Assessment of the level of serum uric acid in patients of pre-eclampsia and their comparison with levels in normotensive pregnancy

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ABSTRACT

Background: Pre-eclampsia is one of the major causes of maternal and perinatal morbidity and mortality. There are various parameters to evaluate pre-eclampsia. S. uric acid levels is one of the important biochemical markers in pre-eclampsia. The objective of current study is to compare the levels of S. uric acid in pre-eclamptic patients and normotensive patients.

Methods: A total of 256 antenatal patients, consisting of two groups, 128 patients in each group diagnosed with pre-eclampsia (either earlier or during examination) and 128 control antenatal patients in their third trimester were considered. Both the groups were compared in relation to age, parity, socio economic status and geographical variations. Blood sample (venous blood) of about 5ml was drawn from the ante cubital vein of the patient under all aseptic precautions to estimate S. uric acid levels.

Results: The observation of present study shows that the level of serum uric acid is significantly higher in the cases of pre-eclampsia. The value of S. uric acid increases with the severity of pre-eclampsia.

Conclusions: It is concluded from this study that high levels of uric acid are found in the serum of pre-eclamptic cases as compared to normotensive cases of the study population. The levels of uric acid are higher in severe cases as compared to the levels in mild and moderate cases.

Keywords: Hypertensive disorders in pregnancy, Maternal and perinatal morbidity and mortality, Pre-eclampsia, S. uric acid levels

INTRODUCTION

Hypertensive disorders are common medical problems encountered during pregnancy with reported incidence between 5-10%. Pre-eclampsia, along with the other hypertensive disorders of pregnancy, complicates around 2-8% of total pregnancies. They form one of the deadly triads along with haemorrhage and infection contributing to maternal and fetal morbidity and mortality.1-4

Hypertensive disorders are third on the list of causes leading to maternal mortality as per the current numbers, preceded by infection (sepsis) and haemorrhage.5

Almost half the pregnant patients with hypertension have pre-eclampsia. Preeclampsia is defined as the triad of gestational or chronic hypertension, proteinuria and oedema occurring after 20 weeks gestation in a previously normotensive woman. It is a multiorgan pregnancy-specific syndrome that can affect virtually every organ system.6 It has also got a multifactorial pathogenesis like immunological factor, endothelial dysfunction factor, genetic factor, remodelling of spiral arterioles etc.

Hyperuricemia is a common finding in pre-eclamptic pregnancies. The elevation of uric acid in pre-eclamptic
women often precedes hypertension and proteinuria, the clinical manifestations used to diagnose the disorder. There are several potential origins for uric acid in preeclampsia that is abnormal renal function, increased tissue breakdown, acidosis and increased activity of the enzyme xanthine oxidase/dehydrogenase. Serum uric acid has got ability to promote inflammation and endothelial dysfunction. It liberates free oxygen radicals which causes vascular endothelial damage and plays an important role in pathogenesis of pre-eclampsia. However, despite hyperuricemia antedating other clinical findings of preeclampsia, it has historically been ascribed to impaired renal function. Outside of pregnancy, hyperuricemia is considered a risk factor for hypertension, cardiovascular and renal disease. This evidence, as well as the observation that severity of preeclampsia increases with increasing uric acid, suggest that uric acid might play a role in the patho-physiology of preeclampsia.7

Hyperuricemia is one of the characteristic findings in preeclampsia. In clinical practice, uric acid determination is considered to be a part of the workup in women with preeclampsia to monitor disease severity and aid management of these women. The association between raised serum uric acid and pre-eclamptic pregnancy was first reported in the beginning of 19th century.

Reduced uric acid clearance secondary to reduced glomerular filtration rate, increased reabsorption and decreased secretion may be the reasons for elevated serum uric acid levels in women with pre-eclampsia. The pathophysiologic mechanisms of pre-eclampsia comprising increased trophoblastic tissue shedding, endothelial dysfunction, and reduced blood flow in the fetomaternal unit have also been hypothesised as the underlying cause of hyperuricemia in this condition.7

Hypertensive disorders are common medical disorders of pregnancy which contribute significantly to maternal and perinatal morbidity and mortality. Recently, national eclampsia registry reveals prevalence of pregnancy hypertension contributes to 9% and of preeclampsia 5% in 2011.

The following classification for diagnosis of hypertensive disorders in pregnancy has been submitted for web upload by chairman GCPR committee Dr. Sanjay Gupte on 26 September 2014.

