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Uric Acid Level as Predictor Preeclampsia in Pregnant Woman at Working Area of Public Health Centers in Kendari City, Southeast Sulawesi Province

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Abstract

Preeclampsia is a common problem that occurs in pregnant women causing morbidity and mortality of mothers and babies to rise around the world. Studies have shown that in normotensive pregnancy, serum uric acid levels will begin to increase before the onset of symptoms of hypertension and proteinuria. This study aimed to determine differences in uric acid levels in healthy pregnant women and preeclampsia, as a predictor of preeclampsia events in the working area of Public Health Center in City of Kendari, Southeast Sulawesi Province. This research was an observational study using case-control study design. The sample of this study were pregnant women with gestational age above 20 weeks, divided into two groups, the case group consisting of pregnant women who experienced preeclampsia and the control group composed of pregnant women who did not experience preeclampsia. The total sample was 60 people. Data were analyzed using ROC, Chi-Square, Odds Ratio (OR) and Mann Whitney test. The value of cut-off point of the uric acid level of preeclampsia was ≥6,2 mg/dl. The levels of uric acid in the preeclampsia group were higher than in the non-preeclampsia group. Pregnant women who had uric acid levels ≥ 6, 2 mg/dl risk 13 times experienced preeclampsia. The result showed, the median value of uric acid level in preeclampsia group, was 7.39 mg/dl. The median value of uric acid levels in the preeclampsia group was 4.94 with a value (p = 0.000), meaning that there was a difference in uric acid levels between the preeclampsia group and the non-preeclampsia group. This research concludes that uric acid levels in the preeclampsia group were higher than those without preeclampsia. Pregnant women who have high uric acid levels risk 13 times experiencing preeclampsia.

Keywords: pregnant women; preeclampsia; uric acid levels.

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1. Introduction

Preeclampsia is a common problem that occurs in pregnant women causing morbidity and mortality of mothers and babies to increase worldwide. Preeclampsia is a syndrome characterized by sudden onset of hypertension and proteinuria in the second trimester. Cases of Preeclampsia accounted for about 22% of maternal deaths and 18% of all preterm births and increased the risk of infant mothers to future cardiovascular disease [1]. World Health Organization (WHO) estimated the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%). The incidence of eclampsia in developed countries such as North America and Europe was estimated to be around 5-7 cases per 10,000 births. On the other hand, the incidence of eclampsia in developing countries varied considerably, ranging from 1 case per 100 pregnancies to 1 case per 1,700 pregnancies. The incidence of preeclampsia in African countries such as South Africa, Egypt, Tanzania, and Ethiopia varied from 1.8% to 7.1%. In Nigeria, the prevalence ranges from 2% to 16.7% [2].

The incidence of preeclampsia in Indonesia continues to increase. Based on data from Indonesia Demographic and Health Survey in 2013, three leading causes of maternal mortality, namely bleeding (30.3%), hypertension (27.1%) and infection (7.3%). This suggested that the purpose of maternal death due to bleeding and infection can be significantly lowered, otherwise hypertensive patients (preeclampsia), due to ignorance and frequent delays in seeking help after clinical symptoms develop into severe preeclampsia and eclampsia, lead to increased incidence [3]. Risk factors for preeclampsia include nullipara, Gemelli pregnancy, history of preeclampsia in previous pregnancies, obesity, diabetes mellitus, vascular and connective disorders such as systemic lupus erythematosus and antiphospholipid antibodies, age >35 years in the first pregnancy, smoking, lifestyle and race African Americans [3,4]. Unfortunately, many of these risk factors cannot be modified or are very difficult to change, especially during pregnancy.

In patients with preeclampsia and eclampsia, there will be anatomic changes in various organs such as kidneys, retinas, hemodynamic systems and blood chemistry. Changes in blood chemistry that can occur, among others, uric acid metabolism, which some researchers say is typical of the increase in uric acid levels. The kidney organ plays a vital role in regulating the body's uric acid balance. The level of uric acid in the body is the result of purine metabolism, which under normal circumstances, will mostly be excreted through the kidneys. In preeclampsia, there will be changes in kidney function where there is a decrease in renal blood, decreased glomerular filtration and uric acid clearance. This results in elevated serum uric acid levels. Serum uric acid levels can be used to determine disease progression and predict intrauterine fetal conditions in patients with preeclampsia and eclampsia. The higher the serum uric acid level, the higher the perinatal death [5]. Some studies showed that in normotensive pregnancy, serum uric acid levels would begin to increase before the onset of symptoms of hypertension and proteinuria [6].

