



URIC ACID LEVEL AS A PREDICTOR OF SEVERITY IN PREGNANT WOMEN WITH SEVERE PREECLAMPSIA

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KEYWORDS :

I. BACKGROUND

Preeclampsia is a pregnancy syndrome affecting multiple organ systems, characterized by hypertension and proteinuria after 20 weeks of gestation. The incidence of preeclampsia is estimated to be 3-10% of pregnancies worldwide and is the leading cause of death for pregnant women. Preeclampsia is a life-threatening obstetric emergency, so it needs prompt and precise treatment to prevent morbidity and mortality. WHO estimates that the incidence of preeclampsia is seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%).^{1,2}

Many pregnant women who come to the hospital are complications of advanced hypertension as severe preeclampsia, even accompanied by haemolysis elevated liver enzyme low platelets count (HELLP) or eclampsia syndrome, so the management is still not satisfactory. Management of this disease will give better results if it can be treated as early as possible.³

Some literature says that in pregnant women with preeclampsia there can be hemodynamic changes, decreased blood flow to the kidneys, a 50% reduction in glomerular filtration rate, increased sensitivity to vasopressors, decreased renin-angiotensin, and decreased prostaglandin E levels, leading to decreased acid excretion. veins due to increased reabsorption in the proximal tubule. Preeclampsia generally begins with hyperuricemia, which is an increase in uric acid levels before causing the onset of clinical manifestations in early pregnancy. Women with preeclampsia tend to have high uric acid, hemoglobin and creatinine levels and low platelet counts, as well as a higher risk of cesarean section.^{4,5}

Uric acid is a product of purine degradation catalyzed by the enzyme xanthine oxidase. Uric acid is a potential mediator of inflammation. Uric acid stimulates monocytes to produce proinflammatory cytokines IL-1 β , IL-6, TNF- α . Gout causes endothelial dysfunction which can promote hypertension, vascular disease and kidney disease. Increased serum uric acid levels in pregnant women who have risk factors for preeclampsia will occur 2–4 weeks before clinical symptoms appear. Uric acid is one of the most sensitive indicators of severity in pregnancies with hypertensive disorders and is very helpful in monitoring the disease process. Several studies have shown a correlation between increased maternal serum uric acid increases in adverse maternal and fetal outcomes.^{6,7}

II. AIM

This study aims to determine uric acid levels as a predictor of severity in pregnant women with severe preeclampsia who are admitted to the ICU RSUP H. Adam Malik Medan, in order to

obtain a biomarker that can be used to predict the severity of pregnant women with severe preeclampsia that is more accessible at a lower cost, can be a consideration in the management of severe preeclampsia patients. and can be used in simple facilities without compromising accuracy.

III. RESEARCH METODE

The study was conducted at the Department of Clinical Pathology, Faculty of Medicine, University of North Sumatera /RSUP Haji Adam Malik Medan in collaboration with the Department of Obstetrics And Gynecology at the Faculty of Medicine, University of North Sumatera. This study was an observational study with a cross sectional design. The study was conducted in August 2020 until November 2020. The research subjects are female patients who were cared for at the RSUP H. Adam Malik Hospital and Madani Hospital who was diagnosed with severe preeclampsia.

The sample size in this study was determined as many as 30 samples. The inclusion criteria in this study were pregnant women who were diagnosed with severe preeclampsia and were willing to attend the study who were treated at the RSUP H. Adam Malik Medan and Madani Hospital Medan. The exclusion criteria were pregnant women with high uric acid before pregnancy, pregnant women with chronic diseases (eg hypertension) and pregnant women with kidney disorders.