**Diagnosis of hypertensive disorders in pregnancy**

1. Hypertension in pregnancy should be defined as a systolic BP of ≥140 mmHg and/or diastolic BP of ≥90 mmHg on two occasions at least 15 min apart, taken on same arm.

2. Preeclampsia is defined as BP ≥140/90 mmHg with two readings taken at least 15 min apart with proteinuria beyond 20 weeks of gestation.

3. Eclampsia is tonic clonic convulsions in women with preeclampsia.

4. Chronic hypertension in pregnancy is defined as BP ≥140/90 mmHg, without proteinuria beyond 20 weeks of pregnancy.

5. Gestational hypertension is defined as BP ≥140/90 mmHg, without proteinuria beyond 20 weeks of gestation, which returns to normal within 42 days postpartum.

6. Superimposed preeclampsia is new occurrence of preeclampsia in pregnant patients with chronic hypertension.

7. Severe hypertension should be defined as systolic BP of ≥160 mmHg and/or diastolic BP of ≥110 mmHg.

(Significant proteinuria is defined as greater than 300 mg protein in 24-hour urine collection (corresponds to DIPSTICK 3+)).

According to them, 1/3rd patients are due to chronic hypertension and 2/3rd are gestational hypertension plus preeclampsia. The main complication of preeclampsia is eclampsia which is associated with 10% of maternal death. About 5100 women dies each year due to it. It cannot be prevented but the prediction is possible with some markers and in present study serum uric acid is one of them. Prediction can reduce the severity due to early treatment.

The main aim of this study is to measure the role of uric acid in predicting the severity of pre-eclampsia and compare the levels in normotensive and hypertensive patients.

Uric acid is a product of purine degradation catalyzed by the enzyme xanthine dehydrogenase/xanthine oxidase (XDH/XO). XDH is converted to its oxidase form XO by several stimuli including ischemia. Purine metabolism by XO couples the production of uric acid with the production of the free radical superoxide (O$_2^-$) and is implicated as a contributor to oxidative stress. XDH/XO is found in most tissues but is concentrated in the liver and gut. Recently, a circulating population of XO has been identified that increase dramatically following ischemic tissue damage.7

Uric acid is also a mediator of inflammation stimulating the production of monocyte chemoattractant protein-1, IL-1β, IL-6 and TNF-α.8,9 Uric acid concentrations are influenced by diet (i.e. high protein, and fructose), alcohol consumption, increased cell turnover, enzymatic defects in purine metabolism or altered kidney function.8 Estrogen is uricosuric and uric acid concentrations are higher in men and post-menopausal women.10 In pregnancy uric acid concentrations initially fall 25-35% due to the effects of estrogen, expanded blood volume and increased glomerular filtration rate.11 However, concentrations slowly rise to those observed in non-pregnant women by term gestation (4-6 mg/dL).12
In women who go on to develop preeclampsia, uric acid concentration is elevated as early as 10 weeks of gestation, a time much earlier than the clinical presentation of the disorder. Increased uric acid often precedes clinical manifestations of the disease, including reduced glomerular filtration rate. Nonetheless, hyperuricemia has historically been attributed to reduced renal clearance. Uric acid is filtered, reabsorbed and secreted by the kidney. Hypovolemia, an early change in preeclampsia, increases uric acid reabsorption which could increase serum uric acid concentrations. However, increased uric acid precedes the reduction in plasma volume. Increased uric acid production from maternal, fetal or placental tissues through heightened tissues breakdown (i.e. increased substrate availability) and/or increased XO activity could also explain the increased concentration. The specific stimuli responsible for increased XO activity in preeclamptic women are unclear. The possible roles of placental ischemia-reperfusion injury, reduced antioxidant capacity and oxidative stress will be discussed below.

The aim is to compare levels of sr.uric acid among pre-eclamptic patients and normotensive patients. The objectives are to measure serum levels of uric acid in pre-eclamptic pregnancy and to compare with those in normal pregnancy and to co-relate levels of sr.uric acid with the severity of pre-eclampsia.

**METHODS**

Before the start of the study, Institute Ethics Committee Clearance will be obtained. Data collected from antenatal patients coming to the ANC OPD.

**Inclusion criteria**

- All pre-eclampsia patients admitted in Department of Obstetrics and Gynecology
- Age groups from 20 to 35 years
- Patients having singleton pregnancy.