This study aimed to determine the difference in uric acid levels between healthy pregnant women and mothers who have preeclampsia, and determine the value of uric acid levels as predictors of the incidence of preeclampsia in the working area of Public Health Centers of Kendari City, Southeast Sulawesi Province.

2. Materials and Method

2.1. Collection of Samples

This research was observational research with the case-control design. This research had been conducted in 7 Public Health Centers in Kendari City consisting of Public Health Center of Lepo-Lepo, Public Health Center of Poasia, Public Health Center of Mokoau, Public Health Center of Mekar, Public Health Center of Kandai, Public Health Center of Labibia and Public Health Center of Benu-Benua. The population in this study was pregnant women with gestational age above 20 weeks which were domiciled in the working area of public health centers where the research took place. The sample in this study amounted to 60 people, consisting of pregnant women who experienced preeclampsia as many as 30 people and pregnant women who did not experience preeclampsia amounted to 30 people. The comparison of case and control samples was 1: 1 (30:30).

2.2. Data Analysis

The data collected, further processed and analyzed using descriptive analysis was conducted to see the characteristics of this research by using frequency distribution tables. Data were analyzed using chi-square test, Odds Ratio (OR) and Mann Whitney test, significant if $p < 0.05$.

2.3. Ethical Clearance

Ethical approval for this study obtained from Research Ethics Committee.

3. Results

The study was conducted in Kendari City from October to November 2016, covering 7 public health centers in Kendari, namely Public Health Center of Lepo-Lepo, Public Health Center of Poasia, Public Health Center of Mokoau, Public Health Center of Mekar, Public Health Center of Kandai, Public Health Center of Labibia and Public Health Center of Benu-Benua. The sample of research was divided into two, i.e., case group (pregnant women with preeclampsia) as many as 30 people and control group (pregnant mother did not experience preeclampsia) as many as 30 people.

Table 1: Characteristics of Respondents

Characteristics	Cases n = 30		Controls n = 30	
	n	%	n	%
Age (year)				
Risk (<20 &>35)	19	63,3	10	33,3
Not at Risk (20-35)	11	36,7	20	66,7
Gravidity				
Primigravida	12	40,0	7	23,3
Multigravida	18	60,0	23	76,7
History of hypertension				
Yes	18	60,0	7	23,3
No	12	40,0	23	76,7

Characteristics of respondents shown in table 1. Most pregnant women who had experienced preeclampsia are mothers with risky age, i.e. <20 years and> 35 years as many as 19 people (63.3%). Based on the number of maternal pregnancies (gravidity), in the group with preeclampsia, the highest percentage were pregnant women with multigravida (60%). Most of the respondents who had preeclampsia had a history of hypertension (60.0%). Table 2 showed the cut-off point values of respondents' uric acid levels. Based on the sensitivity and specificity values, obtained a cut-off point value of uric acid levels, i.e., 6.2 mg/dl. This suggested that uric acid levels ≥6.2 mg/dl were at risk for the occurrence of preeclampsia.

Table 2: Value of Sensitivity and Specificity on Various Cut-off Point of Acid Uric levels as Predictors Preeclampsia.

Cut-ff Point of* Acid Uric levels *(mg/dl)	**Sensitivity Value (%)**	**Specificity Value (%)**
2,8	100	0
3,9	100	3
4,1	100	10
4,2	100	20
4,3	100	23
4,4	100	27
4,5	100	30
4,6	100	43
4,8	100	47
5,0	100	57
5,2	100	63
5,6	100	80
5,8	100	83
5,9	97	83
6,0	93	83
6,1	93	87
6,2*	**93**	**90**
6,3	90	93
6,4	87	93
6,5	83	97
6,6	83	100
6,7	80	100
6,9	70	100
7,0	63	100
7,1	60	100
7,2	57	100
7,4	53	100
7,5	47	100
7,6	40	100
7,7	37	100
7,9	33	100
8,0	23	100
8,1	20	100
8,2	10	100
9,7	3	100
12,2	0	100

Description: * Cut-off Point Value = 6.2.

