# Maternal serum uric acid level and maternal and neonatal complications in preeclamptic women: A cross-sectional study

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#### **Abstract**

**Background:** Preeclampsia is associated with maternal and neonatal complications. It has been indicated that increased uric acid might have a predictive role on preeclampsia.

**Objective:** We aimed to investigate the relationship between the level of uric acid with maternal and neonatal complications in women with preeclampsia.

Materials and Methods: In this cross-sectional study, 160 singleton preeclamptic women at more than 28 wk gestational age were included. Hemoglobin, hematocrit, platelet count, liver and uric acid tests, and maternal and neonatal complications were assessed. The severity of preeclampsia, placental abruption, preterm labor, thrombocytopenia, elevated alanine aminotransferase and aspartate aminotransferase (ALT and AST), HELLP syndrome, eclampsia and required hospitalization in the ICU was considered as the maternal complication. Fetal complications were: small for gestational age (SGA), intrauterine fetal death, hospitalization in the neonatal intensive care unit, and Apgar score <7 at five minutes.

**Results:** Of our participants, 38 women had severe preeclampsia (23.8%). The mean level of uric acid in women with severe preeclampsia was significantly higher than non-severe preeclampsia (p=0.031), also in those with an abnormal liver test (p=0.009). The mean level of uric acid in women with preterm delivery was significantly higher than women with term delivery (p=0.0001). Also, the level of uric acid had no effect on neonatal hospitalization in neonate invasive care unit. Based on logistic regression, the incidence of severe preeclampsia not affected by decreased or increased serum levels of uric acid.

**Conclusion:** With higher level of uric acid in server preeclampsia we can expected more complications such as hepatic dysfunction and preterm delivery. Thus serum uric acid measurement can be helpful marker for severe preeclampsia.

Key words: Pregnancy, High-risk, Preeclampsia, Uric acid, Pregnancy complications.

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#### Introduction

reeclampsia with the prevalence of 10.5% is a blood pressure disorder. It is a multi-systemic disease with unknown etiology. It is indicated by >140/90 mm Hg blood pressure with or without proteinuria after 20 wk of gestation. Hypertension during pregnancy is associated with maternal and neonatal complications (1, 2). In developed countries, 16% of maternal deaths are caused by high blood pressure which is higher than other factors such as bleeding (13%), abortion (8%) and sepsis (2%) (3).In Iran, the prevalence hypertensive disorders during pregnancy is reported as 8.1% (4, 5). Up to now, there is no reliable, valid, and cost-effective screening test for the early detection of preeclampsia. It seems that measuring the blood level of uric acid is one of the available and cheap screening tests that have already been taken into account. Uric acid is the final product of purine metabolism oxidation which is mainly excreted in the urine. Since increased uric acid is the first and earliest laboratory presentation of preeclampsia as a result of reduced clearance of uric acid due to decreased glomerular filtration clearance, increased tubular reabsorption, and reduced secretion, some investigators use serum uric acid as a criterion for preeclampsia (3).

It has been indicated that uric acid might not only have a predictive role in preeclampsia but also play a significant role in the maternal and fetal pathogenesis and presentations (3). However, previous studies mentioned inconsistent results (6, 7). Some previous investigations mentioned a higher level of uric acid in patients with preeclampsia compared to healthy subjects (8, 9). However, other studies mentioned that changes in uric acid levels in preeclampsia might be as a result of associated diseases. They noted no important predictive value for uric acid (10, 11). Also, epidemiological studies on non-pregnant individuals showed that hyperuremia could be with hypertension, metabolic associated syndrome, coronary artery disease, cardiovascular disease and chronic kidney disease (12, 13).

Given the importance of preeclampsia in maternal and neonatal complications, in this study, we aimed to investigate the relationship between the level of uric acid with maternal and neonatal complications in women with preeclampsia. Knowing the effect of uric acid on the severity of preeclampsia and maternal and neonatal complications can help early diagnosis, control, and treatment. Results can be used for clinical decision-making and maternal and prevent from neonatal complications.

