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A Survey of Relationship Between Neonate and Mother Prognosis and Plasma Level of Blood Uric Acid in Preeclampsia Pregnant Women

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The purpose of this study was investigated that whether the measure of the uric acid in pregnant women has cause-effect relationship with severity of preeclampsia, biochemical and urine parameters. This study was targeted the preeclampsia women with uric acid levels = 6 mg dL^{-1} and < 6 mg dL^{-1} for comparing with healthy pregnant women. In order to survey of serum Hb, platelet, liver enzymes and renal function test findings, blood and urine samples of preeclampsia and healthy groups were taken before delivery and analyzed. There was significant differences in the gestational age and mean serum AST, ALT, BUN and urine albumin between preeclampsia groups and healthy women. Also the gestational age variable in preeclampsia women with uric acid levels = 6 mg dL^{-1} were lower than preeclamptic patients who have lower than 6 mg dL^{-1} uric acid. Systolic and diastolic blood pressure were higher in the both preeclampsia cases compared with control group. There was significant differences in Apgar scores in the first and fifth minutes of life between the preeclampsia groups and healthy women. Also Apgar score in the fifth minutes of life has a significant effect on the risk of preeclampsia with more than 6 mg dL^{-1} uric acid compared with preeclampsia with less than 6 mg dL^{-1} uric acid. Neonatal weight in the preeclampsia groups were lower than its levels in the control group. In conclusion our results declared that a cause-effect relationship between the secretion of serum uric acid and severity of preeclampsia, biochemical and urine parameters may in fact exist.

Key words: Uric acid, biochemical parameters, urine parameters, apgar scores, systolic and diastolic blood pressure, preeclampsia

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INTRODUCTION

Preeclampsia is a common disorder during pregnancy period and it is one of the important cause of mortality and side effects of the maternal, fetal and infant (Sibai *et al*., 2003). So that preventing from this problem could have a significant impact on health of the mother and her fetus. Therefore, providing early prediction method in order to timely intervention is essential.

Different processes, to define early symptoms of preeclampsia, have been done for diagnosing of this pregnancy-specific syndrome (Poprawski *et al*., 2012). In general, the renal excretion of urate metabolites i.e., uric acid in preeclamptic pregnant women markedly is reduced (Jeyabalan and Conrad, 2007). Therefore, it seems that serum uric acid measurement in the blood serum can help in detecting early symptoms of the preeclampsia before the appearance of visible signs and may assist in monitoring further functional deterioration in pregnant women (Powers *et al*., 2006). Normally, the serum uric acid level is associated with a relative increase during first semester of pregnancy (Bainbridge and Roberts, 2008). But gradually, with the increase in renal clearance, it is reduced by up to 16 weeks and then increased again in the last quarter of pregnancy (Bainbridge and Roberts, 2008). Apparently, the serum uric acid level in preeclampsia pregnant women is higher than healthy ones. This could be due to decreased renal excretion, glomerular dysfunction or even increased oxidative stress (Watanabe *et al*., 2012). Some studies in addition to observation of elevated levels of uric acid in the preeclampsia, they emphasizes that this risen secretion of uric acid directly is associated with severity of the disease, prognosis of the fetus and also newborn (Bellomo, 2012). Some studies reported that measuring the serum uric acid during pregnancy is more useful compared to the blood pressure control to follow-up fetal health and the prevention of low birth weight (Bellomo, 2012; Bainbridge and Roberts, 2008). So that, some researchers have reported that there is a significant correlation between elevated levels of uric acid and increased fetal mortality, fetal intrauterine growth retardation and premature infants (Koopmans *et al*., 2009; Meads *et al*., 2008). However, a number of researchers were rejected this relationship and also the use of uric acid as an important indicator in predicting preeclampsia (Thangaratinam *et al*., 2006; Phillips *et al*., 2010). So, it seems that more studies must be done to assess the usefulness of uric acid levels in the diagnosis of preeclampsia and its consequences. Therefore, the present study was conducted to examine whether serum uric acid measurement can help in detecting early symptoms of the preeclampsia before the appearance of visible signs and assist in monitoring further functional deterioration in pregnant women.

