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Variations in serum uric acid and serum magnesium levels in pre-eclamptic women

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Abstract
The purpose of the present study was to estimate serum uric acid and magnesium levels in pre-eclamptic, eclamptic and normotensive groups to identify women who are at high risk of developing the disease early in pregnancy. The study may provide possible biochemical parameter in toxemias of pregnancy. This is because early identification of biochemical markers of the disease would not only facilitate to identify those at increased risk for pre-eclampsia but also help in determining those patients likely to benefit from interventional measures. This study was conducted in the Department of Biochemistry, Gandhi Medical College, Secunderabad, Telangana, India. The cases for the study were selected from the antenatal outpatient, Gandhi Hospital, Secunderabad, according to specific criteria like women with age group between 18-29 years, primigravide with known last menstrual period and gestational age between 20-30 weeks.

A total of n = 38 subjects were selected and categorized into three groups. 24 (n = 24) among n = 38 women, were Pregnancy Induced Hypertensive (B.P. >140/90 mmHg), included in experimental group and remaining 14 were normotensive (B.P. <140/90 mmHg) considered as controls (n = 14). The experimental group was further categorized into two groups, with n = 18 subjects in pre-eclampsia, and n = 6 in eclampsia. The data obtained was subjected to one-way analysis of variance statistical analysis. The serum uric acid levels studied in various study groups showed significant increase in pre-eclamptic (n = 18) and eclamptic (n = 6) the difference being statistically significant at $p \leq 0.001$. The mean serum uric acid level values for women with pre-eclampsia (4.02 ± 0.17 mg/dl, n = 18) and eclampsia (4.98 ± 0.57 mg/dl, n = 6) were significantly higher than those of controls (3.88 ± 0.18 mg/dl, n = 14) which is statistically significant at $p < 0.001$. Moreover, it was also experimentally found that the individual values of serum uric acid in pre-eclamptics and eclamptics were relatively higher than those of the average values of normotensives. Although mean serum uric acid values are elevated in women with pre-eclampsia, the clinical utility of serum uric acid values in differentiating various hypertensive diseases of pregnancy appears to be limited. In the setting of chronic hypertension, however, a serum uric acid level of > or = 5.5 mg/dl could identify women with an increased likelihood of having superimposed pre-eclampsia. The mean serum magnesium level in pre-eclampsia (Group II) and eclampsia (Group II) was 1.84 ± 0.09 and 1.77 ± 0.03mg/dl respectively. The serum magnesium levels were observed to be decreased in pregnancy. Serum magnesium levels were observed to be significantly decreased in the experimental group III (eclampsia). Whereas, in pre-eclampsia though there was a marked decrease in serum magnesium level, the decreases were not statistically significant. The prevalence of magnesium deficiency was higher in pregnant women.

Keywords: eclampsia, pre-eclampsia, serum magnesium, serum uric acid

Introduction

Pre-eclampsia is a medical complication occurring during pregnancy and is associated with high incidence of maternal and fetal morbidity and mortality in both developed and developing countries. Its incidence is 4-8% of pregnancies [1, 2].

It is a systemic syndrome of pregnancy clinically characterized by multi-system disorder of pregnancy characterized by high blood pressure and a large amount of protein in the urine [3].

It is well known that pre-eclampsia is one of the most potential complications contributing to pre-term labour, perinatal mortality, maternal mortality, intra-uterine growth retardation, low birth weight infants and many such related complications.

The exact etiology of pre-eclampsia is still unknown. However, the results from many clinical studies show relationship between the aggravation of hypertensive complication and the change in concentration of various chemistries in mother's serum [4-10]. Interestingly, variable serum uric acid and serum magnesium are found in pre-eclamptic mothers [8, 10-13].

The increase in uric acid level appears to coincide with the increase in the blood pressure and proceed the development of proteinuria. Uric acid levels have been used for early diagnosis of pre-eclampsia. A disproportionate fall in uric acid

clearance is a key feature of pre-eclampsia. The serum level of uric acid rises as pre-eclampsia progresses; a level >6.5 mg/dL is a strong indicator of the disease and a level >7.8 mg/dL is associated with significant maternal morbidity. The degree of uric acid elevation correlates with the severity of proteinuria and renal pathological changes, and with fetal demise. Recent studies suggest that hyperuricemia may also play a pathogenic role by contributing to the vascular damage and hypertension [14].