The result of mother characteristic analysis using chi-square test and odds ratio (OR) was shown in table 3 below. For the age variable, the result of the investigation revealed that there was a correlation between age and the incidence of preeclampsia (p = 0,020). Age at risk (<20 years and> 35 years) at risk 1.85 times for preeclampsia. Furthermore, the results of statistical analysis showed no relationship between gravidity with the incidence of preeclampsia (p = 0.165). However, multigravida pregnant women at risk 1.45 times to experience preeclampsia. The result of hypertension history analysis showed there was a correlation between the history of hypertension with preeclampsia incidence (p = 0,001). Respondents who had a history of hypertension had a risk of 2.7 times for preeclampsia (CI = 1,40-5,19).

Table 3: Relation of Respondent Characteristics with Occurrence of Preeclampsia.

Characteristics	**Cases**		**Controls**		***p***	***OR***
	n	**%**	**N**	**%**		***(CI 95%)***
Age (year)						
Risk (<20 &>35)	19	63,3	10	33,3	0,020	
Not at Risk (20-35)	11	36,7	20	66,7		1,85
						(1,07-3,18)
Gravidity						
Primigravida	12	40,0	7	23,3	0,165	
Multigravida	18	60,0	23	76,7		1,44
						(0,88-2,34)
History of hypertension						
Yes	18	60,0	7	23,3	0,001	
No	12	40,0	23	76,7		2,69
						(1,40-5,19)

The results of the analysis of the relationship between uric acid levels and the incidence of preeclampsia were shown in table 4.

Most of the respondents who had preeclampsia had uric acid level ≥6,2 mg/dl counted 28 people (93,3%), while those without preeclampsia had uric acid level <6.2 mg/dl of 27 people (90.0%).

The result of statistic analysis showed that there was a correlation between uric acid level and the incidence of preeclampsia (p = 0,000).

Respondents who had uric acid levels ≥6.2 mg/dl would increase the risk by 13.1 times to have preeclampsia (CI = 3,42-50,13).

Table 4: Relation of Uric Acid Level to the Occurrence of Preeclampsia Based on Cut-off Point Value of Uric Acid Level.

Uric Acid Level (mg/dl)	Cases		Controls		*P*	*OR* (CI 95%)
	n	%	n	%		
≥6,2	28	93,3	3	10,0	0,000	13,1
<6,2	2	6,67	27	90,0		(3,42-50,12)

Table 5: Comparison of Uric Acid Level with Occurrence of Preeclampsia Based on Cut-off Point Value of Uric Acid Level.

Uric Acid Level (mg/dl)	Cases (n=30)	Controls (n=30)	*P*	X^2
Standard Deviation	7,39 (1,01)	4,94 (0,78)	0,000	75,0
Median	7,39	4,94		
Range	5,8-11,2	3,8-6,5		

Description: X^2 (Mann Whitney test)

The result of statistic analysis with Mann Whitney test in table 5 showed the median value of uric acid level in the preeclampsia group of 7.39 mg/dl. The median value of uric acid levels in the non-preeclampsia group of women was 4.94. The results of the analysis by Mann Whitney test showed value (p = 0.000), it means that there was a difference of uric acid level between the group of preeclampsia and group of non-preeclampsia. Higher levels of uric acid were found in the preeclampsia group.

4. Discussion

Preeclampsia is one of the causes of maternal death is still a significant health issue other than bleeding and infection, especially in developing countries such as Indonesia. Preeclampsia accounts for 5 to 10 percent in complicating pregnancy. Preeclampsia with bleeding and infection form deadly triads that play a significant role in morbidity and maternal mortality [1]. The results showed that from 7 public health centers in the study sites there were still cases of preeclampsia. This suggested that preeclampsia is still one of the problems of pregnancy in Kendari City.

The results showed that there was a relationship between age and the incidence of preeclampsia. Age <20 years and> 35 years was at risk for the occurrence of preeclampsia. The results of this study by the results of research

that many cases of preeclampsia occur at age <20 years and >35 years [6, 7]. Similarly, the results of a study that stated that there was a significant relationship between maternal age with preeclampsia. Age at risk for the occurrence of preeclampsia is <20 years and >35 years [8,9].

