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Association of Uric Acid and C-Reactive Protein with Severity of Preeclampsia in Iranian Women

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This study was planned to determine the levels of uric acid (UA) and CRP at preeclampsia and their association with the severity of the disease. In a cross-sectional, case-control study we measured UA and CRP levels in blood samples from 46 women with preeclampsia, 23 normal pregnant women and 23 non pregnant women matched for age, BMI, parity and gestational age were measured. Twenty three patients had developed severe and 23 mild preeclampsia. UA and CRP were measured by enzymatic method and enzyme-linked immunosorbent assay, respectively. Roc curve was used to determine the optimal cutoff value. Results showed CRP and UA concentrations were higher in Preeclamptic group (33.77±25.97, 5.93±0.75) compared with normal pregnant group (17.31±19.54, 5.47±0.41). CRP levels were also significantly elevated in women with severe preeclampsia compared to those mild preeclampsia (42.26±24.04, 16.81±22.03). Determination of serum CRP levels may be used as marker for the severity of preeclampsia. We also suggest that serum UA level of 5.5 mg dL^{-1} is best cutoff point for the diagnosis of preeclampsia.

Key words: Preeclampsia, C-reactive protein, uric acid, severity of disease, pregnancy

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INTRODUCTION

Preeclampsia is a major complication of pregnancy and occurs in about 7-10% of all pregnant women (Ray *et al.*, 1999) and it is still an important cause of both maternal and fetal morbidity and mortality (Funai *et al.*, 2005).

The physiopathology of preeclampsia remains uncertain despite many research efforts (Myatt and Miodovnik, 1999). Several etiologies have been implicated in the development of preeclampsia. Endothelial cell dysfunction and inflammation are considered to have a crucial role in the pathophysiologic mechanism of preeclampsia (Kharb *et al.*, 1998).

Mediators of an inflammatory response are altered in women with preeclampsia, including increased C-Reactive Protein (CRP) (Teran *et al.*, 2001). However, little is known about whether or not there is a correlation with the severity of disease.

Uric Acid (UA) is the major end-product of purine metabolism. The cause of the hyperuricemia in preeclampsia has been attributed to either a decreased excretion or to an increased production of uric acid. Decreased uric acid clearance, reflected by altered tubular function has been documented, while in 1990 Fay proposed an increased breakdown of purines in the placenta as a possible explanation for the overproduction of uric acid (Jeyabalan and Conrad, 2007; Hill, 1987; Fay, 1990). Hyperuricemia in preeclampsia has generally been regarded as a marker of renal disease rather than as a risk factor for the progression of the disease. Few studies have reported correlation of UA with the clinical severity of preeclampsia.

The aim of this study was to determine the levels of UA and CRP in preeclampsia and their association with the severity of the disease.

MATERIALS AND METHODS

This cross-sectional, case-control study was conducted at the Arak University, Medical Faculty, Departments of Immunology and Obstetrics and Gynecology, from April 2006 until May 2007. Ethical approval for this study was obtained from the Ethical Committee of University of Medical Sciences. The study included 23 women in the third trimester of pregnancy with mild preeclampsia at the time of admission (group 1), 23 women in the third trimester of pregnancy with severe preeclampsia (group 2), 23 healthy normotensive women in the third trimester of pregnancy (control group, group 3) and 23 non pregnant women (group 4) matched for age, BMI, parity and gestational age.

Control group was monitored at the Department of Obstetrics and Gynecology of Taleghani hospital with gestational age 25-40 weeks, no chronic medical disorders and not in labor. They were normotensive and had normal blood pressures throughout gestation. Patients with a history of diabetes, renal disease, hypertension, other cardiovascular illness and symptomatic infectious diseases were excluded. Abnormal Liver Function Test (LFT) and renal disease were defined as serum bilirubin >25 μmol L^{-1} and serum creatinine >1.0 mg dL^{-1}, respectively.