MATERIALS AND METHODS

Study design: A comparative randomized clinical trial was carried out in the obstetrics and gynecology ward of Razi and Imam Khomeini teaching hospitals in Ahvaz, Iran. This study was performed between January 2012 to February 2013 and targeted singleton pregnant women that were referred to health centers for receiving prenatal care during the third quarter pregnancy. The Ethics Committee of Jondishapour Ahvaz University of Medical Sciences approved this study.

Pregnant women with normal pressure (control group) and women with high blood pressure (BP = 90/140 mmHg) and also urinary excretion of protein more than normal (300 mg) during 24 h were selected and uric acid levels were determined.

In this study, 114 pregnant women were divided on the three groups: the first group is preeclampsia women (n = 38) with uric acid levels = 6 mg dL^{-1}, the second group is preeclampsia cases (n = 38) with uric acid levels <6 mg dL^{-1} and the third group is healthy pregnant women (n = 38). Patients in the control group in terms of age with preeclampsia cases were matched.

Patients with a history of underlying diseases such as chronic hypertension (CAH), cardiovascular disease, diabetes, thyroid disorders, kidney diseases, gout, epilepsy, initial blood pressure without signs of preeclampsia and certain drugs (amikacin sulfate, cefazolin, keflin, cephradine, pyrazinamide, carbamazepine, thiazides) and renal or other diseases that affect the serum uric acid level were excluded from study. Indeed, only pregnant women with gestational hypertension were enrolled as cases.

In selected patients, the prognosis of their infants is reviewed. All neonates who had the following characteristics: multiple congenital anomalies and in appearance are dsimorphic but the reason is not preeclampsia were excluded from research.

For each patient, questionnaire that included demographic information, pregnancy and medical records, test results, high-eclampsia symptoms, information about birth and pregnancy-related problems through patient interview and any kind examination was completed.

At first, 5-4 mL venous blood sample and urine sample were taken from each patient. Then, after centrifugation and separation of serum, the serums were stored in a freezer at a -20°C or experiments measuring uric acid, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), Hemoglobin (Hb), Platelets (Plt), urea

nitrogen (BUN), Creatinine (Cr) and urine albumin were performed immediately.

The tests on each sample were repeated three times and the values were recorded. Then, for each test, the average results of three replicates were calculated and as Mean±SDM were expressed. Based on the previous study, because the normal level of uric acid in pregnancy is about 4/3 mg dL^{-1}, the more than 6 mg dL^{-1} of uric acid levels was considered as abnormal levels.

End points: The end point of the study was to evaluate the efficacy of serum uric acid measurement in detecting early symptoms of the preeclampsia before the appearance of visible signs and assisting in monitoring further functional deterioration in pregnant women.

Statistical analysis: After gathering and recording the data, for analyzing of the data, SPSS software was used and was examined accurately by t-test, chi-square, Fisher exact test and odds ratio for abnormal AST, ALT, Hb, Plt, BUN, Cr and urine albumin in the patients of preeclampsia and healthy ones. For all other outcomes, a nominal p-value of $p<0.05$ was considered significant.

RESULTS

Demographic characteristics: Demographic characteristics of the study population are given in Table 1. In this study, 114 pregnant women were studied during the third quarter of pregnancy. Thirty eight cases were preeclamptic patients with uric acid levels less than 6 mg dL^{-1} and another 38 women were preeclamptic patients with uric acid levels more than 6 mg dL^{-1} and 38 healthy women as control were selected.

The three groups were similar in the maternal age (18 to 44 years), gestational age (the third 3 months of pregnancy) at admission, the number of deliveries, social and economical situation.

However, there was significant differences in the total gestational age variable between the preeclampsia groups with uric acid levels less/greater than 6 mg dL^{-1} and healthy women (Table 1). Also the gestational age variable in preeclampsia women who have higher than 6 mg dL^{-1} uric acid were lower than preeclamptic patients who have lower than 6 mg dL^{-1} uric acid (34.8 ±4.1 vs. 36.8 ±3.4, respectively $p<0.019$).