## Materials and methods

this cross-sectional 160 study, preeclamptic women (severe and nonsevere) at more than 28 weeks gestational age admitted to Al-Zahra Hospital in Rasht, Iran during 2014-2015 were included. Diagnostic criteria were having hypertension to the extent of 140/90 mmgHg or more after 20 wk of pregnancy in women with or proteinuria in previously normotensive. Also, hypertension in pregnant women with a history of preeclampsia was noted by >30 mm Hg increase in systolic blood pressure or >15 mmHg increase in diastolic blood pressure. Severe preeclampsia was diagnosed when systolic pressure ≥160 mmHg, diastolic pressure ≥110 mmHg with or without proteinuria, headache, visual changes, upper abdominal pain, oliguria, increased serum creatinine and liver transaminases thrombocytopenia (<100,000).

Measurement of blood pressure was performed by a single resident of obstetrics

and gynecology. All pregnant women with smoking, diabetes or gestational diabetes, hemoglobinopathies, nephropathy, acute and chronic renal failure, glomerulopathy, urinary tract infection, hepatic dysfunction, gout, hypothyroidism or hyperthyroidism, fetal and placental malformations, and multiple pregnancies were excluded.

Of all women who met the inclusion criteria, 5 ml of blood from an anterior Cubital vein was taken and hemoglobin, hematocrit, platelet count, and liver and uric acid tests were assessed. For all women, 24-hr urine protein, creatinine, urine dipstick tests, and random urine samples were also performed. Uric acid was assessed using Pars test kit and by BT2000 (Italy) auto-analyzer system. All laboratory tests were conducted in Al-Zahra hospital.

Data including age, gravidity, parity. gestational age, and history of hypertension before pregnancy were collected through interviews. Weight and height were measured and body mass index (BMI) was calculated. Maternal complications included severity of preeclampsia, placental abruption, preterm (PTL), thrombocytopenia, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count), eclampsia and required hospitalization in the ICU were assessed. Neonatal complications including small for gestational age (SGA), intrauterine fetal death, hospitalization in the neonatal intensive care unit, and Apgar score <7 at five minutes were investigated.

## **Ethical consideration**

This study was approved by the Ethics Committee of Guilan University of Medical Sciences (1930596730). Written informed consents were obtained from all participants before enrollment.

## Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (version 21.0, SPSS Inc, Chicago, and Illinios, USA). Independent samples *t*-test was used to compare means between groups. Also, univariate logistic regression analysis using forward: LR method was used to assess the relationship between levels of uric acid and the incidence of maternal and neonatal complications. In the regression analysis, the

effect of uric acid levels, age, gestational age, gravidity, parity, the platelet count, albuminuria, hemoglobin, hematocrit, creatinine, body mass index, and effect of hypertension before pregnancy on maternal and neonatal complications were examined. The p<0.05 indicated statistical significance and 95% confidence interval was noted.

#### Results

In this study, 160 preeclamptic women participated, which 38 of them were severe preeclampsia (23.8%) and 122 of them were none severe (76.3%). The mean age of participants was 31.18±5.41 yr. 14.4% (n=23) hypertension before history of pregnancy and 71.3% (114) had albuminuria. Demographic characteristics and laboratory results have been reported in table I. Mean level of uric acid in women with severe preeclampsia (5.66±1.46) was significantly higher than non-severe preeclampsia (5.12±1.29) (p=0.031). In univariate analysis, the mean level of uric acid in women with hepatic dysfunction was significantly higher than the non hepatic dysfunction group (p=0.009). Also, women with preterm delivery had higher uric acid levels than women with normal term pregnancy (p=0.0001). Uric acid levels in women with neonates hospitalized in Neonate invasive care unit (NICU) were significantly higher than other women (p=0.016). In the case of maternal and neonatal complications. there was no significant difference between groups regarding the level of uric acid (Table II).

