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Original Research Article

A prospective study to determine the relationship of serum uric acid level to maternal and perinatal outcomes in patients with hypertensive disorders of pregnancy

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ABSTRACT

Background: To study maternal and fetal outcomes in patients with hypertensive disorders of pregnancy (According to American College of Obstetrician and Gynaecologists) by the estimation of serum uric acid levels.
Methods: This is a prospective observational study conducted at tertiary hospital in Bokaro Steel city, Jharkhand over a period of 18 months. During this period women diagnosed with hypertensive disorders of pregnancy after 20 weeks (ACOG) were included. Their serum uric acid level was estimated and were divided into two groups, Group A with 60 patients with uric acid ≥6 mg/dl and Group B with 60 patients with uric acid ≥6 mg/dl. Maternal and fetal outcomes were analysed to detect differences between the two groups.
Results: In Group A, 20% had gestational hypertension, 18.3% had mild preeclampsia, 41.67% had severe preeclampsia, 10% had preeclampsia superimposed on chronic hypertension and 16.7% had eclampsia. In Group B 5% had gestational hypertension, 70% had mild preeclampsia,18.3% had severe preeclampsia,5 % had preeclampsia superimposed on chronic hypertension and 1.67% had eclampsia. In group A, the mean serum uric acid (Mean±SD) of the patients were 7.3733±1.4087 mg/dl. In group B, the mean serum uric acid (Mean±SD) of the patients was 4.6633±0.6428 mg/dl. LSCS was the most common mode of delivery in group A whereas in group B majority had spontaneous onset of labour and delivered vaginally ($p<0.05$). Group A had adverse perinatal outcome as compared to Group B ($p<0.05$). Overall, Group A had adverse overall outcome as compared to Group B.
Conclusion: Maternal hyperuricemia was associated with adverse maternal and perinatal outcomes in women with hypertensive disorders of pregnancy.

Keywords: LSCS, Eclampsia, Pre-eclampsia, Uric acid

INTRODUCTION

Pregnancy is a physiological state associated with many alterations in the metabolic, biochemical, physiological, hematological and immunological process. Hypertensive disorders are among the commonest medical disorders during pregnancy and continue to be a major cause of maternal and perinatal morbidity and mortality worldwide.[1] These disorders complicate 5 to 10 % of all pregnancies and together they are one of the deadly triad-along with haemorrhage and infection.[2] The American College of Obstetricians and Gynaecologists describes four types of hypertensive disease. Preeclampsia and eclampsia syndrome, chronic hypertension of any etiology, preeclampsia superimposed on chronic hypertension, gestational hypertension.

It is well known that serial changes occur in serum uric acid level in normal pregnancy 3and pregnancy induced hypertension.[3,4] Uric acid is a terminal metabolite of the degradation of nucleotides. It is influenced by diet (i.e. high protein and fructose), alcohol consumption, increased

cell turnover, enzymatic defects in purine metabolism or altered kidney function.[5] In pregnancy uric acid concentrations initially fall 25-35% due to the effects of estrogen, expanded blood volume and increased glomerular filtration rate.[6] However, concentrations slowly rise to those observed in non-pregnant women by term gestation (4-6 mg/dl). This hyperuricaemia seen in association with pre-eclampsia is hypothesised to result from increased production maternal renal dysfunction (reduced urate clearance or fractional excretion) and placental tissue ischaemia and acidosis. There is a positive correlation seen between the raised serum uric acid level and adverse fetal outcome. Uric acid crystals induces placental inflammation and alters trophoblast function causing stillbirth and fetal growth restriction (FGR).[7-13]

Early screening for preeclampsia may allow vigilant antenatal surveillance and appropriate timing of fetal delivery in order to avoid serious sequelae. So we wanted to revisit uric acid as a useful biochemical marker, which is extremely cheap & widely available, as studies with new biochemical markers have shown variable and inconsistent results.13

METHODS

This prospective, observational comparative study was conducted at a tertiary care hospital, Jharkhand over 18 months. Ethical clearance was obtained from the Institutional Ethical Committee. All antenatal cases as per the inclusion and exclusion criteria attending the OPD or admitted; were recruited. All primi and multigravida patients with blood pressure of 140/90 mmHg at ≥20 weeks of pregnancy on 2 occasions at least 6 hours apart were included. Pregnant women with history of hyperuricemia, pre-existing diabetes mellitus, renal disease, anomalous babies were excluded.

