

ELEVATED LEVELS OF SERUM URIC ACID, CREATININE OR UREA IN PREECLAMPTIC WOMEN

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ABSTRACT

Background: Hypertensive disorders of human pregnancy, such as preeclampsia, complicate a sizeable percentage of all pregnancies, needing its early indication and warning.

Aims & Objective: To measure and compare serum uric acid, serum creatinine and serum urea in pre-eclamptic and normotensive groups.

Material and Methods: This is a cross-sectional, hospital based study involving 105 age – matched women of South India (devoid of diabetes, urinary tract infections, renal or liver disorders), all in their third trimester singleton pregnancy, at the Obstetrics and Gynaecology Department of Sri Ramachandra Medical College and Hospital, Chennai, India during the period of December 2008 to July 2009. The data were collected following standard procedures and statistical analysis was done using unpaired t – test.

Results: The levels of serum uric acid and serum creatinine, expressed in mg/ dL were significantly elevated in pre-eclamptics respectively (5.29 ± 0.84 and 0.72 ± 0.387) when compared to normotensives (3.86 ± 0.92 and 0.58 ± 0.283). There was a statistically insignificant and small increase in serum urea level in pre-eclamptics (28.07 ± 4.97) compared to normotensives (26.46 ± 3.55). There was a lack of any correlation between the positive differences in the values of each parameter with the extent of corresponding raised blood pressure.

Conclusion: The elevated values of uncorrelated serum uric acid, serum creatinine or serum urea thus precludes them to be useful for consideration as consistent predictive indicator(s) for preeclampsia or pregnancy related hypertension.

KEY-WORDS: Preeclampsia; Serum Uric Acid; Serum Creatinine; Serum Urea; Normotension

Introduction

It is well known that preeclampsia, a hypertensive disorder during pregnancy, is one of the most potential complications contributing to preterm labour/delivery, perinatal mortality, maternal mortality, intra-uterine growth retardation, low birth weight infants and many such related problems. Over the years, a lot of interest has been directed at studies on the role of serum uric acid (SUA), urea (SU) and creatinine (SCr) in the pathogenesis of pregnancy induced hypertension, such as preeclampsia. A number of important studies are available which confusingly and often conflictingly describe the dependence of these parameter levels in pre-eclamptic and normotensive groups. For example, the SUA levels were found to be significantly elevated in the pre-eclamptics (with reference to the normotensives) in a number of studies^[1-13], while the same was also complex in nature in several studies as being

described. The measured SCr and SUA levels were significantly elevated in pre-eclamptics^[1,15], but SU levels were not much different in the two cited groups of pre-eclamptics and normotensives.^[1,9] Levels of SUA and SU were higher in pre-eclamptics^[2], but SU and SCr levels did not show much change in yet other studies.^[9] Another study described that there was insignificant changes in the SUA and SCr in both the cited groups.^[16] In some other studies, the change in serum uric acid levels in the pre-eclamptics was on the increasing side with some overlap leading to no predictive importance.^[14,17] Such confusing results have encouraged us to undertake a detailed study on these aspects, with a desire to understand the underlying intricacies. The aim of the study was to measure and compare the SUA, SCr and SU in preeclamptic and normotensive groups, and correlate, if possible, the obtained results with severity of preeclampsia. This report is a continuing one to our earlier studies.^[18,19]

Materials and Methods

This hospital based cross-sectional study involved 50 normal pregnant and 55 pre-eclamptic women in their singleton pregnancy during December 2008 to July 2009, from the outpatients and inpatients wards of Department of Obstetrics and Gynaecology of Sri Ramachandra Medical College Hospital and Research Centre, Sri Rama Chandra University, Porur, Chennai, India. All were age-matched and in their third trimester. The pre-eclamptic subjects were diagnosed to have the disease based on the development of hypertension in the third trimester for the first time and proteinuria with or without edema.

The diagnosis of preeclampsia was based on the definition of American College of Obstetrics and Gynaecologists.^[20]

1. Systolic blood pressure greater than 140 mm Hg or a rise of at least 30 mm Hg, and/ or
2. Diastolic blood pressure greater than 90 mm Hg or a rise of at least 15 mm Hg (manifested on two occasions at least 6 hours apart), and/ or
3. Proteinuria of 300 mg or greater in 24 hours urine collection or protein concentration of 1gm/ L (on two occasions at least 6 hours apart).

Ethical permission was obtained from the institution as a part of the post graduate curriculum. After obtaining informed written consent, personal information of each subject was collected in a supplied questionnaire. Diabetics and patients with history of UTI, renal disorders and liver disorders were excluded from the study. Patients were advised to abstain from having coffee, chocolates, etc. for at least 2 h before coming for blood sampling.

