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The significance of serum uric acid levels in predicting pre-eclampsia: Prospective analysis at a rural tertiary care center

Deepika Kapil[1], Uday Mahajan[2*]
[1] Departments of Obstetrics and Gynaecology and Medicine, Dr Rajendra Prasad Government Medical College, Kangra, Tanda, Himachal Pradesh, India
[2] Senior Resident, Department of Medicine, Dr Rajendra Prasad Government Medical College, Kangra, Tanda, Himachal Pradesh, India

Abstract
Serum uric acid has been recommended to screen pre-eclampsia during pregnancy. Objective: Prediction of preeclampsia by serum uric acid levels at 17-20 weeks. Methods: Eighty pregnant women who reported to the antenatal OPD at 17-20 weeks of period of gestation were enrolled in the study over the period of one year from Jan 2018 to Dec 2018 at Department of Obstetrics & Gynaecology Dr Rajendra Prasad Govt. Medical College, Kangra at Tanda, Himachal Pradesh, India. Preeclampsia was defined as per NHBPEP2000 working group, resting hypertension >140/90 mmHg after 20th weeks of pregnancy. Results. In present study out of 80 patients 8 developed preeclampsia (10%).
Serum uric acid was more than >3.5 mg/dl in 7 (87.5%) and less than 3.5 mg/dl in 1 (12.5%) patients. And the sensitivity of the serum uric acid to predict preeclampsia was 100.00%, the specificity was 63.51 %, the positive predictive value was 18.18 %, the negative predictive value was 100.00% and the accuracy was 66.25.Conclusion: Serum uric acid is useful in predicting preclampsia.

Keywords: serum uric acid, pre-eclampsia

Introduction

Pregnancy can be the most wonderful experience life has to offer. But it can also be dangerous. Around the world, an estimated 529,000 women die during pregnancy or childbirth. [1]Several studies suggest that maternal serum uric acid correlates with both severity of maternal disease and perinatal morbidity and may be used to detect high risk cases which are better managed as inpatients. Serial estimation of uric acid may also allow appropriate timing of delivery of a fetus with improved chance of survival.

Serum uric acid usually falls to well below 4mg/dl during early to mid-pregnancy, in patients with preeclampsia levels often rise to >4.5mg/dl. This rise in serum uric acid has been shown to have correlation with increasing blood pressure and degree of glomerular injury and preceeds the proteinuric stage of the disease explaining the poor perinatal outcome in the absence of proteinuria and minimally elevated blood pressure. Uric acid clearance also drops disproportionately compared to urea and creatinine. The characteristic renal lesion of preeclampsia "glomeruloendotheliosis" has been found to be present only in women with hyperuricaemia.

Recently an additional possibility has been suggested that uric acid might itself be causally related to hypertension. In animal experiments, rats rendered minimally hyperuricaemic by inhibiting uricase had increased blood pressure that could be reversed by lowering uric acid. It has also been suggested that in humans, uric acid might aggravate hypertension by increasing salt sensitivity and vascular smooth muscle proliferation. Uric acid has been shown to reduce endothelial nitric oxide bioavailability and to inhibit endothelial cell proliferation. Because maternal uric acid passes freely into the placenta, a rise in uric acid could lead to an inhibition of angiogenesis in the third trimester, which might lead not only to a small infant but also inhibition of kidney growth with a reduction in nephron number. It is therefore not surprising that adverse fetal manifestations in the form oligohydramnios, intrauterine growth restriction, intrauterine fetal death, intrapartum fetal distress/demise and birth asphyxia have been observed in the absence of maternal manifestations of severe disease. Abnormal umbilical artery Doppler velocimetry, reduced resistance flow in the middle cerebral artery and abnormal waveforms in the ductus venosus which are indicators of fetal compromise have also been demonstrated in the presence of hyperuricaemia without proteinuria [2, 3, 4].

Methods

Eighty pregnant women who reported to the antenatal OPD at 17-20 weeks of period of gestation and who fulfilied the inclusion criteria and were willing to participate in the study were enrolled in the study.