Based on the logistic regression analysis, 1 mg/dl increase in blood uric acid level induced 1.74 fold increase in the risk of hepatic dysfunction (OR: 1.74, 95% CI: 1.12-2.72). Also, with 1% increase in hematocrit, the chance of hepatic dysfunction will be about 1.3 times higher. Other variables had no effect on increasing or decreasing the risk of hepatic dysfunction in pregnant women preeclampsia. In the present study by 1 mg/dl, increase in serum uric acid, 1.54 fold increase in the risk of PTL was noted (OR: 1.54, 95% CI: 1.15-2). Furthermore, by 1 mg/dl increase in serum hemoglobin and creatinin, 1.6 and 1.06 fold increase in the risk of PTL was noted, respectively. While other variables did not increase or decrease the chance of PTL in pregnant women with preeclampsia.

Based on regression analysis, results showed that the level of uric acid had no effect on hospitalization of infants in the NICU. Also, the level of uric acid had no effect on neonatal hospitalization in NICU. However, by 1 mg/dl increase in hemoglobin and AST in pregnant women with preeclampsia, 1.6 and 1.022 fold increase in the risk of hospitalization in NICU was noted, respectively. The positive history of hypertension before pregnancy indicated 3.8 fold increase in hospitalization in NICU. (Table III).

**Table I.** Demographic characteristics and laboratory results of

the study participants

Variables	Mean±SD		
Age (yr)	$31.18 \pm 5.41$		
BMI $(kg/m^2)$	$32.33 \pm 3.72$		
Gestational age (wk)	$34.74 \pm 2.64$		
Parity (n)	$2.03 \pm 1.10$		
Gravidity (n)	$0.74 \pm 0.94$		
Systolic blood pressure (mmHg)	$152.19 \pm 12.55$		
Diastolic blood pressure (mmHg)	$98.19 \pm 8.57$		
Platelets (/cumm)	$201681 \pm 56180$		
Hemoglobin (g/l)	$12.33 \pm 1.09$		
Hematocrit (%)	$37.25 \pm 3.19$		
AST (U/L)	$32.35 \pm 31.72$		
ALT (U/L)	$26.64 \pm 39.63$		
Uric acid (mmol/l)	$5.25 \pm 1.35$		
Creatinine (mg/dl)	$0.76 \pm 0.15$		

BMI: Body mass index ALT: alanine aminotransferase AST: aspartate aminotransferase

**Table II.** Univariate analysis of pregnancy outcomes in study participants

Maternal and fetal	Number	Uric acid level	p-value	
complications	Number	Oric acid level		
Placental abruption				
Yes	1	6.40	0.393	
No	159	159 $5.24 \pm 1.38$		
Thrombocytopenia				
Yes	4	$4.20 \pm 0.86$	0.115	
No	156	$5.28 \pm 1.35$	0.115	
Hepatic dysfunction				
Yes	11	$6.27 \pm 1.40$	0.009	
No	149	$5.17 \pm 1.32$	0.009	
ICU hospitalization (maternal)				
Yes	17	$5.61 \pm 1.67$	0.241	
No	143	$5.21 \pm 1.30$	0.241	
HELLP syndrome				
Yes	3	$6.20 \pm 2.27$	0.210	
No	157	$5.23 \pm 1.33$	0.218	
PTL				
Yes	79	$5.63 \pm 1.38$	0.0001	
No	81	$4.87 \pm 1.21$	0.0001	
IUFD				
Yes	4	$5.90 \pm 1.17$	0.220	
No	156	$5.23 \pm 1.35$	0.329	
SGA				
Yes	30	$5.61 \pm 1.39$	0.102	
No	130	$5.16 \pm 1.33$	0.103	
Apgar score <7 at five minute				
Yes	4	$4.50 \pm 2.10$	0.270	
No	151	$5.24 \pm 1.33$	0.278	
Need to NICU				
Yes	32	$5.74 \pm 1.37$	0.016	
No	124	$5.10 \pm 1.32$		