Complete blood count using Sysmex XN-1000 uses the principle of a combination of electric impedance and flow cytometry, and urinalysis uses the Sysmex XU 2000 where this tool uses the principle of flowcytometry. This tool is a fully automated integrated urine analyzer (UX-2000) which includes strip test methods for urine biochemistry and fluorescence flowcytometry (FCM) for urine sediment particles (erythrocytes, leucocytes, squamous epithelial cells, small round cells, cylinderhialin and pathological, crystals), yeast-like cells, sperm, bacteria) quantitatively, standardized without the need to rotate the urine. uric acid is only done once in pregnant women with severe preeclampsia. Examination of uric acid using serum was examined using an automatic analysis tool Architect Plus C1 8200 with enzymatic principles

IV. STATISTIC ANALYSIS

Data analysis was performed using SPSS (Statistical Package for Social Sciences) software. Characteristics of the research subjects are presented in tabulated form and described. Correlation of uric acid levels as a predictor of the severity of patients with severe preeclampsia was used the Pearson correlation test if the data were normally distributed. If the data are not normally distributed, the Spearman rank test is used. All statistical tests with p value <0.005 were considered significant.

V. RESULT

This study was attended by 30 pregnant women with

preeclampsia who came to the Polyclinic and inpatient treatment of the Department of Obstetrics and Gynecology at RSUP H. Adam Malik Medan from August 2020 - November 2020, who had met the inclusion and exclusion criteria. The mean age of the subjects was 31.73 years with mean body weight and height of 68.6 kg and 61.33 cm, respectively. Blood pressure examination showed a mean systolic blood pressure of 161.33 mmHg and a diastolic blood pressure of 103.33 mmHg. The mean gestational age of the subjects was 36.8 weeks with the mean birth weight of the babies born was 2920 grams. The largest subject tribe is Mandailing, amounting to 17 people (56.7%). The majority of subjects performed ANC (Ante Natal Care) in 24 midwives (80%) and 3 people (10%) at Public health centre and Hospitals. Generally, 26 subjects did not have a history of hypertension in the family (86.7%). All subjects gave birth by sectio area. Most children born with an APGAR score of 7/8 are 21 (70%).

Table 1. Subject Characteristics

Karakteristik Subyek	n = 30
Age, mean (SD), years	31,73 (6,29)
Body weight, mean (SD), kg	68,6 (8,62)
Height, mean (SD), cm	154,87 (4,84)
Systolic Blood Pressure, mean (SD), mmHg	161,33 (26,88)
Diastolic Blood Pressure, mean (SD), mmHg	103,33 (7,58)
Gestational Age, mean (SD), weeks	36,8 (1,27)
Birth weight, mean (SD), grams	2920 (328,42)
Ethnic group, n (%)	
Batak	4 (13,3)
Jawa	5 (16,7)
Karo	2 (6,7)
Mandailing	17 (56,7)
Padang	2 (6,7)
ANC, n (%)	
Tocologist	24 (80)
Public health center	3 (10)
Hospital	3 (10)
Family History of Hypertension, n (%)	
Father	3 (10)
Mother	1 (3,3)
No history of hypertension	26 (86,7)
Mode of Delivery	
Sectio Secarea	30 (100)
APGAR Score, n (%)	
0/0	2 (6,7)
4/5	1 (3,3)
6/7	2 (6,7)
7/8	21 (70)
8/9	4 (13,3)

The results of blood and urine tests are shown in table 4.2. Mean hemoglobin was 12 g / dL. The mean hematocrit was 5.48%. The mean leukocytes and platelets were 15.87 thousand / μ l and 264.43 thousand / μ l, respectively. From the results of urine protein examination, the most subjects were proteinurin +1 as many as 12 people (40%), then +2 as many as 11 people (36.7%) and +3 as many as 7 people (23.3%). The mean uric acid in the subjects was 7.43 mg / dL. A total of 23 patients (76.7%) had severe preeclampsia.