Inclusion criteria for preeclamptic group were: absence of labor contractions and premature rupture of membranes or clinical chorioamnionitis. None of the patients included had underlying diabetes, renal diseases, chronic hypertension or symptomatic infectious diseases, which were excluded during routine interviews, clinical investigations and laboratory tests. The pregnant women were not given corticosteroids at least 7 days prior to inclusion in the study.

Mild preeclampsia was defined as a Blood Pressure (BP) 140 mmHg or greater or a diastolic BP of 90 mmHg confirmed by 6 or more hours apart, where as proteinuria was defined as < 2+ on urine dipstick were observed on at least two random specimens collected more than 4 h apart, after the 20th week of pregnancy. Severe preeclampsia was defined if diastolic BP increased to at least 110 mmHg or diastolic BP 160 mmHg or higher, along with proteinuria > 2+ on urine dipstick and the presence of headache, visual disturbances, upper abdominal pain, oliguria. All women in severe preeclampsia group had a combination of hypertension and proteinuria. Gestational age was calculated from the first day of the last menstrual period, unless ultrasonography results found a discrepancy of 14 days or more. Blood pressures were measured (and controlled twice) at entrance into the study (American College of Obstetricians and Gynecologists, 1996; Kumar *et al.*, 2005).

In all subjects, after gave informed written consent, blood was drawn on admission in the morning after 8 h fasting. In the preeclampsia group, blood samples were collected when the patient presented for evaluation and before initiation of medical therapy. The controls were recruited when they admitted for their routine third trimester control and then observed to ensure that they did not develop disease later. In all patients, UA and CRP were determined. ELISA (STAT FAX 2000-USA) for CRP was performed using a commercial kit (Monobind, INC High Sensitivity CRP-USA). The assay has a detection limit of 0.25 μg mL^{-1}. Serum uric acid was measured by an enzymatic method based on uricase (Ziestchem, Iran).

The sample size was determined by the previous case-control study of Ustun *et al.* (2005). Numerical data were expressed as mean±Standard Deviations (SD). Statistical analysis of the data was performed with the software package SPSS for windows 11.0 (Statistical package for social sciences; SPSS Inc., Chicago, IL). Kolmogorov-Smirnov analysis was used to test if the results were normally distributed. Analysis of variance with the Kruskal-Wallis test was used when three groups were compared. After the difference was detected between the groups, the groups were compared for statistical significance using the Mann-Whitney U-test. A logistic regression analysis has been performed with the confounding factors of the study to investigate the relationship between UA and CRP with preeclampsia, giving an adjusted odds ratio (ORa) and its 95% confidence interval. $p < 0.05$ was considered to be significant. A Receiver Operating Characteristic (ROC) curve was constructed to evaluate the sensitivity and specificity of CRP and UA.

RESULTS AND DISCUSSION

Maternal age, gestational age and body mass index were not significantly different between the groups. As expected, the systolic and diastolic blood pressure values were higher in the preeclampsia group (Table 1). The value of serum CRP in preeclampsia patients was markedly higher than that normal third trimester pregnant women and non pregnant women (Table 2). CRP-a sensitive marker of tissue damage and inflammation was proposed to play a role in eliciting the inflammatory response characteristics of preeclampsia (Redman *et al.*, 1999). CRP acts as a scavenger and is responsible for the clearance of membranes and nuclear antigens (Du Clos, 1996). The relationship between the levels of CRP and preeclampsia

has already been studied. Higher concentration of CRP has been reported during preeclampsia (Teran *et al.*, 2001; Okerengwo *et al.*, 1990). In this study levels of CRP were found to be significantly higher in women with severe preeclampsia than mild preeclampsia with similar chronologic age, gestational age and body mass index (Table 2). Present results support the hypothesis that systemic inflammation is involved in the pathogenesis of preeclampsia.

In accordance with previous reports, preeclampsia is associated with increased CRP levels however, there are few studies concerning correlation of CRP levels due to severity of preeclampsia (Teran *et al.*, 2001; Okerengwo *et al.*, 1990; Belo *et al.*, 2003; Vickers *et al.*, 2003; Tjoa *et al.*, 2003). Present results showed that the diagnosis value of a CRP higher than 30 μg mL⁻¹ was interesting for sensibility and specificity but if the negative predictive value is strange (90.9%), then the positive predictive value is weak (57.1%, Fig. 1). This last point is a limitation for its interest as a diagnosis test.