For this study all women attending antenatal OPD between 17-20 weeks of gestation were enrolled upto the period of intial 7 months of the study and followup was continued upto next 5 months of the study period so that the last enrolled patient can complete the followup process as per methodology. Detailed

obstetric and menstrual history, past history of hypertension, diabetes and family history of hypertension and diabetes was taken and detailed general physical examination was conducted. This was followed by routine microscopic and spot urinary albumin creatinine ratio and serum uric acid levels. Rest of the investigation structure were as per the protocol. All the enrolled patients were followed up every month till 28 weeks of gestation and fortnightly after that upto 36 week and weekly thereafter until delivery.

Any significant event in the form of abnormal signs or abnormal investigation was recorded for example high blood pressure, pedal edema, blurring of vision, pain epigastric.

Table 1: Distribution of Patients According to Serum Uric Acid in Different Groups

N=80	Unaffected N=30	Gest HTN N=16	Preclampsia N=8
Mean Serum Uric Acid (mg/dl)	3.40	6.2	4.4

Normal Range of Investigation

Serum uric acid levels- 3.5 mg/dl

Data Collection

Data was collected and subsequently transferred to Microsoft sheet.

Statstical Analysis

Data was analyzed for frequency, percentages and other statistical test if required.

Results

In the present study mean age of the patients in the study group was 27.25±3.726 years.In the present study out of 80 patients 16 patients (20%) developed gestational hypertension on follow up at subsequent visits. Out of 16 patients who developed gestational hypertension 12 (75%) patients had serum uric acid >3.5 mg/dl and 4 (25%) had serum uric acid levels <3.5mg/dl. And the sensitivity of serum uric acid to predict gestational hypertension was76 47%, the specificity was 63.49%, the positive predictive value was 36.11%, the negative predictive value was 90.91% and the accuracy of the test was 66.25.

In present study out of 80 patients 8 developed preeclampsia (10%).Serum uric acid was more than >3.5 mg/dl in 7 (87.5%) and less than 3.5 mg/dl in 1 (12.5%) patients. And the sensitivity of the serum uric acid to predict preeclampsia was 100.00%, the specificity was 63.51 %, the positive predictive value was 18.18 %, the negative predictive value was 100.00% and the accuracy was 66.25.

In the present study the serum uric acid in patients with gestational hypertension was 6.2 mg/dl, with preeclampsia, 4.4 mg/dl,

The mean bishop score on admission was 5.81±2.672.Mean bishop score of the patients with serum uric acid >3.5 mg/dl was 5.57±2.688 and the mean bishop score in patients with serum uric acid <3.5 mg/dl was 6.08±2.665 and the p value was. 400 which was not significant.

In the present study 19 (45.2%) patients with serum uric acid levels >3.5 mg/dl had spontaneous onset of labour pains and 21 (63.6%) patients with serum uric acid levels >3.5 mg/dl had induction of labour and in patients with serum uric acid levels less 3.5 mg/dl 23 (54.8%) had spontaneous onset of labour pains and 12 (36.4%) had induction of labour.

In the present study 57 patients had normal vaginal delivery and out of these 31 (54.3%) had serum uric acid >3.5 mg/dl and 26 (45.6%) had serum uric acid less than 3.5mg/dl.Twenty three patients had cesarean section and out of them 12 (52.2%) had serum uric acid >3.5 mg/dl and 11 (47.8%) had serum uric acid less than 3.5 mg/dl**.**