After taking informed written consent from all the participants, demographic data like age, gestation, parity etc were recorded on structured data collection sheet. A detailed medical and family history of all participants were taken. Thorough physical examination of every case and controls which was recorded. Blood pressure of all participants was measured using manual mercury sphygmomanometer with woman in sitting position with feet flat on floor and back well supported and with arm at level of heart using appropriately sized cuff.

Blood sample for uric acid were collected in the morning after overnight fasting in a plain bulb with aseptic conditions. In our study groups blood samples were collected when the patients presented for evaluation and before initiation of medical therapy. Serum uric acid was estimated by modified Trinders test using a semi autoanalyzer. Urine protein was measured by dipstick and graded as Trace to 4+ (Trace,0.1 gm/l;1+,0.3 gm/l;2+,1 gm/l;3+3.0 gm/l, 4+10 gm/l). Urine analysis was done in all subjects to measure the degree of proteinuria.

120 pregnant women were enrolled in this study after 20 weeks of pregnancy and divided into two groups: Group A with 60 patients with uric acid ≥6 mg/dl and Group B with 60 patients with uric acid < 6 mg/dl. Maternal outcomes were analysed in terms of gestational age at delivery, mode of delivery and any noted complications. Neonatal variables of birth weight, APGAR score at birth, neonatal mortality and morbidity were recorded. Reference levels of normal serum uric acid levels.[16]

Statistical analysis

All the data were selected randomly and tabulated, and then analyzed with appropriate statistical tools "MedCalc". Data were presented as mean with standard deviation or proportions as appropriate. Mean, median, standard deviation and variance were calculated and following statistical significance tests were applied.

Student's unpaired T-test was used as the statistical tool to test for significance of observed mean differences. Statistical analysis was done using "Chi – square Test" used for comparing qualitative data. test of significance for difference of proportions.

Finally, the calculated value was compared with the tabulated value at particular degree of freedom and finds the level of significance. A "p value" was considered to be not significant if >0.05 and significant if <0.05

RESULTS

Of total 120 pregnant women with hypertensive disorders of pregnancy-

In Group A (60),12 (20%) had gestational hypertension, 11(18.3%) had mild preeclampsia, 25 (41.67%) had severe preeclampsia, 6 (10%) had preeclampsia superimposed on chronic hypertension and 10 (16.7%) had eclampsia.

In Group B (60), 3 (5%) had gestational hypertension, 42 (70%) had mild preeclampsia, 11(18.3%) had severe preeclampsia, 3 (5 %) had preeclampsia superimposed on chronic hypertension and 1 (1.67%) had eclampsia.

The distribution of different HDP in 2 groups is statistically significant except preeclampsia superimposed on chronic hypertension. The socio-demographic features including the age of women, gravidity, and gestation of pregnancy are depicted in Table 1-3 respectively.

In Group A, the mean serum uric acid (Mean±SD) of the patients were 7.3733±1.4087 mg/dl. In Group B, the mean serum uric acid (Mean±SD) of the patients were 4.6633±.6428 mg/dl. Distribution of mean serum uric acid vs. group was statistically significant (p<0.0001).

We can see there were statistically significant differences among the patients according to their serum uric acid between two groups, with p value (p<0.0001) in Table 4

and 6. Table 5 shows mode of delivery among the two groups. The relation between maternal serum uric acid levels and severity of disease and the maternal outcome is depicted in Table 7. Fetal outcome is summarised in Table 8-11.

Table 1: Age distribution among the patients between two groups.

Age (in year)	Group A (n=60)		Group B (n=60)	
	No.	%	No.	%
≤ 20	9	15	2	3.33
21–30	48	80	55	91.67
>30	3	5	3	5

Table 2: Comparison of association of gravidity between two groups.

Gravida	Group A (n=60)		Group B (n=60)	
	No	%	No	%
1	42	70	41	68.33
2	11	18.33	10	16.67
3	6	10	3	5
4	1	1.67	6	10

Table 3: Comparison of association of Gestational age between two groups.

Age (in weeks)	Group A (n=60)		Group B (n=60)	
	No.	%	No.	%
28–32	2	3.33	0	0
33–36	13	21.67	2	3.33
≥ 37	45	75	58	96.67

Table 4: Distribution of mean serum uric acid between two groups.

Serum uric acid (mg/dl)	Group A (n=60)		Group B (n=60)	
	No.	%	No.	%
5 - 6	0	0	60	100
6 – 7	33	55	0	0
>7	23	45	0	0

Table 5: Comparison of mode of delivery between two groups.