Data presented as mean±SD. Independent *t*-test

NICU: Neonate invasive care unit

PTL: Preterm labor

IUFD: Intrauterine fetal death SGA: Small gestational age

**Table III.** Logistic regression analysis on the factors affecting the incidence of hepatic dysfunction, premature birth, and NICU hospitalization in women with preeclampsia

Complication	Regression coefficient	S.E	OR	95% CI		
				Lower bound	Upper bound	p-value
Hepatic dysfunction						
Level of uric acid	0.554	0.227	1.740	1.115	2.176	0.015
Level of hematocrit	0.270	0.111	1.311	1.054	1.630	0.015
Premature birth						
Level of uric acid	0.435	0.151	1.544	1.148	2.077	0.004
Level of hemoglobin	0.477	0.176	1.611	1.142	2.272	0.007
Level of creatinin	0.062	0.018	1.064	1.026	1.120	0.001
NICU hospitalization						
Level of hemoglobin	0.455	0.216	1.576	1.032	2.407	0.035
AST	0.022	0.009	1.022	1.004	1.040	0.015
HTN before pregnancy	1.323	0.523	3.753	1.347	1.457	0.011

Logistic regression OR: Odds ratio

NICU: Neonate invasive care unit CI: Confidence interval

SE: Standard error AST: aspartate aminotransferase

HTN: Hypertension

## **Discussion**

In this study, the mean level of uric acid in with severe preeclampsia significantly higher than non-severe preeclampsia. In a study by Sultana and colleagues, which compared the mean levels of uric acid in subjects with normal blood pressure and preeclampsia, results showed preeclampsia was associated hyperuricemia (14). Also, Gianni et al followed patients for a month after delivery and mentioned uric acid as a reliable predictor of preeclampsia in women with gestational hypertension. They indicated uric acid with cut-off of 309 µm/l as a predictor of preeclampsia (8).

Enaruna et al also showed that uric acid levels in women with severe pre-eclampsia were higher than the control group (11). Chen and co-workers showed a higher level of serum uric acid in women with preeclampsia and the increase occurred with the onset of preeclampsia. There was no significant difference between preeclampsia and normal subjects regarding the mean level of uric acid in the first and second trimesters. Chen et al stated that serum uric acid levels increased with the onset of clinical signs preeclampsia, but it might not be a predictor of preeclampsia and should not be considered as a predictive biomarker (15). According to results, although preeclampsia might cause increase in uric acid, the inverse association did not exist. Laughon et al mentioned that the increase of uric acid in the first trimester of pregnancy was associated with preeclampsia and hypertension during pregnancy was related to hyperuricemia (16).

Hawkins et al reported that hyperuricemia in pregnant women with high blood pressure

was an important finding which might expose women to adverse maternal and fetal complications. Even women with gestational hypertension, without other signs of preeclampsia had adverse embryonic complications such as SGA and pre-maturity. In this study, uric acid was measured nearterm period which was similar to ours (17).

Elmas et al showed higher levels of uric acid, xanthine oxidase and Allantoin activity blood pressure in patients preeclampsia versus the control group (18). Elmas et al suggested that increased uric acid, xanthine oxidase and Allantoin activity might be noted following the death of placental cells consequent the abnormal activity of trophoblast in preeclampsia. Therefore, currently, clinicians prefer the mentioned causes for increased uric acid in preeclampsia instead of the effect of kidney disease following preeclampsia (19).