Discussion

Out of the sixteen patients who developed gestational hypertension twelve (75%) patients had serum uric acid >3.5 mg/dl and four patients (25%) had serum uric acid levels <3.5mg/dl. And the sensitivity of serum uric acid to predict gestational hypertension was 76.47%, the specificity was 63.49%, the positive predictive value was 36.11%, the negative predictive value was 90.91% and the accuracy of the test was 66.25. In a study conducted by Laughon *et al* [5] the incidence of gestational hypertension was 7.2%. Out of 1541 patients 111 developed gestational hypertension and 31 (8%) patients had serum uric acid >3.5mg/dl. Study shows that mean serum uric acid in patients with gestational hypertension was 3.7±0.8 mg/dl and in normotensive patients was 3.1±0.8 mg/dl and there was positive correlation between gestational hypertension and hyperuricemia. Study conducted by Lim *et al*[6] and which shows positive correlation between serum uric acid and gestational hypertension,the mean serum uric acid values for women with preeclampsia (6.2 ± 1.4 mg/dl) and transient hypertension (5.6 ± 1.7 mg/dl) were significantly higher than those of controls (4.3 ± 0.8 mg/dl, $p < 0.05$).

In present study out of eighty patients eleven developed preeclampsia (10%). In a study by Mishra *et al*[34] the incidence of preeclampsia was 12.90%. Incidence of preeclampsia in a study conducted by Laughon *et al* [5] was 3.8% and in a study conducted by Weerskera *et al*[7] incidence of preeclampsia was 23%. In a study conducted by Fatema *et al*[8] the incidence of preclampsia was 8.5%. In present study out of eight patients who developed preeclampsia serum uric acid was more than >3.5 mg/dl in seven patients 87.5% and less than 3.5 mg/dl in one patient 12.5% patients. And the sensitivity of serum uric acid to predict preclampsia was 100.00%, the specificity was 63.51 %, the positive predictive value was 18.18%, the negative predictive value was 100.00% and the accuracy is 66.25. In a study conducted by Zohu *et al* [9] the sensitivity is 56% and specificity is 65%.and serum uric acid levels in normotensive patients was 3.6mg/dl and in PE is 4.0 mg/dl. In study conducted by Laughon *et al* [5] in patients who developed preeclampsia 24 (6.2%) pateints had serum uric acid >3.5 mg/dl. And the serum uric acid in patients with preeclampsia was 3.7±0.8 mg/dl and in normotensive patients was 3.1±0.8 mg/dl. In a study conducted by Wolak *et al* [7] the a significant linear association was found between the serum uric acid levels in second trimester and development of precalampsia. In patients diagnosed with preeclampsia 2.1% had serum uric acid <2.4 meq/l (3.8 mg/dl). And 3.3% had serum uric acid between 2.5-4.4 meq/l and 5.3%

had seum uric acid between 4.1-5.5meq/l. In a study conducted by Conossen *et al* [10] the sensitivity of serum uric acid to predict preeclampsia was 55.6% and specificity was 76.9% and in a study conducted by Salako *et al* [11] the sensitivity of serum uric acid to predict preeclampsia was 43.4% and specificity was 81.3%. Similarly in a study conducted by Jacobson *et al* [12] the sensitivity of serum uric acid to predict preeclampsia was 50% and specificity was 94.9%. In a study conducted by Oskwe *et al* [13] 10.5% of the women developed preeclampsia. The positive and negative predictive values of serum uric acid for preeclampsia were 78.9% and 97.1%, respectively. Serum uric acid was found to be a useful predictor of the occurrence of preeclampsia and its severity. Study conducted by Verma *et al* [14] showed that hyperuricemia is associated with increased risk of preeclampsia.

Similarly When measured early in the second trimester, serum uric acid predicted pre-eclampsia well before the onset of clinical manifestations with high sensitivity of 100% and specificity of 63.51%,PPV of 18.18%, NNV of 100%.So, it can be used as a good screening tool for predicting pre-eclampsia in early pregnancy. however additional studies and cost– benefit analysis are required to confirm these finding before recommending this test for screening purposes. A small sample size is the limitation of our study, and study of larger sample size is recommend before making spot urinary protein/creatinine ratio a routine screening test. We can recommend these tests as a screening method in patients with family history of hypertension or diabetes mellitus or past history of hypertension and diabetes due to high incidence of hypertension in our region of Kangra district.

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