Blood pressure measurements using a sphygmomanometer and proteinuria analysis were performed using standard procedures.^[18] For each experiment, 8 ml of venous blood was collected in EDTA-treated tubes from the cubital vein. Serum uric acid levels were measured by colorimetric assay ^[21]. Serum creatinine or urea levels were measured using standard procedures.^[22, 23]

Statistical Analysis

The observed data were statistically analyzed by a Graph Pad Software using unpaired students t - test. The results were expressed in terms of Mean, Standard Deviation, Confidence interval and Percentage. The two - tailed P values are provided in the table showing the results; P value of < 0.05 was considered statistically significant.

Results

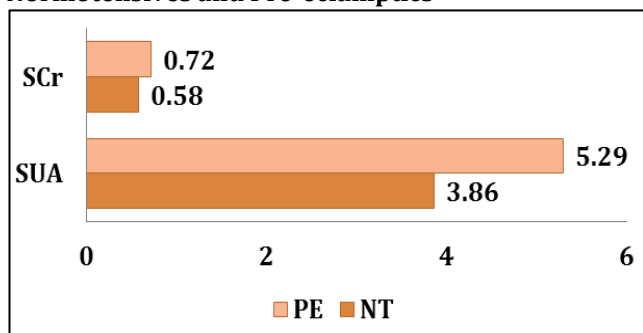
- a. The mean age in years and the mean gestational period in weeks were not statistically different in both the groups of normotensives and pre-eclamptics.
- b. The mean weight in kilograms was statistically different in these two groups, being higher for the pre-eclamptics.
- c. The systolic blood pressure (SBP) was significantly higher for the pre-eclamptic group than for the normal pregnant group. Similar results were noticed for diastolic blood pressure (DBP).
- d. The serum uric acid level (SUA) was significantly higher for the pre-eclamptic group than for the normal pregnant group. The 95 % confidence interval (-1.771 to - 1.088).
- e. The pre-eclamptic group showed slightly higher levels of serum urea (SU) than the normotensive pregnant women, which was statistically insignificant. The 95 % confidence interval (- 3.30 to - 0.07).
- f. The pre-eclamptic women showed a statistically significant higher value of serum creatinine levels than the normal pregnant women. The 95 % confidence interval (- 0.276 to - 0.011).

Average values of observed parameters of age, weight, gestational age, SBP and DBP, SUA, SU, SCr are summarized in Table -1, Figure -1 and 2.

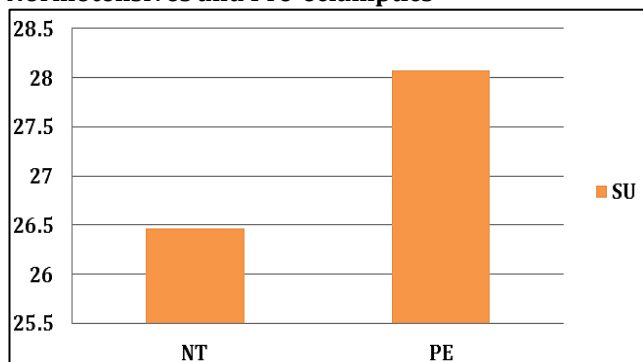
Moreover, it was also experimentally found that the individual values of observed SUA, SU or SCr in preeclamptics were relatively higher than those of the average values of normotensives, but the positive differences in the values in each parameter were not well correlated with the extent of raised blood pressure. Plots of δ SBP or δ DBP versus the incremental value of each of the three parameters were not even remotely linear.

Table-1: Average Values of Measured Parameters for Pre-eclamptics and Normotensives

Characteristics	Groups	Mean Value	Standard Deviation	P Value	% Change
Age in Years	Normal	24.76	3.497	0.689	0.0762
	Pre-eclamptic	25.04	3.554		
Weight in Kilograms	Normal	55.40	8.958	0.000	+24.9
	Pre-eclamptic	69.20	5.091		
Gestational Age in Weeks	Normal	34w 2 d	3.0280	0.305	
	Pre-eclamptic	34w 4 d	2.9885		
Systolic BP in mm of Hg	Normal	114.5	6.664	0.000	+44.4
	Pre-eclamptic	165.42	7.569		
Diastolic BP in mm of Hg	Normal	73.44	6.273	0.000	+39.9
	Pre-eclamptic	102.76	5.894		
Serum Uric Acid (mg/dL)	Normal	3.86	0.92	0.0001	+37
	Pre-eclamptic	5.29	0.84		
Serum Urea (mg/dL)	Normal	26.46	3.55	0.068	+6
	Pre-eclamptic	28.07	4.97		
Serum Creatinine (mg/dL)	Normal	0.58	0.283	0.0336	+24
	Pre-eclamptic	0.72	0.387		

Figure-1: Relative Average Values of SUA and SCr in Normotensives and Pre-eclamptics

NT – Normotensive; PE – Preeclampsia; SUA – Serum Uric Acid; SCr – Serum Creatinine

Figure-2: Relative Average Value of SU in Normotensives and Pre-eclamptics

NT – Normotensive; PE – Preeclampsia; SUA – Serum Urea

Discussion

Several qualitative inferences can be drawn on the basis of the available results of this and other earlier studies.