Mode of delivery	Group A (n=60)		Group B (n=60)		$\|z\|_{cal}$	P value
	No.	%	No.	%		
Vaginal delivery	28	46.67	48	80	12.952	0.0003#
Forceps	2	3.33	0	0	0.507	0.4765*
LSCS	30	50	12	20	10.586	0.0011#

#Significant; *Non-significant

Table 6: Comparison of mean serum uric acid in two groups.

	Group	No	Mean	SD	Minimum	Maximum	Median	P value
Serum uric acid	A	60	7.3733	1.4087	6	12.4	7	<0.0001
	B	60	4.6633	0.6428	3.2	5.8	4.7	

Table 7: Maternal outcomes among the two groups.

Type of maternal complications	Group A (n=60)		Group B (n=60)		$\|z\|_{cal}$	P value
	No.	%	No.	%		
Eclampsia	10	16.67	1	1.67	5.818	0.015#

Continued.

Type of maternal complications	Group A (n=60)		Group B (n=60)		$\|z\|_{cal}$	P value
	No.	%	No.	%		
HELLP	6	10	0	0	4.386	0.0362#
Pulmonary edema	6	10	0	0	4.386	0.0362#
Acute renal failure	3	5	0	0	1.368	0.2422*
Abruption	5	8.33	1	1.67	1.575	0.2095*
ARDS	2	3.33	0	0	0.507	0.4765*
DIC	2	3.33	0	0	0.507	0.4765*
PPH	10	16.67	2	3.33	4.542	0.0331#
Maternal mortality	2	3.33	0	0	0.507	0.4765*

#Significant; *Non-significant

Table 8: Distribution of birth weight of babies among groups.

Birth weight (in kg)	Group A (n=60)		Group B (n=60)		$\|z\|_{cal}$	P value
	No.	%	No.	%		
<2	11	18.33	0	0	10.006	0.0016#
2–2.4	7	11.67	5	8.33	0.0933	0.7600*
2.5–3	28	46.67	34	56.67	0.834	0.3610*
>3	14	23.33	21	35	1.453	0.2280*

#Significant; *Non-significant

Table 9: Comparison of Apgar score between two groups.

Apgar scores	Group A (n=60)		Group B (n=60)	
	No.	Percentage	No.	Percentage
<3	3	5	0	0
3-7	21	35	9	15
>7	36	60	51	85

Table 10: Comparison of NICU admission between two groups.

NICU admission	Group A (n=60)		Group B (n=60)		$\|z\|_{cal}$	P value
	No.	%	No.	%		
No admission	31	51.67%	54	90%	19.52	<0.0001#
1 – 7 days	15	25%	6	10%	3.694	0.0546#
>7 days	14	23.33%	0	0%	13.663	0.0002#

#Significant

Table 11: Comparison of type of perinatal complications between two groups.

Type of perinatal complications	Group - A (n=60)		Group - B (n=60)		$\|z\|_{cal}$	P value
	No.	%	No.	%		
Birth asphyxia	9	15	1	1.67	5.341	0.0208#
IUGR	16	26.67	5	8.33	5.777	0.0162#
MAS	5	8.33	2	3.33	0.607	0.4359*
RDS	14	23.33	4	6.67	5.289	0.0215#
SEPSIS	2	3.33	1	1.67	0.0054	0.9981*
No complications	25	41.67	48	80	16.925	<0.0001#

#Significant; *Non-significant

DISCUSSION

In the present study, it was observed that high maternal serum uric acid levels were associated with increased severity of disease and an overall adverse maternal and fetal outcomes. In present study we observed that in Group A mean serum uric acid was 7.37±1.41mg/dl and in Group B, the mean serum uric acid of the patients was 4.66±0.64 mg/dl. Thus, mean value of serum uric acid is significantly

increased in Group A than Group B (p<0.0001). Similar results were obtained by the following observers Bellomo et al observed that mean value of serum uric acid was 6.6 mg/dl in preeclamptic patients and 3.9 mg/dl in patients with gestational hypertension.[14] Katz et al studying 53 pregnancies complicated by eclampsia detected that uric acid was higher than 6 mg/dl in 43 of 53 cases.[15] Similar results were seen in Paula et al study, mean serum uric acid in preeclampsia group was 5.32±1.45 mg/dl and in eclampsia group it was 6.92±1.93 mg/dl (p <0.001).[16] Regarding the socio-demographic features observed in the present study, it was found that the mean age of patients in Group A was 23.88 years and in Group B was 25.1 years (statistically not significant) (p value=0.059).

