Uric acid as a biomarker for pregnancy induced hypertension

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Abstract
Background: Pregnancy induced hypertension is the most common complication of pregnancy. It affects 5-7% of pregnant women. Pregnancy induced hypertension is characterized by vasospasm which is associated with platelet aggregation and reduced uteroplacental flow. In addition to these, altered renal function tests can also worsens the condition. This influences the maternal as well as fetal outcome.

Aims: To prevent the complications of pregnancy induced hypertension and for proper management of these cases present study was conducted.

Materials and Methods: The present study was conducted in 300 subjects grouped into 120 cases of normal pregnancy, 150 cases of pregnancy induced hypertensives, 30 cases of eclamptics and serum uric acid level was measured in these.

Results and Discussion: elevated level of serum uric acid was seen with increase in gestation period and rise in diastolic blood pressure. The p-value was estimated by student t-test in different groups and was found to be < 0.001 which was highly significant and correlated.

Conclusion: Hence Serum Uric acid is the significant and reliable indicator for pregnancy induced hypertension to prevent the fetal and maternal mortality and morbidity.

Keywords: Eclampsia, Gestational hypertension, Hyperuricemia, Pre-eclampsia, Pregnancy induced hypertension(PIH).

Introduction
Hypertensive disorders are the commonest medical disorders during pregnancy which contributes to maternal and perinatal mortality and morbidity. Approximately 2-10% of pregnancies are complicated by hypertensive disorders.¹ Hypertensive disorders of pregnancy included gestational hypertension and pre-eclampsia.² Gestational hypertension is defined as a sustained rise of blood pressure to 140/90 mm Hg or more on at least two occasions 4 or more hours apart beyond 20th week of pregnancy or within first 48hrs of delivery in previously normotensive women whereas pre-eclampsia can be defined as multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria after 20th week in a previously normotensive and non-proteinuric women and eclampsia can be defined as when pre-eclampsia is associated with generalized tonic-clonic seizures and or coma.³

Gestational hypertension is considered as a risk factor for cardiovascular disease and metabolic syndrome in non-pregnant females.⁴ Patients with gestational hypertension share some common risk factors and pathophysiological abnormalities such as increased maternal age, raised body mass index, and hyperuricemia.⁵ Pregnancy may induce hypertension in women who are normotensive or may precipitate hypertension in hypertensive mothers.⁶ In 1917-Slemons and Bogert first determined that the maternal serum concentration of uric acid is elevated in pre-eclampsia and eclampsia, complications which can result in severe morbidity and even mortality in pregnant females. Raised serum uric acid associated with pre-eclamptic pregnancies has been reported a century ago.⁷ Hyperuricemia is an independent predictor of cardiovascular and renal disease during pregnancy.⁸ Maternal serum uric acid level can be used as a biomarker for pre-eclampsia during pregnancy and serum uric acid level correspond to the severity of pre-eclampsia. Pre-eclampsia increase the risk of fetal death five fold and kills fifty thousand women a year. Women with pregnancy induced hypertension are found with increased level of uric acid in maternal blood due to decreased renal urate excretion. Reduced uric acid clearance may be secondary to decreased glomerular filtration rate and decreased secretion resulting hyperuricemia in patients with pregnancy induced hypertension.⁹,¹⁰

Materials and Methods
The present study of two years of duration from September 2017 to September 2019 conducted in the department of Biochemistry in collaboration with department of Obstetrics and Gynaecology and Microbiology at Acharya Shree Chander College of Medical Sciences and Hospital Jammu. The present study divided in two groups of pregnant women- one with Pregnancy Induced Hypertension and other of healthy pregnant women. Blood pressure measurement and urine analysis was performed at the beginning of pregnancy to exclude pre-existing proteinuria or renal disease.

Inclusion criteria
Both groups were pregnancy of 24-36 gestational weeks. For pregnancy induced hypertension- a systolic blood pressure level of 140 mm Hg or higher or a diastolic blood pressure level of 90 mm Hg or higher that occurred after 20 weeks of gestation without proteinuria in 24hrs urine specimen.

Exclusion criteria
Non pregnant females, females suffering from chronic ailments and renal diseases. Serum uric acid levels were
measured by enzymatic method in cobas C311 autoanalyser. In patients with PIH total urinary protein levels were measured by modification of dye binding method used by Fujita et al and commercial uric 3V SGO 3100. Pregnancy induced hypertension is divided into 3 groups on the basis of Blood Pressure measurement: Mild PIH B.P is > 140/90mmHg Moderate PIH < 160/110mmHg Severe PIH > 160/110mmHg But without convulsions Eclamptic > 160/110mmHg With convulsions

Results
In the present study total number of 300 cases were studied. These included the normal pregnancy of 120 cases which were divided into first, second and third trimester of 40 cases each and 150 cases of pregnancy induced hypertension. 150 cases of pregnancy induced hypertension were subdivided into 50 cases of mild PIH, moderate PIH, severe PIH each and also included 30 cases of eclamptic cases with history of convulsions and high blood pressure. Uric acid levels in different trimesters of pregnancy and different stages of pregnancy induced hypertension studied which was showed statistically in table 1. The mean and standard deviation of uric acid levels estimated in different trimesters of pregnancy, in different stages of PIH, also in eclamptic cases and compared with each other. The p-value in different groups studied were estimated by using student –t test as shown in table 2.