Table 2. Blood and Urine Laboratory Examination Results

Result	n = 30
Hemoglobin, mean (SD), g/dL	12 (1,46)
Hematokrit, mean (SD), %	35,48 (3,71)
Leukocytes, mean (SD), thousand / μ l	15,87 (5,61)
Platelets, mean (SD), thousand / μ l	264,43 (92,42)
Proteinuria, n (%)	
+1	12 (40)
+2	11 (36,7)
+3	7 (23,3)

Eclampsia Rate, (%)	
Pre-Eclampsia Severe	23 (76,7)
Pre-Eclampsia not Severe	7 (23,3)
Uric acid, mean (SD), mg/dL	7,43 (2,55)

Table 3. Characteristics of Subjects Based on Level of Preeclampsia

Characteristics of Subjects	Preeclampsia		p
	severe (n = 23)	Not severe (n = 7)	
Age, mean (SD), tahun	30,7 (5,82)	35,14 (7,01)	0,102 ^a
Body weight, mean (SD), kg	68,78 (9,57)	68 (4,80)	0,924 ^b
Height, mean (SD), cm	154,87 (5,21)	154,86 (3,72)	0,995 ^a
Sistolik Blood Pressure, mean (SD), mmHg	170 (15,67)	147,14 (4,88)	<0,001 ^b
Diastolik Blood pressure, mean (SD), mmHg	105,65 (6,62)	95,71 (5,35)	0,003 ^b
Gestational age, mean (SD), minggu	36,7 (1,40)	37,14 (0,69)	0,265 ^a
Birth weight, mean (SD), gram	2943 (344,87)	2842,86 (276,03)	0,656 ^b
Ethnic group, n (%)			
Batak	2 (8,7)	2 (28,6)	0,053 ^c
Jawa	2 (8,7)	3 (42,9)	
Karo	2 (8,7)	0	
Mandailing	16 (69,6)	1 (14,3)	
Padang	1 (4,3)	1 (14,3)	
ANC, n (%)			
Tocologist	17 (73,9)	7 (100)	0,332 ^a
Public Health Centre	3 (13)	0	
Hospital	3 (13)	0	
Family History of Hypertension, n (%)			
Father	1 (4,3)	2 (28,6)	0,167 ^c
Mother	1 (4,3)	0	
No History of Hypertension	21 (91,3)	5 (71,4)	
Mode of Delivery			
Sectio Secarea	23 (100)	7 (100)	-
APGAR Score, n (%)			
0/0	2 (8,7)	0	0,775 ^c
4/5	1 (4,3)	0	
6/7	2 (8,7)	0	
7/8	15 (65,2)	6 (85,7)	
8/9	3 (13)	1 (14,3)	
Hemoglobin, mean (SD), g/dL	12,03 (1,65)	11,91 (0,53)	0,773 ^a
Hematokrit, mean (SD), %	35,43 (4,16)	35,64 (1,79)	0,895 ^a
Leukocytes, mean (SD), ribu/ μ l	16,96 (5,74)	12,27 (3,39)	0,051 ^a
Platelet, mean (SD), ribu/ μ l	254,35 (94,03)	297,57 (84,8)	0,249 ^b
Proteinuria, n (%)			
+1	7 (30,4)	5 (71,4)	0,111 ^c
+2	9 (39,1)	2 (28,6)	
+3	7 (30,4)	0	

Table 4.4 presents a description of the uric acid data in the subject group with severe and not severe preeclampsia. The mean uric acid in the subject group with severe preeclampsia was 7.98 mg / dL (SD = 2.63 g / dL) with the lowest level being 4.2 g / dL and the highest level being 6.3 mg / dL. Meanwhile, in the group of preeclamptic subjects who were not severe it had a mean of 5.64 mg / dL (SD = 1.09 mg / dL) with the lowest level being 4.6 mg / dL and the highest level being 7.4 mg / dL.

Tabel 4. Relationship between Uric Acid Levels and Preeclampsia Severity

	Preeclampsia		p
	severe (n = 23)	Not severe (n = 7)	
Asam Urat, mg/dL			

Mean	7,98	5,64	0,009
SD	2,63	1,09	
Median	7,7	5,6	
Min – Max	4,2 – 16,3	4,6 – 7,4	

Using the Mann Whitney test showed that there was a significant relationship between uric acid levels and the severity of preeclampsia ($p = 0.009$; $p < 0.05$).