Age >35 years old is too old to get pregnant because at this age condition of mother's health and function of various organs and body systems such as muscle, nerve, endocrine, and reproduction decrease. At age >35 years there is a decrease in cardiac output caused by myocardial contraction and exacerbated by blood pressure and other diseases that weaken the condition of the mother, which can disrupt the blood circulation to the fetus at increased risk of medical complications in pregnancy such as miscarriage, preeclampsia, eclampsia, and bleeding. Age <20 years old is too young to get pregnant because at this age the condition of maternal health and the function of various organs and body systems such as muscles, nerves, endocrine, and reproduction is immature so risky to get pregnant [10].

The results showed that there was no association between gravidity and preeclampsia, but the greatest gravidity for preeclampsia was multigravida. The results of this study were not in line with the theory that primigravida risked experiencing preeclampsia [7,11]. The results showed that there was a relationship between the history of hypertension and the incidence of preeclampsia. The results of this study were in line with the results of research that stated that there was a relationship between the history of hypertension with the incidence of preeclampsia [12]. Pregnant women with a history of hypertension have a higher risk of experiencing preeclampsia.

The cause and pathogenesis of preeclampsia are not yet known for sure, although much research has been done. The development of molecular biology provides new information and hope to explain the occurrence of preeclampsia. Examination of uric acid levels is one of the biochemical tests performed to predict the occurrence of preeclampsia. Increased serum uric acid levels are predictive of preeclampsia. The results showed that there was a difference in uric acid levels between the preeclampsia and non-preeclampsia groups, where uric acid levels in the preeclampsia group were higher than in the non-preeclampsia group. The results of this study were by the results of research stating that there were differences in uric acid levels between preeclampsia and non-preeclampsia. The uric acid levels were higher in the preeclampsia group than in the non-preeclampsia group so that uric acid levels could be considered as one of the preeclampsia biomarkers [13].

The levels of uric acid in pregnancy are affected by factors such as purine intake in food, metabolic production of uric acid by the mother and fetus as well as excretion by the kidneys and gastrointestinal tract. Interference with one of these factors may alter uric acid levels of pregnant women [14,15]. Uric acid is a potent inhibitor of endothelial function that induces systemic and glomerular hypertension found in animal studies [16]. Uric acid blocks endothelial proliferation induced by Vascular endothelial growth factor (VEGF) has a direct role in blocking fetal angiogenesis causing late infant development [6]. In a healthy pregnancy, uric acid levels decreased significantly by 25-30% of normal levels to 16 weeks' gestation. This occurs due to plasma volume expansion, increased renal clearance, and uricosuric effects of estrogen. In the second trimester, uric acid levels remain stable and then increase during the 3rd trimester due to an increase of catabolism [14].

The results of laboratory studies showed that in women with preeclampsia increased serum uric acid. Most claimed hyperuricemia is due to a decrease in glomerular filtration rate, although some other reviews have increased uric acid levels in the pathogenesis of preeclampsia through endothelial dysfunction [16]. In a follow-up study measuring serum uric acid concentrations in healthy pregnant women, pregnant women with preeclampsia and patients with vascular hypertension disease found mean serum uric acid levels in the last trimester of pregnancy for healthy women of 3.5 ± 0.6 mg%. Patients with hypertension had similar serum uric acid concentrations, 3.7 ± 1.1 mg%, while mean rates for patients with histologically proven preeclampsia were 6.4 ± 1.7 mg/dl. This showed a significant increase in the mean of serum uric acid concentrations present in patients with preeclampsia compared with those with abnormal vascular hypertension and healthy pregnant women. Serum uric acid concentrations correlate well with the severity of glomerular lesions. This was in line with studies suggesting that the increased mean value of uric acid in pregnancy associated with the severity of toxemia [17].

