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An Epidemiological Retrospective Study of Serum Uric Acid as a Risk Marker in Hypertensive Pregnancies

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Abstract

Introduction: Preeclampsia (PE) may be associated with complications in fetus, such as intrauterine growth restriction, prematurity, and even death of fetus. In women, there may be development of hepatic and renal failure, pulmonary edema, and even stroke. PE may progress to eclampsia. The present study focused on comparing serum uric acid (SUA) levels in normal pregnant and pregnancy-induced hypertension (PIH) women and to correlate SUA levels with severity of PIH. **Methodology:** Retrospective Analytical Comparative study of 200 of the randomly selected obstetric patients who seeked care for delivery at the randomly selected obstetrical units was retrospectively identified. **Results:** The mean SUA level clearly showed significantly higher levels in case group compared controls. Compared to severity of hypertension SUA levels also tend to increase with increasing severity of PIH. It was clearly observed that maternal and fetal complications during antepartum and postpartum period were higher once SUA >5 mg/dl was taken as a cutoff. **Conclusion:** SUA measurement is probably one of the best markers and a useful surrogate for the diagnosis as well as a measure of severity of PE and will be a useful tool for the management of the same.

Keywords: Hypertensive pregnancy, Preeclampsia, Retrospective analysis, Uric acid

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Introduction

Preeclampsia (PE), the gestational onset of hypertension and proteinuria, increases perinatal mortality by fivefold, kills thousands of pregnant women yearly worldwide and contributes to about 24% of maternal deaths in India.[1,2]

PE may be associated with complications in fetus, such as intrauterine growth restriction, prematurity, and even death of fetus. In women, there may be development of hepatic and renal failure, pulmonary edema, and even stroke. PE may progress to eclampsia, a form of hypertensive disorder of pregnancy with convulsions. Therefore, early screening of gestational hypertension/PE may reduce the maternal and fetal complications.[3]

The exact etiology of PE remains unknown but association with an increased vascular resistance of uterine artery and decreased perfusion of placenta has been seen.[4] Hyperuricemia from decreased renal excretion, as a consequence of PE or production secondary to tissue ischemia and oxidative stress[4] has been cited as a better predictor of fetal risk than blood pressure.[1] It may identify women at increased risk of adverse maternal and particularly fetal outcome.[5]

Studies to find out the relationship between elevated serum uric acid (SUA) levels and PE, severity of PE or associated perinatal outcomes and the role of SUA as a prognostic index of maternal and fetal welfare in pregnancy-induced hypertension (PIH) is inconclusive.

The present study focused on comparing SUA levels in normal pregnant and PIH women and to correlate SUA levels with severity of PIH. Association of SUA levels with maternal and fetal complications in hypertensive pregnancy was also assessed.

Methodology

This retrospective analytical study involved Prior Consent from Hospital Authorities/Medical Superintendents of the Local Randomly selected tertiary care hospitals to see the records of the patients from medical records department. The study was conducted within ethical standards. The obstetrical patients who were admitted in randomly selected tertiary care hospitals including our teaching hospital in the city were selected for the study. Randomization was done using computer tables in selecting data. It was observed in the records that the obstetric patients who seek care for delivery at the medical centers were admitted to the obstetrics department for delivery after initial evaluation at the emergency department. All patients underwent standard clinical examinations, routine biochemical and hematological investigations, ultrasonography of whole abdomen and received treatment as decided by their treating physician and surgeon. Medical record numbers were used to generate the data for analysis. After delivery, those patients who required intensive care because of a postpartum cause complicating the delivery were admitted to the ICUs, where the intensive care medicine/Intensivist/Anesthesiologist assume the primary responsibility along with attending obstetricians. For the purpose of the present study, 200 of the randomly selected obstetric patients (candidates/study subjects) who seeked care for delivery at the obstetrical units between March 2019 and September 2019 were retrospectively identified. Hundred being patient with PIH (case group) of varying severity and 100 normal pregnant women (control group). The age and parity in both groups were comparable. However, in case group,

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majority were nullipara. The medical records for these patients were reviewed for the collection and classification of data including the patient characteristics, the obstetric history, the preexisting medical disorders, and the causes that necessitated admission to the ICU. The data collected included the demographics, obstetric, and medical history, including admitting diagnosis, gestation age, gravida status, the mode of delivery, any obstetric complication, and outcome of baby delivered. The ICU-related data included the critical illness severity scores, organ failures, any sepsis, treatment given during ICU admission, including mechanical ventilation, inotropic support, and the ICU stay.