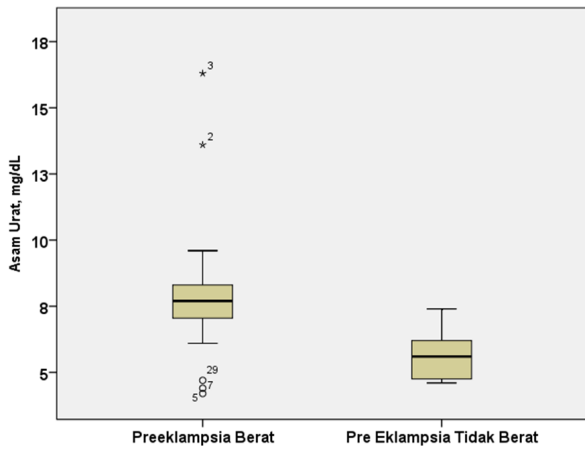


Figure 1 Boxplot Graph of Uric Acid Levels Based on the severity of preeclampsia

Based on the results of the analysis with the ROC curve, it shows that uric acid levels can predict the severity of preeclampsia in pregnant women. The AUC obtained was 83.2% (95% CI = 68.5% - 98%).

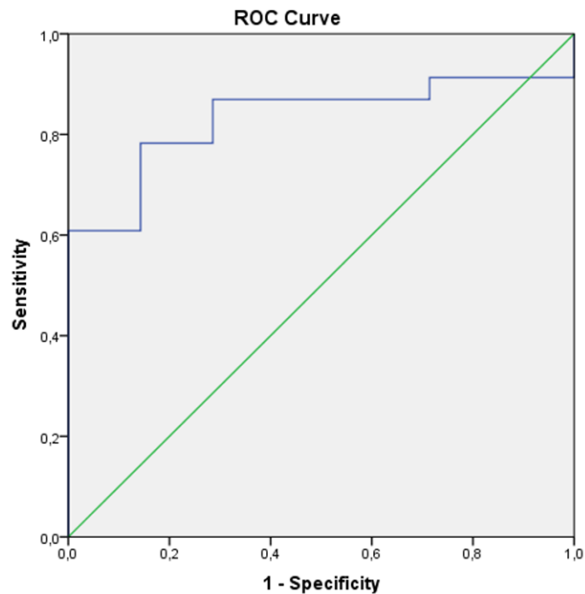


Figure 2 ROC curve of uric acid levels on the severity of preeclampsia

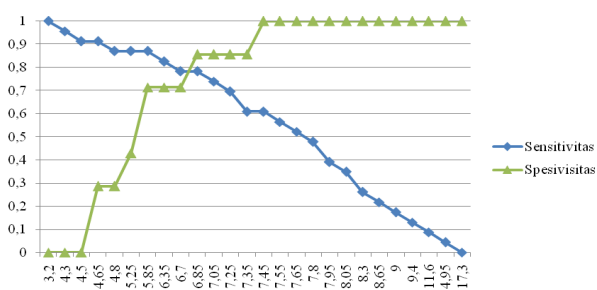


Figure 3 Sensitivity and specificity curves of uric acid levels on the severity of preeclampsia

Based on the sensitivity and specificity curves in Figure 3, the Cut Off Point (CoP) value for uric acid levels in this study was 6.85 mg / dL. By using CoP6.85 mg / dL, the sensitivity and specificity values of uric acid levels to the severity of preeclampsia were 78.3% and 85.7%, respectively. The Positive Predictive Value (NPP) of uric acid levels was 94.7% and the Negative Predictive Value (NPN) was 54.5% with an accuracy value of 80%.