The patients with hypertensive disorders of pregnancy in our study groups were with significant low gravidity and parity. In Group A, 70.0% patients were primigravida,18.3% patients were second gravida,10.0% patients were third gravida and 1.7% patients were fourth gravida In Group B, 68.3% patients were primigravida,16.7% patients were second gravida, 5.0% patients were third gravida and 10.0% patients were fourth gravida. The distribution of gravidity between two groups was not statistically significant (p=0.2009).

In the study (Table 3) in Group A, 3.33% were between 28 and 32 weeks, 21.67% were between 33 and 36 weeks and in 75 % gestational age of patients at delivery was found to be 37 weeks. In Group B, 3.33% were between 33 and 36 weeks and in 96.67% gestational age of patients at delivery was found to be 37weeks. So, in Group A 25% patients delivered preterm babies (<37 weeks) as compared to group B which was 3.33%. Hence, there was statistically significant difference between Group A and Group B according to their gestational age at the time of delivery between two groups, with p value=0.0029 (p<0.05).

In Group A (Table 3) the mean period of gestational age at delivery was 37.11±2.07 weeks. In Group B, the mean period of gestational age at delivery was 38.36±1.23 weeks (p<0.0001). It shows significant decrease in mean gestational age in Group A as compared to Group B. The reason of more preterm deliveries in Group A as compared to Group B is requirement of early termination of pregnancy to prevent complications associated with hypertensive disorders of pregnancy with uric acid ≥6 mg/dl. Le et al showed that at high uric acid level 6.607 mg/dl (393 mol/l), the risk of preterm birth was increased 6.367 times (95% CI 3.009–13.084) which is comparable with the present study.[17]

Paula et al showed mean gestational age decreased with increased uric acid levels.[16] The mean gestational age at delivery in patients with preeclampsia with mean uric acid 5.32±1.45mg/dl was 36.2±3.5 weeks and mean gestational age at delivery in patients with eclampsia with mean uric acid level 6.92±1.93 mg/dl was 34.5±3.9 weeks which is slightly different from present study which may be because of difference in sample size and moreover they may have included patients with more complicated disease picture.

In Group A, 13.3 % had gestational hypertension, 18.3% had mild preeclampsia, 41.67% had severe preeclampsia, 10% had preeclampsia superimposed on chronic hypertension and 16.7% had eclampsia. In Group B 5% had gestational hypertension,70% had mild preeclampsia, 18.3% had severe preeclampsia,5 % had preeclampsia superimposed on chronic hypertension and 1.67% had eclampsia. The distribution of different HDP in 2 groups is statistically significant except preeclampsia superimposed on chronic hypertension.

In Tejal et al study, in group A patients (with serum uric acid ≥6 mg/dl) 12% had superimposed on chronic hypertension,20% had mild preeclampsia,50 % had severe preeclampsia and 8% had eclampsia.[18] In group B patients (with serum uric acid<6 mg/dl), 4 % had preeclampsia superimposed on chronic hypertension, 70% had mild preeclampsia, 18% had severe preeclampsia and 2% had eclampsia.

Thus, authors observe that hyperuricemia is closely related to severity of hypertensive disorders. In the study, (Table 5) statistics reveal that in HDP patients with serum uric acid ≥6 mg/dl in group A, 50% delivered by caesarean section, 46.67% vaginally and forceps was applied in 3.33% cases to cut short the second stage of labour. While in group B, 20% underwent caesarean section and 80% delivered vaginally. The high rate of caesarean section could be because of early intervention to avoid serious sequelae and also because of strict departmental policy to limit the induction of labour in eclamptic and severe pre-eclamptic patients. Le et al reported caesarean rate of 48.78% in patients with uric acid >6 mg/dl which is closer to the result.[17] The result is consistent with Patel et al who observed that increased risk of caesarean section by 3.4-fold in patients with a uric acid level ≥6 mg/dl as compared to those with a level of uric acid <6 mg/dl at p value=0.006.[18] From table authors analysed that maternal complications occurred in 43.33% patients in Group A and 6.67% patients in Group B. In Group A, 10(16.67%) patients had PPH during delivery which was managed well with oxytocin, prostaglandin and bimanual massage, 6(10%) developed pulmonary oedema which responded well to diuretics and 100% oxygen. The study is comparable with other study. Out of 43.33% patients who develop complications, 2 (3.3%) patients died. One patient died due to acute renal failure and other patient died due to complicated pulmonary oedema.