**Exclusion criteria**

- Age group less than 18 years and above 35 years
- Multiple pregnancy
- Other medical disorders like diabetes, hypothyroidism
- Patients with chronic hypertension
- Patients not willing to participate in the study.

Type of study-case control study of 256 cases. Period of study-June 2016 to May 2018 (data collection and analysis). Place of study- Department of Obstetrics and Gynaecology, Dr. D. Y. Patil Medical College, Pimpri, Pune. Source of data-ANC OPD of Dr. D. Y. Patil Medical College, Pimpri, Pune.

A total of 128 antenatal patients coming to ANC OPD, diagnosed with pre-eclampsia (either earlier or during examination) and 128 control antenatal patients in their third trimester were considered.

The patients were categorized according to their age, parity, socio-economic status, literacy, geographical variation, rural or urban dwelling. Patients between 20-35 years of age who were not suffering from any other medical disorders like hypothyroidism, gestational diabetes mellitus, chronic hypertension, chronic renal disease, haemoglobinopathies were considered.

The patients underwent thorough clinical examination and anthropometric evaluation. The blood pressure-systolic as well as diastolic, of the patients was assessed carefully by measuring it with mercury sphygmomanometer in the right arm, sitting position. 2 readings were taken 6 hours apart and then the patients were divided into 2 groups-study group and control group. The severity of proteinuria was assessed using the dipstick method and all the patients with reading of 1+ or more and blood pressure equal to or more than 140/90 were included in the study group.

The subjects in the study group were further be divided into 3 groups based on their blood pressure according to the National Institute for Health and Care Excellence (NICE) guidelines updated in June 2017 into:

**Mild**

Systolic blood pressure between 140-149 mmHg, diastolic blood pressure between 90-99 mmHg.

**Moderate**

Systolic blood pressure between 150-159 mmHg, diastolic blood pressure between 100-109 mmHg.

**Severe**

Systolic blood pressure 160 mmHg or greater, diastolic blood pressure 110 mmHg or greater.

Blood sample (venous blood) of about 5ml was drawn from the ante cubital vein of the patient under all aseptic precautions. The sample was collected in plain bulbs and allowed to clot. The samples were sent Erba Mannheim XL-300 auto analyser using absorption photometry to the clinical laboratory where they were centrifuged at the rate of 3000RPM and the levels of uric acid were measured by analyzing the sample in Cobas Integra 400 plus or Erba Mannheim XL-300 auto analyser using absorption photometry. Serum uric acid was estimated by the uricase method.

Uric acid in the presence of uricase enzyme is converted to allantoin and H₂O₂. 4 aminophenazone is converted to quinoid pigment in the presence of H₂O₂ and enzyme peroxidase. The pigment gives violet colour to the solution which is then measured by photometry.
During early pregnancy serum uric acid levels fall, often to 3 mg/dl or below, related to the uricosuric effects from estrogen and from the increase in renal blood flow. Uric acid levels then increase during the third trimester, reaching levels of 4–5 mg/dl by term.16

RESULTS

Pre-eclampsia is a multi-factorial disease as a result of which it poses a huge challenge for accurate diagnosis since many factors are to be considered while coming to the diagnosis. In this study a total number of 256 cases in the third trimester of pregnancy were selected and divided into study and control groups of 128 each after confirming their willingness to participate in the study and taking their informed consent. These cases then underwent physical and clinical examination. Their blood samples were sent to determine the levels of serum uric acid. The groups were comparable in relation to their age, parity and gestational age. Distribution of cases with respect to their risk factors and severity of disease was confirmed with statistical test of significance. The results obtained after examination and blood tests were as follows. It can be seen from Table 1 that both the groups - study and control were comparable in terms of age as each one of the groups had similar number of cases. The study consisted of 256 cases between the ages of 20-35 years. It has been hypothesized that the incidence of pre-eclampsia is more common in very young patients (teenage pregnancies) and in patients beyond the age of 30 year which is quite evident in the present study (Table 1).

