavati et al., 2009; Grünebaum, 2019). Meanwhile, blood pressure will be measured with an aneroid sphygmomanometer (Bhatt et al., 2016).

The results of checking blood pressure and uric acid levels of pregnant women are recorded on an observation sheet which will then be analyzed using SPSS with a two-

sample T test and if the data does not meet the requirements for a T test, the Wilcoxon signed rank test will be used. This test is carried out to compare two independent groups whether they have statistically significant different results. The correlation between pregnant women's variables: maternal age, gestational age, BMI, increase in blood pressure and uric acid levels will be tested using descriptive analysis and analysis using the Chi-Square technique and to determine the strength of the association between variables measured by conducting independence tests on the size of the association, namely: phi coefficient ( $\Phi$ ) and Pearson contingency coefficient (P). The significance level was set at  $P < 0.05$ .

## RESULTS

Of the 258 pregnant women who had their pregnancies checked at the Jorongan and Wonoasih Community Health Centers: From of all the pregnant women who returned and had to be excluded because they met the inclusion criteria 107 were pregnant women without pregnancy complications, 59 were pregnant with gestational hypertension, 83 were preeclampsia, and 8 were disturbed fetal growth and development (**table 1 & 2**).

Researchers assessed the amount of uric acid in serum during pregnancy. Serum uric acid levels in women with preeclampsia increase drastically compared to pregnancies that did not previously suffer from hypertension. The increase in uric acid levels in pregnant women with gestational hypertension at a gestational age of more than 37 weeks is not significant. Pregnant women with IUGR fetuses also did not show a significant increase in uric acid levels compared to pregnant women without complications (**table 1**). This is different from research results which state that uric acid levels in pregnant women have a significant correlation with the incidence of IUGR (Le et al., 2019; Liu et al., 2019).

There was no correlation between Uric Acid and parity ( $p=0.256$ ) or women's BMI ( $p=0.303$ ).

**Table 1. Population Characteristics**

	Uncomplicated pregnancies	Gestational hypertension	Preeclampsia	IUGR without preeclampsia
<i>n</i>	107	56	78	8
Maternal age (years)	19.54 ± 5.71	24.6 ± 7.6	20.87 ± 7.9	30.6 ± 6.54
Gestational age (weeks) <sup>1</sup>	36.72 ± 3.44	33.85 ± 2.88	38.1 ± 2.03	35.7 ± 1.05
Birth weight (g)	3138.9 ± 455.6	2803.6 ± 778.3	2826.0 ± 781.3	2041.6 ± 659.22***
Body mass index (BMI), kg/m <sup>2</sup>	25.1 ± 5.9	28.6 ± 7.9	29.21 ± 8.9	24.13 ± 5.44
Systolic blood pressure (mmHg)	110.0 ± 4.1	152.6 ± 6.7***	155.10 ± 5.3***	140.2 ± 4.5
Diastolic blood pressure (mmHg)	75.1 ± 1.5	100.0 ± 3.8***	101.1 ± 8.4***	67.3 ± 5.2
Proteinuria <sup>2</sup>	Negative	+	Negative	Negative

**Table 2. Characteristics based on the incidence of preeclampsia**

Preeclampsia	<i>n</i>	Gestational age (weeks)	Birth weight (g)
Gestational age <34 wks	23	23.07 ± 1.48	2422.6 ± 501.4
Gestational age between 34 & 37 wks	33	38.88 ± 1.68	2530.0 ± 201.0
Gestational age >37 wks with IUGR	5	27.08 ± 0.75	2105.8 ± 94.9
Gestational age >37 wks without IUGR	17	34.42 ± 1.62	3299.7 ± 472.7

Likewise, the correlation between uric acid and maternal age is shown by the results of the Phi coefficient statistical test (0.090) and the contingency test (0.087) even though the *p* value is 0.009.

In this study, uric acid levels were found to be higher than 1.5 in pregnant women with gestational hypertension and pregnant women who experienced preeclampsia. If seen based on when the first clinical symptoms appeared; So the group of mothers who experienced preeclampsia before 34 weeks of gestation and the group of mothers who experienced preeclampsia after 37 weeks of gestation with IUGR were the groups that had the highest uric acid levels (**Table 3**). Meanwhile, in the gestational age group of more than 37 weeks with IUGR or without IUGR, uric acid levels only increased after gestational age above 30 weeks (**table 4**).

**Table 3. Uric acid ratio (UAr)**

	Uric Acid ratio (UAr)			
	Stage 2/1	Stage 3/1	Stage 4/1	
Uncomplicated pregnancies	1.12 ± 0.02	1.22 ± 0.02	1.31 ± 0.03	±
Preeclampsia	1.63 ± 0.18	1.79 ± 0.21	2.17 ± 0.22	±

Gestational Hypertension	1.32 ± 0.18	1.49 ± 0.17	1.67 ± 0.22	±
IUGR without PE	1.14 ± 0.07	1.36 ± 0.02	1.37 ± 0.11	±

The table above states that if a pregnant woman has been diagnosed with preeclampsia since the beginning of pregnancy, then her uric acid level will exceed 1.5. And if a pregnant woman suffers from gestational hypertension, her uric acid level will be higher than 1.5 at the end of pregnancy. However, in pregnancies without complications and healthy fetuses, the uric acid level value is lower than 1.5 in pregnancy.