Our findings support the hypothesis that elevated uric acid level is associated with the severity of maternal disease, especially to the risk of developing eclampsia, abruption, PPH, pulmonary oedema and HELLP syndrome which is closely associated with maternal mortality. The present study observed a significant correlation between poor perinatal outcome and maternal serum uric acid levels. Incidence of low birthweight (<2.5 kg), was found to be in

18 (30%) patients in group A and 5 (8.33%) patients in group B. In Group A, the mean birth weight was 2.7 kg. In Group B, the mean birth weight was 2.93 kg. Distribution of mean birth weight in both groups is statistically significant (p=0.0084).

Kumar et al showed that mean neonatal birth weight in groups I with serum uric acid <6 mg/dl was 2.956±0.273 kg and group II with serum uric acid >6 mg/dl was 2.177±0.282 kg. The mean birth weight was lower in group II (serum uric acid >6) which may be due to severity of disease.[20] Paula et al result showed that in group I (mean uric acid >6 mg/dl) 62.2% babies were low birth weight and in group II (mean serum uric acid <6 mg/dl) 38% babies were low birth weight.[16] The result is higher as compared to our study which may be due to sample size and severity of disease.

In the study in Group A, the mean Apgar was 5.95. In Group B, the mean Apgar was 7.95. The table shows that in group A greater number of babies had low Apgar score (<7) in patients with serum uric acid ≥6 mg/dl as compared to patients with serum uric acid <6 mg/dl. Among patients with serum uric acid ≥6 mg/dl,40% babies had low Apgar score <7 which is closer to Tejal et al and slightly higher than study done by Paula et al.[16,18] In Group A, 23.3% babies required NICU admission for >7 days and 25% babies required <7 days. In Group A, the mean NICU stay of babies was 4.4833±6.4374. In Group B, the mean NICU stay of the babies was 0.3000±1.0783. Distribution of mean NICU stay in both groups was statistically significant (p<0.0001). In study done by Kumar et al 31 (27.93%) babies suffered respiratory distress and 14 (12.61%) had severe birth asphyxia and required ventilator support in group with serum uric acid >6 mg/dl.[20] In another study Sachan et al showed that 20.3% required hospital admission in uric acid >6 mg/dl compared with only 6.5% in the group II with serum uric acid<6 mg/dl.[19] The NICU stay is greater in the result as compared to other result which may be due to increased severity of disease and sample size. In present study, in Group A, 9 (15%) babies had birth asphyxia,16 (26.67%) babies were IUGR, 5 (8.33%) babies had meconium aspiration syndrome, 14 (23.33%) babies had respiratory distress syndrome, 2 (3.33%) babies had sepsis. In Group B, 1 (1.67%) baby had birth asphyxia, 5 (8.33%) babies had IUGR, 2 (3.33%) babies had meconium aspiration syndrome, 4 (6.67%) babies had respiratory distress syndrome, 1 (1.67%) baby had sepsis. There was significant association between perinatal complications except sepsis and meconium aspiration syndrome.

In Kumar et al study in mean serum uric acid ≥6 mg/dl, 31 (27.93%) suffered minimal respiratory distress, which was higher than our present study and 14 (12.61%) severe birth asphyxia and required ventilatory support, which was lower than our study. The difference may be due to different sample size. Out of 10 babies (16.67%), 7 (11.67%) were still born and 3 (5%) babies died in early neonatal period due to extreme prematurity in eclamptic patients. In the present study, perinatal mortality is similar to the study done by Patel et al and higher than study done by others which may be due to extreme prematurity, increased severity of disease difference in sample size, poor antenatal checkups.[16,18,21]

In the study we found a strong correlation between high maternal serum uric acid and increased morbidity and mortality in women with eclampsia. Hence, serum uric acid can be used as a sensitive index of severity of HDP as well as a useful indicator of overall maternal and fetal outcome.

Limitations

The study included a small group of population, so the role of uric acid as a predictor of severity in preeclampsia and eclampsia patients could not be studied in a wider range of population. Hence a large-scale study is warranted to emphasize its clinical role as a strong predictor.

CONCLUSION

The present study observed that maternal serum uric acid levels show a significant correlation with the severity of hypertensive disorders of pregnancy (HDP). A direct correlation was also observed with the adverse maternal and fetal outcomes as well as with increased rate of interventions during labour and the mode of delivery. Therefore, serum uric acid can be considered as one of the biomarkers for severity of HDP and its related outcomes. Estimation of serum uric acid as a biochemical marker is cheap, easily available and non-invasive test which can be offered to all the patients with hypertensive disorders in pregnancy. This would lead to a decrease in the global burden of maternal and perinatal morbidity and mortality.

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