Blood pressure characteristics: Systolic and diastolic blood pressure characteristics of the study population are given in Table 1. Systolic and diastolic blood pressure variables were higher in both the preeclampsia cases with more than 6 mg dL^{-1} uric acid groups and the preeclampsia ones with less than 6 mg dL^{-1} uric acid compared to control group (Table 1). Its note to mentioning that from 38 preeclamptic cases with less than 6 mg dL^{-1} uric acid, 18 cases (47/4%) had a blood pressure of 159/109 mmHg = BP = 140/90 mmHg and 20 patients (52/6%) had a blood pressure of 160/110 mmHg = BP. Also from 38 preeclamptic cases with more than 6 mg dL^{-1} uric acid, 19 cases (50%) had a blood pressure of 159/109 mmHg = BP = 140/90 mmHg and 19 patients (50%) had a blood pressure of 160/110 mmHg = BP. But all cases of the control group had a normal blood pressure (139/89 mmHg = BP).

Biochemical and urine parameters: The levels of serum AST, ALT, Hb, Plt, BUN, Cr and urine albumin characteristics of the study population are given in Table 1.

Table 1: Maternal demographic, biochemical and urine parameters, blood pressure and clinical characteristics in preeclampsia women and matched pregnant control subjects

Characteristics	Preeclampsia (N = 34) (Uric acid = 6 mg dL^{-1})	Preeclampsia (N = 34) (Uric acid <6 mg dL^{-1})	Control (N = 34)	p-value
Maternal age (years)	28±6.5	28±7.2	26.2±4	0.84*, 0.82**
Gravidity	2.4±1.9	2.3±1.8	2.3±1.4	0.96*, 0.99**
Gestational age	34.8±4.1	36.8±3.4	38.7±1.5	0.001*, 0.037**
Uric acid	6.9±1.7	4.45±0.8	3.3±0.7	-, -
Systolic B.P (mmHg)	153.7±13.6	156.6±16	113.2±8.7	0.001*, 0.001**
Diastolic B.P (mmHg)	99.2±10.2	100.5±8.7	72.4±5.9	0.001*, 0.001**
AST (mg dL^{-1})	96.9±203.2	49.2±59.8	24.7±6	0.03*, 0.036**
ALT (mg dL^{-1})	93.6±230.4	43.1±64	23.4±6	0.03*, 0.05**
Hb (mg dL^{-1})	11.55±2.3	11.4±1.4	11.1±1.2	0.96*, 0.97**
Plt (mg dL^{-1})	184.5±87.3	225.3±83.6	217.9±74.2	0.47*, 0.89**
Urine albumin (mg dL^{-1})	2.026±1.052	1.8±1.027	0	0.001*, 0.001**
BUN (mg dL^{-1})	16±5.6	13±5.3	9.9±2.13	0.01*, 0.05**
Cr (mg dL^{-1})	0.9±0.3	0.75±0.19	0.7±0.13	0.69*, 0.98**
Apgar(First Minute)	6.34±3.2	7.7±2	8.6±0.8	0.001*, 0.01**
Apgar(Fifth Minutes)	7.5±3.5	9.16±1.5	9.7±0.6	0.001*, 0.29**
Weight of newborn	2310±820	2506.3±764	3035±366	0.001*, 0.001**

*For comparison preeclamptic women, with Uric acid = 6 mg dL^{-1}, with healthy ones (control), **For comparison preeclamptic women, with Uric acid <6 mg dL^{-1}, with healthy ones (control)

There were significant differences in the mean serum AST, ALT, BUN and urine albumin between the preeclampsia groups with uric acid levels less/greater than 6 mg dL^{-1} and healthy women (Table 1). However, these differences were not observed significantly in the mean serum Hb, Plt and Cr between the preeclampsia women with uric acid levels less/greater than 6 mg dL^{-1} and healthy ones. Its worthing to mention that in case of urine albumin, from 38 preeclamptic patients with less than 6 mg dL^{-1} uric acid, 55/26% cases had a urinary albumin (1+), 10.53% patients had a urinary albumin (2+), 28.95% patients had a urinary albumin (2+) and remain ones 5.26% had a urinary albumin (4+). Also, from 38 preeclamptic patients with more than 6 mg dL^{-1} uric acid, 42/11% ones had a urinary albumin (1+), 23.68 % cases had a urinary albumin (2+), 23.68 % patients had a urinary albumin (3+) and remain ones 10.53% had a urinary albumin (4+). But all cases of the control group didn't have urinary albumin.

Moreover, with exclude of Hb ($p \geq 0.97$), urine albumin ($p \geq 0.86$) and Cr ($p \geq 0.74$), there was significant differences in the mean serum levels of BUN ($p \geq 0.05$), Plt ($p \geq 0.05$), AST ($p \geq 0.03$) and ALT ($p \geq 0.03$), between preeclampsia women who have higher than 6 mg dL^{-1} uric acid and preeclamptic patients who have lower than 6 mg dL^{-1} uric acid (Table 1).