Pregnant women require higher magnesium intakes for the function of new tissues. Recommended daily allowance of magnesium in normal non-pregnant women is between 300 - 400mg/day. Pregnant women require 550-600mg/day for the formation of new tissue (maternal and fetal) during pregnancy. Magnesium plays an important role during pregnancy. Therefore, pregnant women tend to have low blood magnesium level than non-pregnant women because of increased demand for mother and growing fetus and increased renal excretion of magnesium about 25% more than non-pregnant women due to increase in glomerular filtration rate (GFR) and haemodilution in 2nd and 3rd trimester [15, 16] and rapidly return to pre-pregnancy concentrations after delivery.

Pregnancy is marked by a state of hypomagnesaemia. The magnesium deficiency during pregnancy has been reported to be associated with hypertension, IUGR, pre-eclampsia, eclampsia, toxaemia of pregnancy [17], pregnancy induced hypertension, fetal growth retardation, preterm labour/births, leg cramps [18], increased maternal hospitalization, incidence of low birth weight babies and small for gestational age infants [19, 20].

Magnesium has been established as an essential element for fetal well-being. The administration of magnesium sulphate helps in the treatment of convulsions. Trials have documented that oral magnesium supplementation during pregnancy reduces hypertension miscarriage, prenatal birth and fetal growth retardation [20, 21].

Generally, magnesium has been known as an essential cofactor for many enzyme systems. It also plays an important role in neurochemical transmission and peripheral vasodilatation. Magnesium sulfate appears to be safe and effective for the prevention of seizures and has been used as the drug of choice in severe pre-eclampsia and eclampsia treatment [10, 22]. Besides, the alterations in the levels of serum magnesium, hyperuricemia is believed to result from the decreased renal excretion that occurs as a consequence of pre-eclampsia, increased tissue breakdown, acidosis and a rise in the activity of xanthine oxidase/dehydrogenase enzyme [23].

Recent studies have shown the relationship between the hypertensive complications and the changes in concentration of various biochemical parameters such as serum uric acid, calcium, magnesium in pre-eclamptic women [24].

Therefore, the modification of magnesium and uric acid metabolism during pregnancy could be one of the potential causes of pre-eclampsia [6, 10, 24-27]. However, the role and status of serum uric acid and serum magnesium in pre-eclamptic women is still being discussed.

Limited data is available on the serum magnesium and serum uric acid levels among pregnant women hence, the present study was conducted which involves estimations of serum uric acid and serum magnesium levels in pre-eclamptic, eclamptic and normotensive groups. Clinical prediction of pre-eclampsia may facilitate initiation of timely management to avert mortality and morbidity in the mother and as well as infant.

Material and methods

This study was conducted in the Department of Biochemistry, Gandhi Medical College, Secunderabad, Telangana, India. The subjects for the present study were selected from the antenatal outpatient, Gandhi Hospital, Secunderabad, Telangana, India, according to specific criteria like women with age group between 18-29 years, primigravide with known last menstrual period and gestational age ranging between 20-30 weeks. If menstrual history and examination findings were not correlating, ultrasonography was done to find out the exact period of gestation. The subjects with known hypertension, diabetes mellitus, multiple pregnancy and ultrasound proven congenital malformation in the fetus were excluded from the study. Consent from the pregnant women was taken to participate after explaining the objective of the study.

A total of n = 38 subjects were selected in this study. All the 38 subjects included in the present study were subjected to a detailed history taking, systematic examination, obstetric examination and routine antenatal investigations. Among n = 38 women, n = 24 were Pregnancy Induced Hypertensive (B.P. >140/90 mmHg), who were considered as experimental group and remaining n = 14 were normotensive (B.P. <140/90 mmHg) taken as controls.

The experimental group was further categorized into two groups, having n = 18 subjects in pre-eclampsia (Group II) and n = 6 in eclampsia (Group III).

Collection of samples

3 ml of venous whole blood sample was collected from each subject in a plain, dry and properly labeled bottle under strict aseptic conditions. Precautions were taken to prevent hemolysis.

Samples were brought to Clinical Biochemistry Laboratory, Gandhi Hospital and were centrifuged after clotting at 3500 rpm at 4 ºC for 30 min for separating the serum and retraction at room temperature. Clear serum was collected and subsequently analyzed for serum uric acid and serum magnesium levels measured in triplicates by colorimetric assay [28]. The mean of the three values was considered as the serum uric acid and serum magnesium concentration of the study subject.