The results of data analysis show that uric acid can be a tool to diagnose preeclampsia in pregnant women diagnosed with preeclampsia at a gestational age of more than 34 weeks with a statistical test value of 0.918 [95% confidence interval (CI): 0.858–0.979] for the preeclampsia group and 0.955 (95% CI: 0.908–1.000) for the group of pregnant women who had been diagnosed with preeclampsia at <34 weeks' gestation.

**Table 4. Uric acid ratio (UAr) in females with various preeclamptic presentations.**

	Uric Acid ratio (UAr)			
	Stage 2/1	Stage 3/1	Stage 4/1	
Uncomplicated pregnancies	1.22 ± 0.12	1.25 ± 0.18	1.80 ± 0.20	±
PE Gestational age <34 wks	1.85 ± 0.47	2.33 ± 0.47	0.46 ± 0.12	±
PE Gestational age between 34 & 37 wks	1.38 ± 0.62	1.91 ± 0.38	1.68 ± 0.26	±
PE age >37 wks with IUGR	1.83 ± 0.56	1.96 ± 0.58	2.78 ± 0.68	±
PE Gestational age >37 wks without	1.40 ± 0.36	1.72 ± 0.28	2.12 ± 0.58	±

Statistical test results show the uric acid ratio in the uric acid analysis test which is used as a diagnostic tool to help confirm the diagnosis of preeclampsia, showing differences in uricemia between pregnant women who do not experience complications and those who experience preeclampsia complications. However, the accuracy of the uric acid level test results in helping to establish preeclampsia is better in the group of pregnant women who are suspected of suffering from preeclampsia at a gestational age of <34 weeks.

## DISCUSSION

Elevated uric acid levels have long been believed to pose serious health risks for pregnant women. These risks are very detrimental to the mother and fetus, such as gestational hypertension, preeclampsia, gestational diabetes mellitus, premature birth, and IUGR.

Preeclampsia is the most severe occurrence of hypertension in pregnancy. Preeclampsia According to ACOG guidelines, occurs when: the patient meets or exceeds the criteria for hypertension and has a protein level in the urine of more than 300mg or 1+ on urine protein examination with a dipstick (ACOG, 2019).

In vitro research, elevated uric acid decreases endothelial cell proliferation and migration, which could lead to poor placental development, and ultimately preeclampsia (Hu et al., 2022).

In vivo mouse trials, it was concluded that an increase in serum uric acid could cause hypertension through activation of ENaC (epithelial sodium channel) and regulation of ERC (ENaC Regulatory Complex) expression (Xu et al., 2016).

Renin-angiotensin system activation along with uric acid-mediated renal vasoconstriction, which was caused by a decrease in nitric oxide levels in endothelial cells, led to the development of hypertension. Although we showed that maternal renal function has a significant impact on hyperuricemia, we did not go into this association in further detail in our study.

The use of uric acid levels as a prognostic tool for preeclampsia is approved in many studies, but there are also those who argue that

the positive diagnostic value is low (Chen et al., 2016; Abbas et al., 2020; Ugwuanyi et al., 2021); other research indicates that high uric acid is a predictor that cannot be used to predict the outcomes of parents and fetus (Pecoraro & Trenti, 2020b).

In the current investigation, we found that in women with straightforward pregnancies, uric acid levels started out lower—between 25 and 35%—than in women who were not pregnant. They subsequently gradually grew and reached their peak at the end of the pregnancy. similar principles as women who are not expecting. Experimental research; estrogen-progesterone can significantly reduce serum uric acid levels (Jung et al., 2017).

Calculating serum uric acid levels before and after 20 weeks of gestation needs to be done considering the variability of uricemia because if the ratio is greater than 1.5 then it is necessary to pay attention to the possibility of preeclampsia (Meena et al., 2019).

This is a prospective study to evaluate the diagnostic results of uricemia as a diagnostic tool for preeclampsia. However, one of our biggest research challenges is the lack of pregnant women as research subjects, especially in various subgroups. We found that all pregnant women diagnosed with preeclampsia had increased serum uric acid levels. However, the rate of increase in uric acid levels depends on the severity of the disease. So, in women who experienced preeclampsia before 34 weeks of gestation or in women who experienced preeclampsia after 37 weeks of gestation with IUGR, uric acid levels were found to increase significantly. Meanwhile, in pregnant women who experience preeclampsia after 34 weeks of gestation without IUGR, uric acid levels increase at the end of pregnancy.

In pregnant women without complications of preeclampsia and fetuses experiencing IUGR, uric acid levels are within normal limits. and this is in accordance with research which states that increased uric acid levels are associated with maternal endothelial dysfunction and worsen the systemic inflammatory response in preeclampsia (Redman et al., 2022).

For this reason, it is necessary to add other supporting examinations such as



ultrasound and other biochemical examinations in monitoring pregnant women with preeclampsia and IUGR.

Based on the curve in Figure 1, it is shown that a uricemia ratio of less than 1.5 is a parameter that has high sensitivity for diagnosing preeclampsia in pregnant women. There's more and more evidence indicates that high blood and uric acid during pregnancy have a role in the pathophysiology maternal and fetal as a marker of preeclampsia.

## CONCLUSIONS

With knowledge of the effects of uric acid on the endothelium, oxidative stress, inflammation and the pathogenesis of preeclampsia; strengthens the belief that monitoring uric acid levels can help prognosticate preeclampsia.

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