The causes that necessitated admission to the ICU were identified as PE, eclampsia, hemorrhage, sepsis, and respiratory failure. PE required the presence of hypertension (defined as blood pressure more than 140/90 mm Hg, systolic blood pressure +30 mm Hg, and diastolic blood pressure +15 mm Hg) and proteinuria (more than 0.3 g/24 h). Severe PE required the presence of severe hypertension (defined as blood pressure more than 160/110 mm Hg), severe proteinuria (more than 2.0 g/24 h), oliguria (defined as urine output <60 mL/2 successive h or <500 mL/24 h), epigastric pain, liver pain, headache, blurred vision, or pulmonary edema. Eclampsia required the presence of any seizure during pregnancy. Severe hemorrhage was defined as blood loss ≥1.5 mL at once; blood loss ≥2500 mL in 24 h; blood loss requiring ≥2500 mL of packed cells; blood loss requiring plasma expanders; or blood loss resulting in death and was required to occur during the pregnancy, at the time of the pregnancy outcome, or immediately after the time of the pregnancy outcome (vaginal birth or cesarean delivery). Sepsis was defined as the systemic inflammatory response to an infection in the presence of a body temperature more than 38°C or <36°C, a heart rate more than 90/min, a respiratory rate more than 20/min, a $PaCO_2$ <32 mm Hg, a white blood cell count more than 12,000/mm^3 or <4000/mm^3, or more than 10% immature leukocytes. Hemolytic anemia, elevated liver enzymes, and low platelet (HELLP) count syndrome, when present, was separately recorded. The diagnosis of HELLP syndrome required the presence of hemolysis (bilirubin level ≥1.0 mg/ dL or 17.1 μmol/L), hepatic cytolysis (alanine aminotransferase level ≥70 U/L), and thrombocytopenia (platelet count <100 000/mm^3).

The complications that were encountered at the ICU, such as disseminated intravascular coagulation (DIC) and multiorgan failure, were recorded. The diagnosis of DIC required a low platelet count (<100 × 10^9/L), a low fibrinogen level (<3 mg/L), a prolonged prothrombin time (more than 14 s), a high international normalized ratio level (more than 1.3), and a prolonged partial thromboplastin time (more than 40 s). Multiorgan failure was defined as the failure of three or more critical physiological systems, including the respiratory system, the cardiovascular system, the nervous system, the hepatobiliary system, or the urinary system. Continuous data were expressed as mean ± standard deviation (SD). The data were analyzed by IBM SPSS Statistics 23. Overall, $P < 0.05$ was proposed to represent statistical significance after correction.

Results

The level of SUA (mg/dl) in both groups is shown in Table 1.

The mean SUA level of 5.0 ± 1.84 mg/dl clearly shows significantly higher levels in case group compared to 2.76 ± 0.34 g/dl in controls.

When compared to severity of hypertension SUA levels also tend to increase with increasing severity of PIH, increasing from 3.69 mg/dl in gestational hypertension to 6.36 mg/dl in severe PE. The difference among three categories was again highly significant [Table 2].

It was clearly observed that maternal complications during antepartum and postpartum period were higher once SUA >5mg/dl was taken as a cutoff. Proteinuria (98%), coagulopathy (12.3%), need for blood/platelet transfusion (37%), eclampsia (14%), and HELPP syndrome (7%) were significantly more [Table 3].

Complications were found to be higher, in babies born to mothers having SUA more than 5 mg/dl compared to others in case group. Birth weight though not significant, tended to be lower. Two deaths occurred in neonatal ICU while two additional still-births were observed [Table 4].

Discussion

Gestational hypertension, PE (a triad of gestational hypertension, edema, and proteinuria), and eclampsia (PE with convulsions) are all various shades of PIH. A rising SUA has been recognized as an early feature of PE and its measurement supposedly increases the accuracy of diagnosis and helps in differentiation from other essential or chronic forms of pre-existing hypertension complicating pregnancy.[6]

SUA in the normal pregnant women has been observed to be slightly higher in other patients having hypertensive vascular disease.[6] In our study, the SUA in controls was having mean value of 2.66 mg/dl compared to case group having a mean value of 5.00 mg/dl. The level rose with increasing severity of hypertension, in consonance with the fact noted earlier in patients with histologically proven PE. Similar observations have been made by Sarmah[3] (7.3 + 2.7 mg/dl) and Kamath *et al*.[1] (5.57 mg/dl) that in PE, SUA levels rise significantly when compared to normal pregnant woman.[6]

Elevation of SUA level tends to follow the degree of toxemia and appears to correlate well with severity of glomerular involvement. In the present study, SUA levels were significantly higher in women with gestational hypertension as compared to normotensive pregnant women and in severe PE compared to mild disease. Kamath *et al*.[1] Nischintha *et al*.,[2] and Sirajwala *et al*.[7] have made similar observations. It likely results from reduced uric acid clearance due to diminished glomerular filtration, increased tubular re-absorption, and decreased secretion from tubules, though possibility from increased placental urate production, compensatory to increased oxidative stress has been proposed.[8]

Maternal complications were noted to be higher in hypertensive pregnant woman, especially so with SUA levels >5 mg/dl as compared to those with <5 mg/dl [Table 3] in our study. Significant correlation exists between elevated SUA (above 5 mg/dl) and 24 h proteinuria, abruptio placentae, HELLP syndrome or deranged coagulation profile, etc., in this study, an observation also reported by Pereira *et al*.,[9] Nischintha *et al*.,[2] and Patel and Dudhat.[6] During healthy early pregnancies, the SUA levels are low (≤3 mg/dl) due to the effects of estrogen and increased renal blood flow, but the levels in women who are on the verge of developing PE are relatively high even during their first trimester and continue to rise with increasing complications of reduced placental perfusion, platelet consumption, etc. The uric acid levels come down rapidly by 6th day of delivery.[10]