Statistical analysis

The data obtained was subjected to statistical tests of mean and standard deviation utilizing the SPSS-7.5 version. To compare the mean serum magnesium and serum uric acid levels among pregnant women of different parity, one-way analysis of variance (ANOVA) was utilized. The results were considered significant at $p \leq 0.001$ level of significance.

Results

The mean serum uric acid and serum magnesium levels in various study groups are presented in Table 1.

Table 1: The mean and standard deviation of serum uric acid and serum magnesium levels in various study groups selected for the

present study

Subjects	Serum Uric Acid	Serum magnesium
	Mean ± SD	Mean ± SD
Control group (I)	3.88 ± 0.18	1.99 ± 0.04
Pre-eclampsia (Group II)	4.02 ± 0.17	1.84 ± 0.09
Eclampsia (Group III)	4.98 ± 0.57	1.77 ± 0.03
p	0.000	0.000

P at 0.001% level of significance

Table 2: Serum uric acid and serum magnesium levels in various study groups

S No.	Uric acid (mg/dl)			Magnesium (mg/dl)		
	Control	Pre-eclampsia	Eclampsia	Control	Pre-eclampsia	Eclampsia
1	3.8	3.9	5.0	2.0	1.85	1.76
2	4.0	4.2	4.9	1.88	1.76	1.82
3	3.9	4.0	5.2	2.2	1.85	1.78
4	3.7	3.7	5.1	1.90	1.86	1.76
5	4.0	4.2	4.8	2.0	1.97	1.74
6	4.1	4.2	5.2	1.92	1.86	1.81
7	3.8	3.9		2.2	1.89	
8	3.7	4.2		2.0	1.92	
9	3.7	4.0		2.1	1.72	
10	4.0	4.2		1.8	1.72	
11	4.1	4.2		1.9	1.68	
12	4.2	4.2		2.0	1.96	
13	3.6	3.8		1.82	1.72	
14	3.8	4.1		2.2	1.89	
15		3.9			1.96	
16		3.9			1.92	
17		4.0			1.72	
18		3.8			1.82	
Mean	3.88	4.02	5.03	1.98	1.84	1.77
SD	± 0.18	± 0.17	± 0.16	± 0.14	± 0.09	± 0.03
SE	0.04	0.04	0.06	0.04	0.07	0.01

In the present study, the experimental group subjects (n = 24) were categorized into two groups, with n = 18 subjects in pre-eclampsia as Group II and n = 6 subjects in eclampsia as Group III and n = 14 subjects in control as Group I. The mean serum uric acid and serum magnesium levels in various study groups selected for the present study are presented in Table 1.

The serum uric acid levels studied in various study groups showed significant increase in pre-eclamptic (group II, n = 18) and eclamptic (group III, n = 6) the differences being statistically significant at p≤0.001. The mean serum uric acid level values for women with pre-eclampsia (4.02 ± 0.17 mg/dl, n = 18) and eclampsia (4.98 ± 0.17 mg/dl, n = 6) were significantly higher than those of controls (3.88 ± 0.18 mg/dl, n = 14) which is statistically significant at p<0.001. Moreover, it was also experimentally found that the individual values of observed SUA in pre-eclamptics and eclamptics were relatively higher than those of the average values of normotensives (Fig 1). The difference in the mean serum uric acid concentration in the two groups was however statistically significant (p<0.001) with higher values in the pre-eclampsia and eclampsia groups.

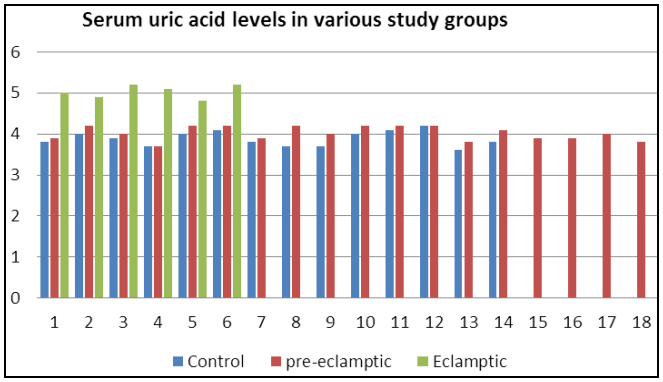

Fig 1: Serum uric acid levels in various study groups

The mean serum magnesium levels in eclampsia (Group III) showed a significant (p≤0.001) decrease compared to control group (Group I). The mean serum magnesium levels were decreased in pre-eclampsia (Group II) compared to the control group (Group I), however, the differences were not statistically significant. The serum magnesium levels were observed to be decreased in pregnancy. This decrease was more marked in the experimental groups. The serum magnesium levels significantly decreased in the experimental group III (eclampsia) (p≤0.000). Whereas, in pre-eclampsia though the serum magnesium levels showed considerable decrease, the decreases were not statistically significant.