Many studies have been devoted to the association of hyperuricemia and preeclampsia (Redman *et al.*, 1976; Acien *et al.*, 1990; Boneu *et al.*, 1980; Lancet and Fisher, 1956; Yoshimura *et al.*, 1990). Present results show that UA level was significantly higher in the severe preeclamptic group than in the control group and non pregnant women (Table 2). Although elevated, the lack of significant differences between mild and severe preeclampsia regarding UA level may be due to small sample size and corresponding low statistical power.

Redman (1987) showed that the basal serum uric acid level in normal women in the third trimester was 2.112 ± 0.40 mg dL⁻¹, with an increase of 1.20 mg dL⁻¹ between 16 and 40 weeks of gestation. In the same study, the serum uric acid levels in the preeclamptic women were observed between 3.27 ± 1.02 (preeclampsia severity 1+)

Table 1: Demographic and medical characteristics of study subjects

| Demographic's criteria | Patients | | | | |
	PE (n = 46)	Mild PE (n = 23)	Severe PE (n = 23)	Normal pregnant (control group) (n = 23)	Non pregnant (n=23)
Maternal age (years)	27.79±4.43	28.25±5.39	27.56±4.00	26.19±4.44	24.52±3.24
Body mass index (kg m⁻²)	25.33±2.48	24.73±1.97	25.63±2.71	26.88±2.43	24.43±2.37
Gestational age (w)	36.75±2.90	37.25±2.25	36.50±3.24	38.68±1.07	
Systolic blood pressure (mmHg)		141.25±3.53	168.12±11.09	114.20±14.6	
Diastolic blood pressure (mmHg)		95.00±7.56	119.06±5.84	70.50±8.50	
Proteinuria	+2(+1,+3)	+2(+1,+2)	+2(+1,+3)		

Values are given as mean±SD, PE: Preeclampsia

Table 2: Laboratory data of study subjects

| Demographic's criteria | Patients | | | | |
	PE (n = 46)	Mild PE (n = 23)	Severe PE (n = 23)	Normal pregnant (control group) (n = 23)	Non pregnant (n=23)
UA (mg dL⁻¹)	5.93±0.75*	5.77±0.67	6.01±0.8*, **	5.47±0.41	4.98±0.37
CRP (μg mL⁻¹)	33.77±25.97*	16.81±22.03	42.26±24.04*, ***	17.31±19.54	2.48±1.78

Values are given as mean±SD, PE: Preeclampsia, *$p < 0.05$ compared with normal pregnant group and non pregnant group, **p: Not significant compared with mild preeclampsia, ***$p < 0.05$ compared with mild preeclampsia
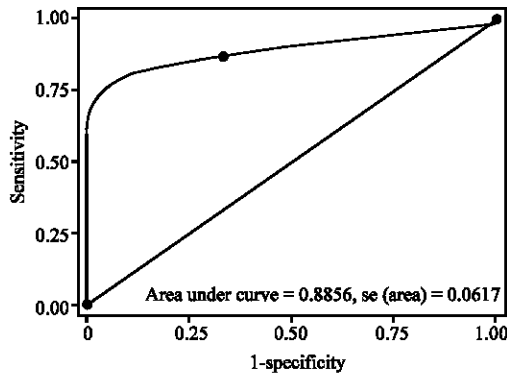
Fig. 1: Receiver Operating Characteristic (ROC) curve of
CRP to predict women with preeclampsia. Best
cutoff value for CRP is 30 μg mL^{-1}, which gives a
sensitivity of 87% and specificity of 66.7%. The
ROC curve revealed the continuum of sensitivity
and specificity encountered as the cutoff point
was varied. CRP with a cutoff point of 30 μg mL^{-1}
identified women with preeclampsia with
sensitivity of 87% (95% CI, 65.3-96.6) and
specificity of 66.7% (95% CI, 50.9-79.6). Its
negative predictive value of 90.9% (95% CI,
74.5-97.6) was high; the positive predictive value
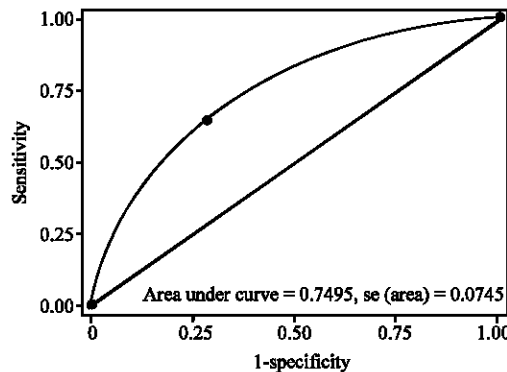of 57.1% (95% CI, 39.5-73.2) was low