Hyperuricemia in the setting of gestational hypertension is associated with adverse fetal outcome. The fetal complications are also related to SUA levels. In cases, with higher than 5 mg/dl

Table 1: Level of serum uric acid

Serum uric acid level	*Cases (n=100)*			*Controls (n=100)*			*P-value*
	Mean±standard deviation	*Median*	*Min-Max*	*Mean±SD*	*Median*	*Min–Max*	
Serum uric acid (mg/dl)	5.00±1.84	4.91	2.1–8.1	2.76±0.34	2.60	2.1–3.6	<0.001

Table 2: Correlation of serum uric acid with severity of pregnancy induced hypertension

Level of severity	*No.*	*Mean±standard deviation*	*Median*	*Min–Max*	*P-value*
Gestational hypertension	22	3.69±0.95	3.600	2.1–5.6	<0.001
Mild preeclampsia	29	4.85±1.09	5.200	3.1–6.8	
Severe preeclampsia	49	6.36±1.38	6.800	3.1–8.1	

Table 3: Associated maternal complications

Complications	*Serum uric acid >5 mg/dl in cases (n=57)*		*Serum uric acid <5 mg/dl in cases (n=43)*		*P-value*
	Frequency	*%*	*Frequency*	*%*	
Proteinuria	52	91.2	19	44.1	<0.001
Oliguria	1	1.75	0	0.0	0.456
Blood transfusion	11	19.2	2	4.6	0.006
Platelet transfusion	10	17.5	2	4.6	0.012
Deranged coagulation	7	12.2	0	0.0	0.003
Abruptio placenta	2	3.5	0	0.0	0.202
Eclampsia	8	14	0	0.0	0.001
Hemolytic anemia, elevated liver enzymes, and low platelet syndrome	4	7	0	0.0	0.041
Preterm labor pain	6	10.5	4	9.3	0.533
Maternal mortality	1	1.80	0	0.00	1.000

Table 4: Associated fetal complications

Fetal complications	*Serum uric acid>5 mg/dl in cases (n=57)*		*Serum uric acid<5 mg/dl in cases (n=43)*		*P-value*
Birth weight (kg) Mean±standard deviation	*2.375±0.697*		*2.549±0.607*		*0.104*
Variables	*Frequency*	*%*	*Frequency*	*%*	
Still-birth/IUD	3	5.3	1	2.3	0.330
Low APGAR 1 min	19	33.3	5	11.6	<0.001
Prematurity	18	31.6	8	18.6	0.042
Neonatal ICU admission	18	31.6	7	16.2	0.024
Hyperbilirubinemia	2	3.5	0	0.0	0.202
Low-birth weight (<2.5 Kg)	31	54.4	9	20.9	<0.001
Expired in neonatal ICU	2	3.5	0	0.0	0.202
Congenital anomalies	2	3.5	1	2.3	0.591

SUA a lower average birth weight, chances of Low APGAR score at 1 min, prematurity, NICU admission low-birth weight, and fatal events such as stillbirth/IUD or death in neonatal ICU were significantly higher. Similar observations have been made for low-birth weight (Pereira *et al*.,[9] Alam *et al*.,[11] Kamath *et al*.,[1] Enaruna *et al*.,[12]), prematurity (Alam *et al*.,[11]), and Low APGAR (Patel and Dudhat,[6] Enaruna *et al*.[12]) increased chances of admission in NICU (Alam *et al*.,[11] Patel and Dudhat[6]) showing clear association of hyperuricemia with adverse fetal outcome.

The presence of hyperuricemia, therefore, identifies a population of hypertensive pregnant women at increased risk of maternal and fetal morbidity and mortality. A quick review of recent studies focusing on hyperuricemia and fetomaternal complications (Kamath *et al*.,[1] Patel and Dudhat,[6] Sirajwala et al.,[7] Prakash *et al*.,[10] Alam *et al*.,[11] and others) has clearly revealed that if a value of 4.5 mg/dl or higher is used maternal and fetal complications are much higher. More recent studies have also confirmed the predictive value of SUA to be useful in predicting maternal/perinatal complications or adverse fetal outcomes and also to assist with management of PE.[13] SUA levels of 5 mg/dl or higher indicates a significantly higher risk of maternal complications, a fact that clearly emerged from this study as well and is recommended to be used for risk stratification for preventing fetomaternal complications in pregnancies complicated by hypertension.

Conclusion

SUA measurement is probably one of the best markers and a useful surrogate for the diagnosis as well as a measure of severity of PE and will be a useful tool for the management of the same. The presence of hyperuricemia, especially higher than 5 mg/dl levels, identifies a sub-population of hypertensive pregnant women at increased risk of maternal and fetal complications and timely intervention can reduce adverse events. Being cheap, highly accessible, easily available and a non-invasive method, deserves to be considered as a diagnostic, and prognostic tool in risk stratification and management of PIH.

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