Table 1: Comparison of mean and SD Value of Uric acid in normal Pregnancy and PIH

<table>
<thead>
<tr>
<th>Types of cases</th>
<th>Mean</th>
<th>SD</th>
<th>No. of cases</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester</td>
<td>3.13</td>
<td>0.67</td>
<td>40</td>
<td>2.0-4.6</td>
</tr>
<tr>
<td>2nd Trimester</td>
<td>2.09</td>
<td>0.88</td>
<td>40</td>
<td>1.0-4.0</td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>4.8</td>
<td>1.08</td>
<td>40</td>
<td>2.6-6.2</td>
</tr>
<tr>
<td>Mild PIH</td>
<td>6.9</td>
<td>0.75</td>
<td>50</td>
<td>5.4-8.0</td>
</tr>
<tr>
<td>Moderate PIH</td>
<td>7.8</td>
<td>0.83</td>
<td>50</td>
<td>6.0-9.0</td>
</tr>
<tr>
<td>Severe PIH</td>
<td>8.01</td>
<td>0.32</td>
<td>50</td>
<td>6.2-8.5</td>
</tr>
<tr>
<td>Eclamptic</td>
<td>9.03</td>
<td>0.40</td>
<td>30</td>
<td>7.5-9.5</td>
</tr>
</tbody>
</table>

Discussion
In the present study table 1 showed the different ranges of uric acid level in different groups of pregnancy and also in pre-eclamptic and eclamptic stages. It varies from minimum value of 2.0 to maximum value of 9.5 in different stages of normal pregnancy to pregnancy induced hypertension. This showed that serum uric acid level slowly decreases in normotensive pregnancy until 16 weeks of gestation due to expansion of plasma volume, increased renal clearance and the uricosuric effect of estrogen. During 2nd trimester the uric acid level remain stable and increases during 3rd trimester due to increase production of uric acid.11 The pregnant with history of pre-eclampsia are more prone to cardiovascular disorders and hypertension later on.12,13 It was observed in the present study that serum uric acid level rises in pregnancy induced hypertension and eclampsia. It also showed that uric acid level correlates with plasma rennin activity.14 The mean and standard deviation of uric acid estimated in different trimesters of normal pregnancy were 3.13±0.67 in 1st trimester, 2.09±0.88 in 2nd trimester, 4.8±1.08 where as the mean and standard deviation of uric acid estimated in different stages of pregnancy induced hypertension were 6.9±0.75 in mild PIH, 7.8±0.83 in moderate PIH, 8.01±0.32 in severe PIH and 9.03±0.40 in eclamptic cases as shown in table 1 whereas the study done by Kondareddy et al15 also correlates with the present study in which mean and standard deviation of uric acid level in normotensives was 3.52±0.23, mild pre-eclampsia it was 5.50±0.34, severe pre-eclampsia it was 6.25±0.33 and in eclampsia it was 7.43±1.16. Table No. II showed the p-values of different studied groups which were highly significant in all the groups studied i.e. <0.001 except in moderate to severe PIH where it was non significant. Thus uric acid was a significant predictor of pregnancy induced hypertension with p-value <0.001 which was highly significant and correlates with the study done by Prakash et al16, Gianni Bellomo, et al17, Hawkins et al,18 Tejai, et al.19 Although numerous studies have been conducted to find out the relationship between elevated uric acid level and pre-eclampsia.20 The uric acid is a product of purine metabolism. Most of the purines are synthesized in liver but some come directly from food. 2/3rd of uric acid is excreted in kidneys and remainder via gastrointestinal tract. In the kidneys uric acid undergoes both reabsorption and secretion but there is net reabsorption in the renal tubules (88-93% of filtered load). In normal pregnancy the serum uric acid concentration is 25-35% lower than non-pregnant levels during most of the pregnancy. Toward the end of pregnancy

Table 2: Comparison of P values of different groups studied

<table>
<thead>
<tr>
<th>Different groups</th>
<th>P value</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester</td>
<td>&lt;0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>2nd Trimester</td>
<td>&lt;0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>&lt;0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>Mild PIH</td>
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</tr>
<tr>
<td>Severe PIH</td>
<td>&lt;0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>Eclamptic</td>
<td>&lt;0.098</td>
<td>Non significant</td>
</tr>
</tbody>
</table>
the level rises towards normal. The mechanism involved is increased glomerular filtration during pregnancy and decreased fractional reabsorption of uric acid in the proximal renal tubules during pregnancy. Defective second stage of trophoblastic invasion in the placenta and production of an ischemic metabolite. That ischemic metabolite causes peripheral vasoconstriction in systemic vessels, glomeruli, liver, central nervous system, eyes. Glomerular vasoconstriction and capillary bed damages (glomerular endotheliosis). Reduced glomerular filtration rate and increased proximal tubular uric acid net reabsorption leading to raised serum levels. Other less significant mechanism of increased uric acid tubular reabsorption are increased sympathetic activity, suppressed angiotensin system activity and reduced estrogen level. Some have argued that raised serum lactate levels in pre-eclampsia also decreases tubular secretion of uric acid. Studies have used probencid which reduces tubular reabsorption is the predominant mechanism of elevated uric acid level in pre-eclampsia. Besides reduced renal clearance, increased production of uric acid secondary to placental ischemia resulting in fetal hypoxia due to increased serum level of purine metabolites. These metabolites can cross the maternal circulation which are degraded by maternal xanthine oxidase and there is increase level of uric acid and fetal growth retardation seen.

Conclusion
Hyperuricemia also predicts the development of hypertension. In the present study positive correlation is seen between the increase in serum uric acid level and diastolic blood pressure. Plasma uric acid is a better indicator than blood pressure for fetal outcome. Hence forth the serum uric acid level detection in normotensives in normal pregnancy as well as in pregnancy induced hypertensives and eclamptics can prevent the complications. This can also help in the management of these cases to avert the maternal and fetal outcome.

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Conflict of Interest
None.

References