Significant increases in systolic blood pressure and/ or diastolic blood pressure, and the mean weight changes in pre-eclamptics (with reference

to the normotensives) are in line with the several studies reported earlier.^[18,19]

There appears a conflict and confusion in the extent of the elevated values of the SUA (as those also of the SU or SCr) levels in pre-eclamptic women. While a majority of available studies generally observe significant elevation in SUA levels in the former group, several studies also find no such clear cut significance in the respective results. Similarly, with reference to the extent of SU or SCr levels in preeclampsia, often differing results have been observed. Furthermore, whether or not the elevated levels of SUA (as those of the SU or SCr) can be taken as a predictive indicator for the pre-eclamptic disorder remains to be considered.

For example, in several studies it was found that the extent of the elevation in SUA level in pre-eclamptics was an indicator for the degree of severity of this disorder.^[1-6,8-10] Elevated SUA levels have also been interpreted to act as an important cofactor involved in the pathogenesis and manifestation of pre-eclamptic disorder.^[7]

In the present study, though the serum uric acid level was higher in pre-eclamptics when compared to the normotensives, the elevated levels of uric acid did not correlate with the raised systolic blood pressure or the raised diastolic blood pressure. This is in line with an earlier study predicting that the changes in the plasma concentrations of serum uric acid can more prominently be correlated with the degree of

proteinuria rather than with the level of hypertension.^[1]

On the basis of observed TOS (Total Oxidant Status) and TAS (Total Antioxidant Status) levels, it has been inferred that increased oxidative stress and antioxidative defence mechanisms may contribute to the disease process in preeclampsia.^[13]

One of the most commonly accepted explanations for elevated SUA has been said to be increased reabsorption and decreased excretion of uric acid in proximal tubules, similar to the physiologic response to hypovolemia.^[11] Recently, increased oxidative stress and formation of reactive oxygen species (ROS) have been proposed as another contributing source of hyperuricemia noted in preeclampsia apart from renal dysfunction.^[24] Uric acid (as also creatinine and to some extent urea), possessing water soluble or hydrophilic antioxidant characteristics, may delay or inhibit cellular damage mainly through the free radical scavenging property; it also presents strong antioxidant activity towards ROS in aqueous phase.^[25] Uric Acid contributes to about 60% of free radical scavenging activity in human serum.^[26] The observed uric acid elevation may be a protective response, capable of opposing harmful effects of free radical activity and oxidative stress. Elevated serum uric acid concentrations predict the development of hypertension.^[27] In addition, an elevated SUA concentration may reflect impaired endothelial integrity, in which endothelial dependent vascular relaxation produced by nitric oxide (NO) is reduced.^[28] Uric acid thus may function as a marker of oxidative stress tissue injury dysfunction. During uncomplicated pregnancies serum uric acid concentrations decrease by about 25 % to 35 % in early pregnancy, but then increase throughout the pregnancy until towards the end of it when they approach non-pregnant levels.^[29] It has been proposed that these pregnancy mediated changes in serum uric acid are often the result of altered renal handling. Increased serum uric acid in preeclampsia is secondary to reduced renal urate clearance because of renal dysfunction.^[30] and also due to increased xanthine oxidase activity.^[24] It is also possible that increased serum uric acid values

may indicate the presence of undiagnosed sub-clinical renal disease in some subjects and this may increase the risk for preeclampsia.

However, in several studies it was concluded that the measured elevated SUA level can be taken as an unreliable indicator for development of hypertension.^[14,15] Another review inferred that uric acid (SUA) is not a consistent predictive factor for the development of preeclampsia, but its level generally increases once the disease manifests and plasma levels of uric acid may often correlate with disease severity.^[17]

The differences in each of the mean SUA or SCr concentrations between the preeclamptics and the normotensives respectively were not statistically significant and that these parameters are of little value in the prediction of preeclampsia.^[16]

Few studies^[9,16] observe insignificant change in SCr level in the two cited groups. On the other hand, an early study showed increased SCr level but said the latter to be of no predictive value in preeclampsia.^[1] Our present study is also in line with two earlier studies^[1,9] wherein small change in SU levels both in pre-eclamptics and normotensives are insignificant.

Certain aspects of the study have few limitations like the following:

1. Small sample size
2. A lack of urinary measurements of uric acid, creatinine and urea

A lack of measurements of various oxidative stress inducing substances

Conclusion

In sum, a lack of correlation between differences of average SBP or DBP with average differences of significantly elevated serum uric acid, or that of serum creatinine or that of small and insignificant elevated serum urea in pre-eclamptics in relation to normotensives, clearly suggests that the elevated values of latter parameters cannot be considered as a consistent predictive indicator for preeclampsia. Further probes with larger samples and other important measurements appear necessary to clinch the issue.

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