Fig. 2: Receiver operating characteristic (ROC) curve of
UA to predict women with preeclampsia. Best
cutoff value for UA is 5.5 mg dL^{-1}, which gives a
sensitivity of 65.2% and specificity of 71.1%. UA
with a cutoff point of 5.5 mg dL^{-1} identified
women with preeclampsia with sensitivity of 65.2%
(95% CI, 42.8-82.8) and specificity of 71.1% (95%
CI, 55.5-83.2). Its negative predictive value of 80%
(95% CI, 63.9-90.4) was high; the positive
predictive value of 53.6% (95% CI, 34.2-72) was
low. The study revealed that when UA and CRP
were high the risk of preeclampsia was high.
The adjusted odds ratio were 4.62 (95% CI,
1.58-13.5; p> 0.001) and 13.33 (95% CI, 3.41-52.09;
p>0.001), respectively

and 4.59±0.91 mg dL^{-1} (severity 3+). These values were
smaller than the maximal level reported in our study
(6.01 mg dL^{-1}). Dekker and Sibai (1991) reached the
opposite conclusion in their study, compared to ours
where the only case of preeclampsia occurred in the
control group.

Serum uric acid was like in other studies
(Frenkel *et al.*, 1991; Sanchez-Ramos *et al.*, 1991) of
course, significantly higher in preeclamptic women than
in controls. Maternal serum uric acid level of 5.5 mg dL^{-1}
was found to be the most useful cutoff values for the
diagnosis of preeclampsia (Fig. 2).

CONCLUSION

We found evidence of inflammation in preeclampsia.
High CRP level was associated with severe preeclampsia.
CRP correlated positively and significantly with the
severity of disease in preeclampsia.

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REFERENCES

Acien, P., G. Lloret and M. Lloret, 1990. Perinatal
morbidity and mortality in pregnancy hypertensive
disorders: Pronostic value of the clinical and
laboratory findings. Int. J. Gynaecol. Obstet.,
32 (3): 229-235.

American College of Obstetricians and Gynecologists,
1996. Hypertension in pregnancy. Am. Coll. Obset.
Gynecol. Technol. Bull., 219: 1-8.

Belo, L., A. Santos-Silva and M. Caslake, 2003. Neutrophil
activation and C-reactive protein concentration in
preeclampsia. Hypertens Pregnancy, 22 (2): 129-141.

Boneu, B., A.S.P. Fournie, H. Grandjean, R. Bierme and
J. Pontonnier, 1980. Platelet production time, uricemia
and some hemostasis tests in pre-eclampsia. Eur. J.
Obstet. Gynecol. Reprod. Biol., 11 (2): 85-94.

Dekker, G.A. and B.M. Sibai, 1991. Early detection of pre-
eclampsia. Am. J. Obstet. Gynecol., 165 (1): 160-172.

Du Clos, T.W., 1996. The interaction of C-reactive protein
and serum amyloid P component with nuclear
antigens. Mol. Biol. Rep., 23 (3-4): 253-260.

Fay, R.A., 1990. Uric acid in pregnancy and preeclampsia:
An alternative hypothesis. Aust. N.Z. J. Obstet.
Gynecol., 30 (2): 141-142.