The mean serum magnesium level in the experimental groups, pre-eclampsia (Group II) and eclampsia (Group II) were 1.84 ± 0.09 and 1.77 ± 0.03mg/dl respectively and in control 1.98 ± 0.14 mg/dl (Table 2). The present study results revealed that pre-eclamptic and eclamptic women had deficiency of magnesium (Fig 2) as revealed by their serum levels.

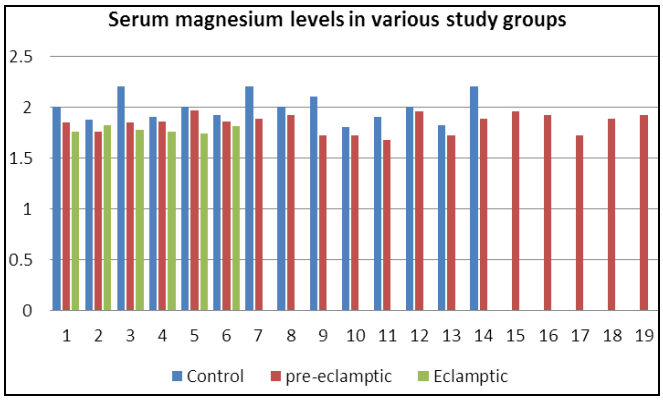

Fig 2: Serum magnesium levels in various study groups

Discussion

Toxemia of pregnancy is a common complication of pregnancy, particularly in our country. Pre-eclampsia and eclampsia are the two major categories of toxemias of pregnancy. Various factors are involved in the development of toxemias of pregnancy. The study may provide possible biochemical parameters in toxemias of pregnancy.

Etiology of pre-eclampsia and eclampsia includes abnormal trophoblastic invasion, coagulation abnormalities, vascular

endothelial damage, cardiovascular maladaptation, immunological phenomena, genetic predisposition and dietary deficiencies or excesses.

Increased uric acid levels in pre-eclampsia and eclampsia are also due to increased purine catabolism. Serum uric acid levels were seen to be increased significantly in both pre-eclampsia and eclampsia. Hyperuricemia is associated with the severity of the pre-eclampsia and foetal outcome. Traditionally the high uric acid concentration in pre-eclampsia has been attributed to renal dysfunction.

Increased serum uric acid concentration precedes the signs and symptoms of the disease and frequently antedates any change in glomerular filtration rate. A correlation between high serum uric acid and severity of disease and perinatal mortality has been suggested earlier. Boyle and his associates [29] proposed that increased production of uric acid occur in addition to altered renal handling.

Uric acid is an antioxidant and has been proposed as potentially important in pregnancy. Therefore, high serum uric acid levels act as both marker of pre-eclampsia and also a protective agent against free radicals. Pre-eclampsia leads to altered renal excretion of uric acid leading to increased levels of serum uric acid [30]. Increased levels of uric acid are observed to be associated with increasing number of maternal complications in various studies. Severe pre-eclampsia leads to maternal complications, such as abruption, eclampsia, renal failure and fetal complications, such as low birth weight including pre-term and small gestational age and increased perinatal mortality. According to Wakwe and Abudu [31], in women with pre-eclampsia who developed convulsions, serum uric acid levels were invariably raised. Monitoring the serum uric acid levels, help to identify serum uric acid value that could be used to differentiate hypertensive disease. Hence, monitoring of serum uric acid level in those with pre-eclampsia will help to predict those women who will develop eclampsia.

In several study reports it was found that the extent of the elevation in serum uric acid level in pre-eclamptics was an indicator for the degree of severity of this disorder [32, 33]. Elevated serum uric acid levels have also been interpreted to act as an important cofactor involved in the pathogenesis and manifestation of pre-eclamptic disorder [34]. It has been proposed recently that increased oxidative stress and formation of reactive oxygen species (ROS), as another contributing source of hyperuricemia noted in pre-eclampia apart from renal dysfunction [33]. 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 [35].

Uric Acid contributes to about 60% of free radical scavenging activity in human serum [36]. 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 [37]. Uric acid thus may function as a marker of oxidative stress tissue injury dysfunction. However, in several studies it was concluded that the measured elevated serum uric acid level can be taken as an unreliable indicator for development of hypertension [38]. Another review inferred that serum uric acid is not a consistent predictive factor for the development of pre-eclampsia, but its level generally increases once the disease manifests and plasma levels of uric acid may often correlate with disease severity [39].