Table 5. Sensitivity, specificity, positive and negative predictive value of uric acid levels on the severity of preeclampsia

Uric acid, mg/dL	Severity of Preeclampsia		Sens.	Spes.	NPP	NPN
	Severe	Not severe				
$\geq 6,85$	18	1	78.3 %	85.7 %	94.7 %	54.5 %
$< 6,85$	5	6				

VI. DISCUSSION

This study was attended by 30 pregnant women, the mean age of the subjects was 31.73 years with a mean weight and height of 68.6 kg and 61.33 cm, respectively. Blood pressure examination showed a mean systolic blood pressure of 161.33 mmHg and a diastolic blood pressure of 103.33 mmHg. The mean gestational age of the subjects was 36.8 weeks. The characteristics of research subjects in this study include maternal age and parity. These characteristics are used because they act as a risk factor for the incidence of preeclampsia.

This is in line with a study conducted by Maryam et al 2017. Maternal serum uric acid level and maternal and neonatal complications in preeclamptic women: A cross-sectional study They conducted a study to investigate the relationship between uric acid levels and maternal and neonatal complications in women. with preeclampsia. In this cross-sectional study, 160 women with preeclampsia over 28 weeks' gestation were included. Checked hemoglobin, hematocrit, platelet count, liver function and uric acid, as well as maternal and neonatal complications. In this study, 160 female patients, 38 of whom were severe preeclampsia (23.8%) and 122 of whom were none (76.3%). The mean age of the participants was 31.18 ± 5.41 years. 14.4% (n = 23) had a history of hypertension before pregnancy and 71.3% (114) had albuminuria.⁸

Various research results regarding the effect of maternal age and parity on the incidence of preeclampsia have been suggested that young people and primigravidas have a greater risk of developing preeclampsia. The risk factors for preeclampsia are more common in primigravida, nulliparous, maternal age less than 25 years or more than 35 years, racial and ethnic factors, heredity (genetic), low education, low socio-economic factors, obesity, multiple pregnancy, hydramnios, hydrops fetalis, hydatidiform mole and a history of maternal diseases such as a history of hypertension, kidney disease, liver disease, and diabetes mellitus. The incidence increases with increasing gestational age.^{8,9}

In this study, the mean uric acid levels in women with severe preeclampsia were significantly higher than those with non-severe preeclampsia. The mean uric acid in the subject group with severe preeclampsia was 7.98 mg / dL (SD = 2.63 g / dL) with the lowest level being 4.2 g / dL and the highest level being 16.3 mg / dL. Meanwhile, in the group of preeclamptic subjects who were not severe it had a mean of 5.64 mg / dL (SD = 1.09 mg / dL) with the lowest level being 4.6 mg / dL and the highest level being 7.4 mg / dL.

This is in line with research conducted by Neli et al., 2013. Serum uric acid levels as a Preeclampsia Biomarker. They obtained the results of the study that the mean serum uric acid levels in the study subjects who experienced preeclampsia

were higher when compared to normal pregnancies, namely 7.37 mg / dL with a standard deviation of 2.67 and a median of 6.3. The mean serum uric acid level of normal pregnancy study subjects was 4.1 mg / dL with a standard deviation of 1.05 and a median of 4.2.¹⁰

In a study by Sultana et al 2013, which compared mean uric acid levels in subjects with normal blood pressure and preeclampsia, the results indicated that preeclampsia was associated with hyperuricemia.¹¹ Also, Gianni et al followed patients for a month after delivery and mentioned gout as a reliable predictor of preeclampsia in women with gestational hypertension. They showed uric acid with a cut-off of 309 mol / l as a predictor of preeclampsia.¹²

Hawkins et al 2012 reported that hyperuricemia in pregnant women with high blood pressure is an important finding that can expose women to adverse maternal and fetal complications. Even women with gestational hypertension, without other signs of preeclampsia will experience adverse embryonic complications such as Small Gestational Age and pre-maturity. In this study, uric acid was measured in the near term which is similar to the study we did.¹³

Previous studies have shown a significant association between hyperuricemia and adverse obstetric outcomes in pregnant women with hypertension, higher mean uric acid levels are associated with increased preterm births and consequently an increased need for NICU hospitalization. In a study conducted by James et al 2005, showed that women with hypertension and hyperuricemia had the same or higher risk than women with high blood pressure and proteinuria. Risks include a shorter gestation period, a lower percentile of birth weight, an increased risk of preterm birth.¹⁴