Frenkel, Y., G. Barkai, S. Mashiach, E. Dolev, R. Zimlichman and M. Weiss, 1991. Hypocalciuria of preeclampsia is independent of parathyroid hormone level. Obstet. Gynecol., 77 (5): 689-691.

Funai, E.F., Y. Friedlander, O. Paltiel, E. Tiram, X. Xue, L. Deutsch and S. Harlap, 2005. Long-term mortality after preeclampsia. Epidemiology, 16 (2): 206-215.

Jeyabalan, A. and K.P. Conrad, 2007. Renal function during normal pregnancy and preeclampsia. Front Biosci., 1 (12): 2425-2437.

Hill, L.M., 1978. Metabolism of uric acid in normal and toxemic pregnancy. Mayo Clin. Proc., 53 (11): 743-751.

Kharb, S., N. Gulati, V. Singh, G.P. Singh, 1998. Lipid peroxidation and vitamin E levels in preeclampsia. Gynecol. Obstet. Invest., 46 (4): 238-240.

Kumar, A., B.K. Ghosh and N.S. Murthy, 2005. Thyroid hormonal status in preeclampsia maternal. Indian J. Med. Sci., 59 (2): 57-63.

Lancet, M. and I.L. Fisher, 1956. The value of blood uric acid levels in toxaemia of pregnancy. J. Obstet. Gynaecol. Br. Emp., 63 (1): 116-119.

Myatt, L. and M. Miodovnik, 1990. Prediction of preeclampsia. Semin Perinatol., 23 (1): 45-57.

Okerengwo, A.A., A.I. Williams and P.A. Ibeziako, 1990. Immunological studies on preeclampsia in Nigerian women. Int. J. Gynaecol. Obstet., 33 (2): 121-125.

Ray, J., K. Vasishta, S. Kaur, S. Majumdar and H. Sawhney, 1999. Calcium metabolism in pre-eclampsia. Int. J. Gynecol. Obstet., 66 (3): 245-250.

Redman, C.W., L.G. Beilin, J. Bonnar and R.H. Wilkinson, 1976. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. Lancet, 1 (7974): 1370-1373.

Redman, C.W., 1987. Hypertension in pregnancy: A case discussion. Kidney Int., 32 (1): 151-160.

Redman, C.W., G.P. Sacks and I.L. Sargent, 1999. Preeclampsia: An excessive maternal inflammatory response to pregnancy. Am. J. Obstet. Gynecol., 180 (2): 499-506.

Sanchez-Ramos, L., S. Sandroni, F.J. Andres and A.M. Kaunitz, 1991. Calcium excretion in preeclampsia. Obstet. Gynecol., 77 (4): 510-513.

Teran, E., C. Escudero, W. Moya, M. Flores, P. Vallance and P. Lopez-Jaramillo, 2001. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with preeclampsia. Int. J. Gynecol. Obstet., 75 (3): 243-249.

Tjoa, M.L, J.M.G. Van Vugt, Go ATTJJ, M.A. Blankenstein, C.B.M. Oudejans and I.J. Van Wijk, 2003. Elevated C-reactive protein levels during first trimester of pregnancy are indicative of preeclampsia and intrauterine growth restriction. J. Reprod. Immunol., 59 (1): 29-37.

Ustun, Y., Y. Engin-Ustun and M. Kamaci, 2005. Association of fibrinogen and C-reactive protein with severity of preeclampsia. Eur. J. Obstet. Gynecol. Reprod. Biol., 121 (2): 154-158.

Vickers, M., I. Ford and R. Morrison, 2003. Markers of endothelial activation and atherotrombosis in women with history of preeclampsia or gestational hypertension. Thromb. Haemost., 90 (6): 1192-1197.

Yoshimura, A., T. Ideura, S. Iwasakis and S. Koshikawa, 1990. Significance of uric acid clearance in pre-eclampsia. Am. J. Obstet. Gynecol., 162 (6): 1639-1640.