These findings suggest that serum uric acid level may be a high risk marker of progression to pre-eclampsia among patients and development of adverse maternal/infant conditions in patients with an initial presentation of gestational hypertension.

Uric acid is one of the most sensitive indicators of the disease severity in pregnancy induced hypertensive disorders and can be of great help in monitoring the cause of disease process. In preeclampsia, serum uric acid level has been known to be increased and to correlate with maternal and fetal morbidity.

Historically, increased serum uric acid levels in pre-eclampsia have been attributable to reduced excretion of uric acid in the proximal tubules secondary to hypovolemia which may occur early in the development of pre-eclampsia [40].

Previous studies suggest more complex roles of uric acid in hypertensive pregnancy. 21, 22 Koopmans and colleagues [41] linked higher uric acid levels to the development of eclampsia in gestational hypertension and pre-eclamptic pregnancies.

Uric acid may be directly involved in the pathogenesis of pre-eclampsia by promoting inflammation, oxidative stress and endothelial dysfunction (Bainbridge and Roberts 2008). These bioactivities of uric acid may explain why it seems to be a risk marker for the progression to preeclampsia and the development of adverse maternal/infant conditions.

The association between serum uric acid and pre-eclampsia has been investigated in many studies. In the present study, there was a statistically significant increase in uric acid levels in pre-eclamptic group compared to the control group. Our findings are in agreement with previous study results [42] who observed increase in serum uric acid level with the severity of pre-eclampsia.

Similarly, Taner *et al.* [43] has reported increase in serum uric acid in pre-eclamptic patients compared to controls. Hyperuricaemia is believed to result from decreased renal urate excretion and is frequently found in women with pre-eclampsia. Soluble uric acid impairs nitric oxide generation in endothelial cells and also hyperuricaemia induces endothelial dysfunction and may induce hypertension and vascular disease. The findings of the present study show that alteration in magnesium, uric acid metabolism during pregnancy could be one of the potential causes of pre-eclampsia.

There were no significant differences in the serum levels of magnesium in pre-eclamptic group over control group. The findings of the present study are similar to the findings of the previous study [44]. The prevalence of magnesium deficiency status was higher in the present study. The haemodilution during the last trimester of pregnancy could probably be a contributing factor leading to a higher prevalence of deficiency of magnesium. These findings are in agreement with the findings of previous studies [13, 27].

Generally, the hypomagnesaemia in most pregnant women is associated with hemodilution, renal clearance during pregnancy and consumption of minerals by the growing fetus. Earlier studies reported a relationship between hypomagnesemia and pregnancy induced hypertension.

Magnesium levels may have significant effects on cardiac excitability and on vascular tone, contractility and reactivity. They proposed that magnesium promoted vascular muscle relaxation [27]. However, some studies reported contradictory results with higher serum magnesium in the pre-eclamptic group over normal pregnancy [27, 45]. The difference may be explained by the variations of the studied population and the dietary intake.

Early diagnosis and prompt treatment in pre-eclamptic patients can reduce the morbidity and mortality, associated with hypertensive disorders of pregnancy.

Larger multicenter prospective studies are required to elucidate the clinical utility of uric acid in predicting the progression to preeclampsia and the development of adverse conditions.

Conclusion

Based on the results of the present study and data available from literature, it is clear that in pre-eclampsia, the serum levels of uric acid and magnesium are altered, suggesting the possible role of these factors in the etiology and severity of pre-eclampsia. But it needs to be known whether these changes are a cause or consequence of the disease. It is not clear which is the primary event that triggers the onset of hypertension in pre-eclampsia. In conclusion, higher serum uric acid levels may indicate risk of progression to pre-eclampsia and development of adverse maternal/ infant conditions. Pre-clampsia is one of the major challenges for the obstetrician, as it may result into multi-organ dysfunction. Our present study shows the significant changes in biochemical parameters like serum uric acid and serum magnesium levels in pregnant women with significant increase in serum uric acid levels which could confirm the severity that is associated with it. Effective strategies need to be developed and applied for the prevention of pre-clampsia.

Regarding the role of magnesium supplement, due to the properties of vasodilatation and uterine relaxation of magnesium, a magnesium-rich diet as well as magnesium supplement should be an advantage to pre-clamptic pregnant women in prevention of the aggravation of hypertension.

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