In this study with a 1 mg / dl increase in serum hemoglobin and creatinine, 1.6 and 1.06-fold increased risk of preterm birth. Meanwhile, other variables do not increase or decrease the likelihood of preterm birth in pregnant women with preeclampsia. However, a 1 mg / dl increase in hemoglobin and AST in pregnant women with preeclampsia, 1.6 and 1.022-fold increased risk of neonatal hospitalization in the NICU.¹⁵

Using the Mann Whitney test showed that there was a significant relationship between uric acid levels and the severity of preeclampsia ($p = 0.009$; $p < 0.05$). This is in line with research conducted by Zangana et al. 2018. Serum Uric Acid as a Predictor of Perinatal Outcome in Women with Preeclampsia. They conducted a cross-sectional study of 200 women with preeclampsia over 34 weeks of gestation. After informed concern, all patients were diagnosed with hypertension and proteinuria. Blood samples were obtained by assessing uric acid, in addition to other routine investigations and fetal examinations including (birth weight, gestational age, intrauterine mortality, Apgar score, admission to the neonatal care unit, intrauterine growth restriction and early neonatal death) were evaluated.^{16,17}

Their results: Serum uric acid ≥ 6 mg / dL in 127 (63.5%) among all pre-eclamptic women. There was a significant positive relationship between mean serum uric acid at various levels of hypertension and $p = 0.000$ in the ANOVA test. This study revealed a significant association between elevated serum uric acid levels and poor fetal growth outcomes (birth weight, gestational age, intrauterine mortality, Apgar score, neonatal admission to the intensive care unit, intrauterine growth restriction and early neonatal mortality and Apgar score in minutes. number 1). Their conclusions showed a significant increase in serum uric acid levels among preeclamptic women and a significant effect on fetal growth and increased perinatal morbidity and mortality.¹⁸

Serum uric acid levels in pregnant women are significantly reduced by about 25-30% from normal levels. Theoretically, serum uric acid levels during pregnancy are determined by several factors, including purine intake in food and metabolic production of uric acid by the mother and fetus, and excretion by the kidneys and gastrointestinal tract. Interference with one or more of these factors can change the serum uric acid level. In normal pregnancy there is a change in the hemodynamic system in the form of hemodilution due to the addition of a larger plasma volume. As a result of these hemodynamic changes, there is an increase in renal blood flow which increases the renal clearance for uric acid, urea, and creatinine.¹⁹

Serum uric acid levels will be high in mild preeclampsia and severe preeclampsia, in severe preeclampsia there is a pathological deterioration in the function of a number of organs and systems due to vasospasm and ischemia. In severe preeclampsia, renal function changes and decreased renal blood flow, as well as decreased glomerular filtration rate and uric acid clearance. As a result, it will increase serum uric acid levels which can occur before clinical symptoms appear. Increased serum uric acid levels in severe preeclampsia will increase the risk of complicating pregnancy, both in the mother and in the fetus and can also describe the severity of the disease.²⁰

Researchers calculated the sensitivity, specificity and receiver operator characteristic curve (ROC) values for each serum uric acid level and obtained a uric acid level of 6.85 mg / dL which is the meeting point between the sensitivity and specificity values, so that these values are determined as the cutoff point. with a sensitivity value of 78.3% and a specificity of 85.7%.

VII. CONCLUSION

There was a significant relationship between uric acid levels and the severity of preeclampsia ($p = 0.009$; $p < 0.05$). Serum uric acid levels can be used to predict the severity of preeclampsia in pregnant women, using CoP of 6.85 mg / dL, the sensitivity and specificity of uric acid levels to the severity of preeclampsia were obtained respectively 78.3% and 85.7%. The Positive Predictive Value (NPP) of uric acid levels was 94.7% and the Negative Predictive Value (NPN) was 54.5% with an accuracy value of 80%. The higher the uric acid level of pregnant women, the risk of suffering from severe preeclampsia will also increase.

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