Corominas et al showed that up to 20 weeks of gestation, the mean level of uric acid in preeclampsia and normal women were similar. But after 20th wk of gestation, the mean level of uric acid in women with preeclampsia was 1.5 fold higher than control and healthy subjects. This increase coincided with stable creatinin and urea in patients and showed increased uric acid should from kidney disorders separated (20).However, Zhao et al associated increased uric acid in women with preeclampsia with the systemic inflammation of maternal blood vessels. which could be presented increased Tumor necrosis factor alpha TNFalpha and Intercellular adhesion molecule- 1 (21). Matias et al as also expressed the increased uric acid by inflammatory reactions, and this phenomenon was associated with that expression of nod-like intracellular

receptors with a pyrin domain NLRP3 gene in pregnant women with preeclampsia (22).

Previous studies showed a significant association between hyperuricemia and adverse obstetric outcomes in pregnant women with hypertension (23, 24) which was similar to the current study. As in this study higher mean level of uric acid was associated with increased rate of PTL and consequently NICU hospitalization. In a study by James et showed results that women hypertension and hyperuricemia had a similar or higher risk comparing women with high blood pressure and proteinuria. Risks included shorter period of pregnancy, percentiles of birth weight, increased risk of preterm birth and SGA. They concluded that hyperuricemia was at least as effective as proteinuria to identify pregnancies with the risk of high blood pressure (25).

In this study, although uric acid levels in women who were hospitalized in the NICU was higher than non-hospitalized women, this association significant. was not Andrews et al which assessed Indian patients with high blood pressure for two years showed that the rate of maternal death in those with increased uric acid levels, LDL, AST, alanine aminotransferase, APTT was higher than the control group (26). In the present study, although the incidence of neonatal complications such as intrauterine fetal death, low Apgar score and SGA in preeclamptic women was slightly higher than the control group, this relation was not significant. While Patel et al which compared levels of uric acid (<6 and ≥6) in women with high blood pressure Indicated hyperuricemia in patients with high blood pressure as a risk factor for several serious maternal and perinatal complications such as <7 Apgar score, intrauterine death, eclampsia, and cesarean delivery in patients with ≥6 level of uric acid versus <6 (27).

Results showed that by 1 mg/dl increase in serum uric acid and hematocrit in pregnant women with preeclampsia, 1.7 and 1.3 folds increases in the risk of hepatic dysfunction were noted, respectively. In addition, by 1 mg/dl increase in serum uric acid and hemoglobin, 1.5 and 1.6 fold increases in the risk of hepatic dysfunction were noted, respectively. In a study by Hawkins *et al*, with increasing levels of uric acid, the risk of kidney failure which could be diagnosed by the

increased level of creatinin in the mothers was four times higher compared with the control group (17).

In the present study by 1 mg/dl increase in serum hemoglobin and creatinine, 1.6 and 1.06 fold increases in the risk of PTL was noted, respectively. While other variables did not increase or decrease the chance of PTL in pregnant women with preeclampsia. Also, the level of uric acid had no effect on neonatal hospitalization in NICU. However, by 1 mg/dl increase in hemoglobin and AST in pregnant women with preeclampsia, 1.6 and 1.022 fold in the risk of increases neonatal hospitalization in **NICU** were noted. respectively.

The positive history of hypertension before pregnancy indicated 3.8 fold increase in neonatal hospitalization in NICU. Livingston et al stated that level of uric acid was associated with prenatal and maternal complications in women with preeclampsia (3). Wu et al also declared that with one increase in standard deviation of serum uric acid, 1.5 fold increases in the chance of maternal and fetal complications were noted (28). In this study, uric acid was higher in severe preeclampsia and PTL. Whereas in severe preeclampsia, clinicians ought to terminate the pregnancy to save the patient's life, the higher rate of PTL would be expected.

#### Conclusion

In this study, we found a significant relationship between the level of uric acid with hepatic dysfunction and PTL in pregnant women with preeclampsia. As assessing serum uric acid in the laboratory can be easily performed, it seems that it might be diagnostic and prognostic criteria for determining the early complications of preeclampsia and can be used to treat and manage women with preeclampsia.

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## **Conflict of interest**

The authors declare that they have no conflicts of interest.

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