Table 1: Age wise distribution of cases in study and control group.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Study</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20</td>
<td>27</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>21-25</td>
<td>58</td>
<td>74</td>
<td>132</td>
</tr>
<tr>
<td>26-30</td>
<td>33</td>
<td>25</td>
<td>58</td>
</tr>
<tr>
<td>31-35</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>128</td>
<td>256</td>
</tr>
</tbody>
</table>

Chi-square=4.08, P=0.25

From Table 2, authors can conclude that both the groups - study and control were comparable in terms of their gravidity. Another factor that plays a role in the occurrence of pre-eclampsia is the gravidity of the patient. Pre-eclampsia is more common in very young primigravidas and also, its incidence increases as the gravidity goes in increasing. A similar picture can be seen in the present study (Table 2).

Table 2: Gravida wise distribution of cases in study and control group.

<table>
<thead>
<tr>
<th>Gravida</th>
<th>Study</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primi</td>
<td>58</td>
<td>57</td>
<td>115</td>
</tr>
<tr>
<td>Gravida 2</td>
<td>36</td>
<td>54</td>
<td>90</td>
</tr>
<tr>
<td>Gravida 3</td>
<td>24</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Gravida 4</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Gravida 5</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>128</td>
<td>256</td>
</tr>
</tbody>
</table>

Chi-square=0.02, P=0.90 (by applying test primi versus multi)

Table 3: Risk factors wise distribution of cases in study and control group.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Study (n=128)</th>
<th>Control (n=128)</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR</td>
<td>41 (32.03%)</td>
<td>6 (4.69%)</td>
<td>6.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous LSCS</td>
<td>23 (17.97%)</td>
<td>15 (11.72%)</td>
<td>1.41</td>
<td>0.16</td>
</tr>
<tr>
<td>PROM</td>
<td>10 (7.81%)</td>
<td>11 (8.59%)</td>
<td>0.23</td>
<td>0.82</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (10.94%)</td>
<td>7 (5.47%)</td>
<td>1.60</td>
<td>0.11</td>
</tr>
<tr>
<td>Oligohydroamnios</td>
<td>3 (2.34%)</td>
<td>8 (6.25%)</td>
<td>1.55</td>
<td>0.12</td>
</tr>
<tr>
<td>Breech</td>
<td>4 (3.12%)</td>
<td>3 (2.34%)</td>
<td>0.38</td>
<td>0.69</td>
</tr>
<tr>
<td>Low lying placenta</td>
<td>1 (0.78%)</td>
<td>1 (0.78%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IUD</td>
<td>5 (3.91%)</td>
<td>0</td>
<td>2.28</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Most of the high-risk factors were present in both groups by which authors can deduce that both the groups are comparable in terms of high-risk factors apart from the occurrence of intrauterine fetal demise. The incidence of IUGR was 32% in the study group as opposed to a mere 4.69 in the control group asserting that the existence of pre-eclampsia affects the growth and development of the fetus. Also, of the total of 5 fetal demises seen, all of them were in the study group. This too proves that the fetal outcome is greatly affected in cases of pre-eclampsia since pre-eclampsia related complications are known to have an adverse effect on the mother and baby. Anemia is seen in 10.94% of the study group which is almost double of the control group. This is an incidental finding in this case control study. The higher number of anemia cases in the study group can be explained by the fact that majority of the women enter pregnancy in an iron deficient state and continue to have dietary deficiencies of micronutrients throughout pregnancy. One more aspect that can explain the high number of anemia cases in the study group is the noncompliance of the patients towards iron and calcium supplementation provided to them.
throughout pregnancy; each of them responsible for anemia and pre-eclampsia respectively (Table 3).

Table 4: Severity of pre-eclampsia wise distribution of cases in study group.

<table>
<thead>
<tr>
<th>Severity of pre-eclampsia</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>8</td>
<td>6.3</td>
</tr>
<tr>
<td>Moderate</td>
<td>46</td>
<td>35.9</td>
</tr>
<tr>
<td>Severe</td>
<td>74</td>
<td>57.8</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>100</td>
</tr>
</tbody>
</table>

As seen in the table, maximum number of cases from the study group (57.8%) belonged to the severe pre-eclampsia category. The 128 cases in the study group were further divided into 3 subgroups-mild, moderate and severe based on their blood pressure readings. 57.8% of cases were from the severe subgroup followed by 35.9% of the moderate subgroup. This can be because of improper antenatal follow up and missed identification or improper identification and management of the disorder in the earlier stages at lower levels of health care set ups. Hence it is essential that once the diagnosis or pre-eclampsia is made or there is confusion regarding the neo appearance of hypertension in previously normotensive patients beyond 20 weeks of gestation at the primary centre of health care, the patient should be referred to a tertiary centre for proper diagnosis and management (Table 4).