Clinical and maternal and fetal outcomes characteristics: Clinical outcomes characteristics of the study population are given in Table 1. In examining the effect of high levels of uric acid on the outcome of fetal and neonatal, there was significant differences in the Apgar scores in the first and fifth minutes of after delivery between the preeclampsia groups with uric acid levels less/greater than 6 mg dL^{-1} and healthy women (Table 1). Also Apgar score variable in the fifth minutes of life has a significant effect on the risk of preeclampsia with more than 6 mg dL^{-1} uric acid compared to preeclampsia with less than 6 mg dL^{-1} uric acid (Table 1, $p < 0.001$).

Neonatal weight variable in the preeclampsia groups with uric acid levels less/greater than 6 mg dL^{-1} were lower than its levels in the control group. Both these differences with $p<0.001$ considered to be as significant (Table 1).

DISCUSSION

Preeclampsia is a systemic disease characterized by undesirable endothelial function, vascular spasm, increased oxidative stress, decreased antioxidant, hyperlipidemia, activation of the coagulation system (Boulanger and Flamant, 2007; Vazquez-Rodriguez and Rico-Trejo, 2011; Genest *et al*., 2012). Over the years, various theories to clarify the pathophysiology of preeclampsia, including vascular endothelial damage, lack of coordination and implementation of the cardiovascular, immunological phenomena, abnormal trophoblast invasion, inflammation, production of cytokines, dyslipidemia, elevated homocysteine levels, reduced calcium excretion, thromboxane, prostacyclin and impaired imbalance between coagulation system have been proposed (Schwartz *et al*., 2000; Genest *et al*., 2012; Bellomo, 2012). Nevertheless, despite these findings, the exact etiology of preeclampsia remains yet unknown.

One of the methods that may be used to predict the preeclampsia and its severity is measuring of serum uric acid (Bainbridge and Roberts, 2008). As it was reported that the mean time of termination of pregnancy was decreased in the preeclamptic maternal, in the current study also the gestational time was significantly reduced in preeclampsia cases especially with hyperuricemia compared with healthy pregnant subjects. In keeping line with this study, Hawkins *et al*. (2012) reported that in the preeclampsia women associated with hyperuricemia, the mean rates of preterm delivery are higher than healthy pregnant women. Indeed, most of these deliveries were performed for protecting and saving life of the mother and her fetus. However, the premature finding of Low and Yeo (1995) from preeclampsia maternal compared to the incidence premature in the healthy pregnant ones was not notable and this it may be due to differences in the Low and Yeo (1995) treatment protocols and providing the suitable service of treatment-care to deal with these complications.

It's noteworthy to mention that the mean increase levels of uric acid in preeclampsia subjects are so variable. This differences and variations in serum uric acid levels could be due to diversity in different populations in different geographical areas, nutrition, diet and different breeds (Choi *et al*., 2005; Li *et al*., 2007). However, the mean level of uric acid is associated with the severity of preeclampsia (Bainbridge and Roberts, 2008). Some studies were regarded 5/5 mg dL^{-1} as the criteria for the high level of uric acid and as a symptom of prognosis of the disease (Brien, 1992). In the present study, the more or less than 6/5 mg dL^{-1} levels of the serum uric acid was regarded as a marker to predict the preeclampsia and it severity. Witlin *et al*. (1999) higher than 8/1 mg dL^{-1} levels of the uric acid were considered as criteria for hyperursemia and as well as to predict the incidence of preeclampsia. However, Lim *et al*. (1998) observed a weak association between uric acid and severity of the preeclampsia and so suggested that serum uric acid measurement is not more reliable to predict this diseases and its severity. It seems that the weak or negative

association that Lim *et al.* (1998) reported between uric acid and preeclampsia, is due to unsuitable time of the analysis and long time up to delivery.