The timing of the onset of preeclampsia is essential in determining the outcome of the fetus because the only treatment for this disorder is direct labor. Since preeclampsia is usually a progressive disease, if it begins between 24 and 30 weeks of gestation, intrauterine fetal death (IUFD) may occur or a dangerous illness that requires immediate labor with the low life expectancy of the neonatal. The time at which serum uric acid concentration begins to rise is an approximate indicator of the time of onset of preeclampsia. The value of serum uric acid measurements in the highest hypertensive pregnancy was between 24 and 32 weeks' gestation. A low value indicates a good prognosis for the fetus. A steep increase or grade at this time suggests a high-risk case that should be treated and treated at the hospital. Early bed rest, fetal welfare monitoring in utero and anticipation of maternal problems associated with preeclampsia then ensures the best chance of delivering delivery to the stage where birth planning is to prevent severe maternal complications and provide the best opportunity for fetal safety [18].

More and more evidence suggests that increased serum uric acid in pregnancy may not only be a biomarker of value from preeclampsia but may also have a contributing role in the pathogenesis of maternal and fetal manifestations. The association between increased serum uric acid concentration and preeclampsia has been studied for decades with inconsistent results from studies assessing the usefulness of maternal serum uric acid in predicting outcome [16].

In preeclampsia, elevations in uric acid levels exceeding normal gestational concentrations are likely to be affected by changes in maternal renal function (e.g., increased tubular reabsorption) and uric acid production; but the fetus and placenta may play an additional role. We have found a weak association between serum uric acid and creatinine serum, with elevated serum uric acid probably more than a marker of Glomerular Filtration Rate (GFR) abnormality. There is a mechanism found in which the placenta may contribute to uric acid production through hypoxia-induced changes in the production and activity of xanthine oxidase/dehydrogenase. Increased uric acid concentrations may be a marker of inadequate placental perfusion and fetal hypoxia. There is also in vitro evidence for the effects of uric acid that may contribute to fetal outcomes. In this study, uric acid reduces the transport of placental amino acids, trophoblast invasion, and the incorporation of trophoblasts into endothelial monolayers [16]. The exact mechanisms of how uric acid plays a role in the development of

hypertension in humans cannot be explained, but some evidence suggests that uric acid plays a significant role since uric acid levels correlate with renin plasma activity. On the pathophysiological changes of preeclampsia that include increased sensitivity of the presser, activation of the coagulation cascade, and increased vascular permeability, suggest that endothelial vascular dysfunction is an essential component of this disorder.

Several studies had shown that preeclampsia was associated with an imbalance between lipid peroxidase and antioxidant systems. Patients with preeclampsia have elevated free radicals as indicated by elevated lipid peroxidase levels and decreased antioxidant concentrations such as superoxide dismutase, catalase, and glutathione peroxidase. In other studies, plasma concentrations of uric acid, malondialdehyde (MDA), ascorbic acid and vitamin E did not differ significantly in preeclampsia compared with healthy pregnancies. However, the level of uric acid increased dramatically in eclampsia compared with healthy pregnancy and preeclampsia. They suggested that uric acid as an antioxidant has a protective role [16].

The results suggested that there was a difference in uric acid levels between healthy pregnancy and preeclampsia. The mean maternal uric acid level of preeclampsia was 7.6 ± 0.76, whereas healthy pregnant women were 4.6 ± 0.42, so that blood uric acid levels could serve as one indicator for preeclampsia [5]. Similarly, other research results stated that blood uric acid levels could be used as one of the signs to detect preeclampsia [18]. High blood uric acid levels during pregnancy can cause fetal distress, IUFD, eclampsia. High uric acid levels when uric acid level ≥6 mg/dl, so it is necessary to check the uric acid levels to avoid further complications of pregnancy that can result in fetal death [19].

5. Conclusion

The cut-off point value of the uric acid level of preeclampsia was ≥ 6.2 mg/dl. The levels of uric acid in the preeclampsia group were higher than in the non-preeclampsia group. Pregnant women who had uric acid levels ≥ 6,2 mg/dl 13 times the risk of experiencing preeclampsia. Uric acid levels can be considered as one of the biomarkers of preeclampsia. Levels of uric acid can be used as a routine examination of pregnant women in the first and last trimester of any antenatal care at the public health center.

6. Recommendations

This study recommends for Comprehensive midwifery care for every pregnant woman during pregnancy, childbirth, and puerperium.

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7. Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

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