Table 5: Comparison of serum uric acid according to severity of pre-eclampsia in study group.

<table>
<thead>
<tr>
<th>Severity of pre-eclampsia</th>
<th>Sr. uric acid</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8</td>
<td>6.07</td>
<td>0.32</td>
</tr>
<tr>
<td>Moderate</td>
<td>46</td>
<td>6.02</td>
<td>0.31</td>
</tr>
<tr>
<td>Severe</td>
<td>74</td>
<td>6.21</td>
<td>0.47</td>
</tr>
</tbody>
</table>

The level of serum uric acid is significantly higher in the severe cases of the study group as compared to the mild and moderate cases. The mean of serum uric acid in mild and moderate subgroup was somewhat similar but it increased considerably in the severe subgroup, the mean being 6.21. The P value noted in this category was 0.042 which showed that the increased levels of serum uric acid were a finding of significance (Table 5).

DISCUSSION

This study was conducted to measure the levels of serum uric acid in patients of pre-eclampsia and compare them with normotensive patients.

The mean of gestational age of the study group is 38.30 and that of the control group is 38.55; i.e. both the means are in the same range. So, from the data of the cases considering the age, gravida and gestational age authors can say that both the groups are comparable in terms of those 3 parameters.

Hyperuricemia is very commonly found in pre-eclampsia patients. In many cases, increased levels of uric acid are seen to appear before elevation of the blood pressure and proteinuria. Uric acid has multiple origins in cases of pre-eclampsia like abnormal renal function due to renin activity and vasoconstriction, increased issue breakdown, acidosis and increased activity of xanthine oxidase dehydrogenase.17 Even though the levels of uric acid cannot determine the extent of complications of pre-eclampsia and whatever be the origin of uric acid, raised levels of uric acid are a significant finding in cases of pre-eclampsia by itself. In this case control study, the mean of levels of uric acid in the study group was 6.13 which was higher than the mean of the same in the control group 5.11, which is consistent with the finding that hyperuricemia is more commonly seen in pre-eclampsia patients. Sirajwala et al and Thangavatinam et al have also drawn similar conclusions.18,19

Elevated uric acid concentrations were first noted in pre-eclamptic women in the late 1800s. Since that time numerous reports have demonstrated a relationship between uric acid concentrations and severity of disease. Nonetheless, the clinical utility of hyperuricemia in the management of preeclampsia is controversial. Recently authors examined the relationship of high uric acid elevations in pregnant hypertensive women to the endpoints of preterm birth (largely indicated preterm birth for the management of preeclampsia) and growth restriction. Hyperuricemia was present in 16% of women with gestational hypertension without proteinuria and 75% of women with clinically diagnosed PE. Pregnancy hypertension with hyperuricemia was associated with an excess of these adverse foetal outcomes. The increased frequency of preterm birth and growth restriction was present in hypertensive women with elevated concentration of uric acid even in the absence of proteinuria.7

In women who go on to develop preeclampsia, uric acid concentration is elevated as early as 10 weeks of gestation, a time much earlier than the clinical presentation of the disorder. Increased uric acid often precedes clinical manifestations of the disease, including reduced glomerular filtration rate. Nonetheless reabsorbed and secreted by the kidney. Hypovolemia, an early change in pre-eclampsia, increases uric acid reabsorption which could increase serum uric acid concentrations. However, increased uric acid precedes the reduction in plasma volume. Increased uric acid production from maternal, foetal or placental tissues through heightened tissues breakdown (i.e. increased substrate availability) and/or increased XO activity could also explain the increased concentration.7

Hyperuricemia is one of the earliest and most consistent observations noted in preeclamptic pregnancies. While elevated concentrations of circulating uric acid are not uniformly seen in every woman with preeclampsia, they do appear to identify a subset of preeclamptic women.
who are at greater risk for maternal and foetal morbidities. Also, hyperuricemia in pregnant women without proteinuria is at least as good a predictor of foetal morbidity as hypertension and proteinuria.7

CONCLUSION

It is concluded from this study that high levels of uric acid are found in the serum of pre-eclamptic cases as compared to normotensive cases of the study population. The levels of uric acid are higher in severe cases as compared to the levels in mild and moderate cases.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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