In the present study, with increasing of the uric acid some biochemical and urine parameters such as liver enzymes (i.e., ASP and ALT), renal function test findings (i.e., BUN and urine albumin) were significantly increased in the preeclamptic patients. Additionally, the mean serum of these parameters is more notable when the level of uric acid is more than 6/5 mg dL^{-1}. In accordance with this study, Schwartz *et al.* (2008) showed that some liver enzymes levels and renal function test findings in women with preeclampsia increased in compared to the healthy ones. Moreover,McMaster-Fay (2008) reported that the plasma liver enzymes and homocysteine in preeclamptic patients were higher than healthy cases and also there is a direct relationship between liver enzymes secretion and homocysteine plasma levels. Also Zargar *et al.* (2012) suggested that a cause-effect relationship between the concentration of serum liver enzymes and preeclampsia may in fact exist. Powe *et al.* (2011) reported a four times increase in the level of liver enzymes and urine parameters of preeclamptic subjects compared to normal pregnant women. Burwick and Feinberg (2013) also declared a considerable increase in liver enzymes levels in preeclampsia pregnant women.

In generally, there are evidences that show increased levels of oxygen free radicals, lipid peroxide and antioxidant levels in preeclampsia cases (Watanabe *et al.*, 2012). High production of oxygen free radicals through increasing liver enzymes levels could be resulting from increased oxidative damage in these patients Zargar *et al.* (2012). These Reactive Oxygen Species (ROS) are capable to oxidize a biomolecule including membrane lipids. It is possible that the lipid peroxides and free radicals have been involved in the pathogenesis of preeclampsia and in turn cause the increase secretion of biochemical and urine parameters (Zargar *et al.*, 2012). The results of the Sharma *et al.* (2006) are indicating the increased oxidative stress and reduced antioxidant in the preeclamptic women. However, Regan *et al.* (2001) did not observed any evidence of increasing lipid peroxidation in preeclampsia cases. Consequently, it seems that antioxidant activity may suppress the dynamics of preeclampsia. So, if the antioxidant activity decrease remarkably in the pregnant women, the oxidative stress and as well as lipid peroxide levels will increase. Thus, these disorders could lead to liver, renal and endothelial dysfunction in preeclamptic women.

The association between greater increase in serum uric acid and high blood pressure in pregnancy has not been fully known. However, there is a theory that uric acid causes relaxation of vascular smooth muscle tone. Therefore, it's increasing leading to vasoconstriction and so increasing blood pressure. The findings of the present study also have been emphasized on the increasing systolic and diastolic blood pressure in the preeclamptic women with hyperuricemia compared to healthy ones that with the studies in this field is a fully coordinated (Watanabe *et al.*, 2012).

As in other studies, the high incidences of maternal and fetal complications in preeclampsia were more reported, in the current examine, the results showed that the relationship of reducing mean Apgar scores (less than 7) in the first and fifth minutes, with increasing of the uric acid was significant. Its worthing to mention that in the more than 6/5 mg dL^{-1} levels of the serum uric acid group, five infants with Apgar zero was delivered. Kang *et al.* (2004) reported that preeclampsia that is associated with hyperuricemia is related as well with maternal and fetal morbidity. However, Williams and Galerneau (2002) and Roberts *et al.* (2005) revealed that although, the level of uric acid in pregnant cases with hypertension and also preeclampsia is a quit higher than women with high normal blood pressure, it can not a well index to predict fetal or maternal complications. In addition, (Thangaratinam *et al.*, 2006) showed that there is no evidence of an association between perinatal mortality and uric acid levels in patients with severe preeclampsia.

In this study, the incidence of prematurity, intrauterine fetal growth cessation or reduction in severe preeclampsia was much more observed as well. All fetal deaths were occurring in preeclampsia especially in hyperuricemia preeclamptic cases. Also, induction was higher in severe preeclampsia. Vazquez-Rodriguez and Rico-Trejo (2011) also reported that the induction labor in the hyperuricemia cases was more done than spontaneous deliveries. It seems that the main reason to considering early termination of pregnancy for severe preeclampsia is lack of proper uterine contractions.

CONCLUSION

In conclusion, with increasing of the uric acid in preeclamptic women through the third trimester of pregnancy, the mean amount of some biochemical and urine parameters i.e., liver enzymes, renal function test findings and as well as severity of preeclampsia i.e., reducing of Apgar scores, incidence of prematurity, intrauterine fetal growth cessation or reduction were increased. Therefore, measuring these compounds as adjunctive tests may be can useful in the diagnosis and or even in assessment of the severity of preeclampsia.

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