Maternal Serum Uric Acid as a Biochemical Prognostic Marker for Predicting Maternal and Fetal Outcome in Pregnancy-Induced Hypertension – A Prospective Study

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ABSTRACT

Introduction: Pregnancy-induced hypertension (PIH), encompassing conditions such as gestational hypertension, pre-eclampsia, and eclampsia, remains a significant cause of maternal and perinatal morbidity and mortality worldwide, particularly in developing countries. It typically manifests after 20 weeks of gestation and is characterized by elevated blood pressure with or without proteinuria or other systemic involvement. Despite advancements in obstetric care, early prediction and effective management of PIH remain challenging due to its unpredictable progression and complex pathophysiology. Among various biomarkers explored for early detection and prognostication of PIH, serum uric acid has emerged as a potential candidate. Uric acid, a final product of purine metabolism, is known to increase during normal pregnancy, but elevated levels beyond the expected physiological range have been correlated with adverse maternal and fetal outcomes in hypertensive pregnancies. Hyperuricemia in PIH is believed to reflect reduced renal clearance, oxidative stress, endothelial dysfunction, and systemic inflammation—all of which are central to the disease process. The aim was to study serum uric acid as a biochemical prognostic marker for predicting maternal and fetal outcome in pregnancy-induced hypertension.

Material & Methods: A total of 200 antenatal women were enrolled in the study. The control group consisted of 100 healthy normotensive women with no history of raised blood pressure or renal disease, and the case group consisted of 100 preeclamptic antenatal women. All patients' blood pressure was measured at admission and after 4 hours, and their venous samples were taken and sent for serum uric acid estimation and compared for their significance in predicting pre-eclampsia, correlating severe grades of hypertension and fetomaternal outcome. Statistical analysis was done using various tests like Mann-Whitney, chi-square test, Fisher test, etc.

Results: The mean uric acid value in normotensives was 4.20 ± 0.83 mg/dl, increased with increasing severity of hypertension, maximum in the eclamptic group, 9.75 ± 3.31 mg/dl. There is a positive correlation between uric acid and the severity of hypertension. The maternal complications like LSCS, HELLP

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syndrome, post-partum eclampsia, and fetal complications like low APGAR score, low birth weight, and NICU admission were higher when the uric acid level was above 6.5 (p < 0.05).

Conclusion: Serum uric acid was found to be a useful prognostic indicator for fetomaternal outcomes in women with pre-eclampsia and eclampsia.

Keywords: Serum uric acid, pre-eclampsia, eclampsia, SBP, DBP, MAP, Hypertensive disorders of pregnancy, HELLP, LVF, PPH, IUGR.

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INTRODUCTION

Hypertension is defined as a persistent rise in blood pressure greater than 140/90 mmHg.¹ Hypertensive disorders of pregnancy complicate about 7 to 10% of all pregnancies.² Worldwide, 10 to 15% of all maternal deaths are caused by pre-eclampsia and eclampsia. HDP increases perinatal morbidity and mortality by 10 to 15%. Hypertensive disorders of pregnancy are considered a significant cause of adverse maternal and fetal outcomes globally, more so in developing areas of the world.⁴ Hypertensive disorders of pregnancy include a spectrum of diseases ranging from mildly elevated blood pressure to multi-organ dysfunction. ACOG classifies HDP into four categories: pre-eclampsia-eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia, and gestational hypertension. Maternal complications include abruptio placentae, hemolysis, elevated liver enzymes, HELLP syndrome, acute LVF with pulmonary edema, acute renal failure, PPH, and DIC. Fetal complications include intrauterine demise, IUGR, prematurity, antepartum, and intrapartum asphyxia. 5 Hyperuricemia is a common finding in HDP. It is also found that elevation of uric acid precedes the onset of hypertension, proteinuria and disease manifestations in HDP(20). Uric acid is the final metabolite in the process of purine metabolism during the breakdown of DNA, RNA and ATP, produced by the enzyme Xanthine Oxidase

Table 1: Norma	I uric acid levels	during pregnancy
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Non-pregnant	First trimester	Second trimester	Third trimester	
3.026-5.88 mg/dl	2.35-3.80 mg/dl	2.35–4.70 mg/dl	3.52-6.38 mg/dl	

/Xanthine dehydrogenase & excreted mainly in urine.⁶ Pathogenesis of hypertension in pregnancy includes abnormal placentation, defective placenta formation due to oxidative stress and imbalance in angiogenic factors. There is an excessive level of antiangiogenic factors like sFlt-1, sEng (serum endoglin) and reduced levels of angiogenic factors like VEGF(vascular endothelial growth factor), PIGF (placental growth factor) and transforming growth factor-β.⁷ There are various genetic factors involved in the pathogenesis of HDP, like the MTHFR gene, factor V gene, HLA genes, and NOS3 gene, etc. There are many clinical, biochemical, and biophysical, for the prediction of the onset of pre-eclampsia, like: multimarker screening, Doppler ultrasound, mean arterial pressure in the second trimester > 90 mmHg, roll over test, gestosis score, etc. In normal pregnant women, due to physiological adaptations, GFR and renal plasma flow increase by 50% after conception. Serum uric acid concentration initially falls up to 16 weeks, stabilizes between 17 and 28 weeks of gestation and then, in the third trimester, serum uric acid levels increase (Table 1). This is due to an increase in fetal production, decreased binding to albumin and a decline in uric acid clearance. The normal serum uric acid values⁸ in non-pregnant women & in pregnancy are different in different trimesters.

However, uric acid values increase more in preeclampsia and eclampsia. There are many reasons for raised serum uric acid levels in women with hypertensive pregnancies, which include increased fetal production,⁹ impaired clearance from kidneys, increased tissue breakdown, acidosis, increased oxidative stress and increased activity of xanthine oxidase enzyme causing more conversion of xanthine to uric acid. Uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, so hyperuricemia is associated with a severe form of pre-eclampsia. The degree of elevation of serum uric acid levels correlates with the severity of the disease and its outcome, as there is more tissue damage, inflammation and oxidative stress in disorders of hypertensive pregnancy. 10 We hypothesized that serum uric acid can be used as a useful biochemical predictor for early detection of hypertensive disorder of pregnancy, its correlation with severe grades of hypertension, and maternal and fetal outcomes. The aim is to Study Serum uric acid as a biochemical prognostic marker for predicting maternal and fetal outcome in pregnancyinduced hypertension.

MATERIAL AND METHODS

This is a prospective case-control study conducted on all patients presenting to the department of Obstetrics & Gynaecology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly. Patients were recruited over a period of one and a half years from 1st Feb 2021-31st July 2022 according to the following inclusion and exclusion criteria. The inclusion criteria were singleton pregnancy, gestation age >20 weeks, all patients diagnosed to have BP \geq 140/90 mmHg, and normotensive antenatal patients > 20 weeks. The patients with chronic hypertension, chronic renal disease, previous history of pre-eclampsia, immunological or vascular disorder, and urinary tract infection were excluded.

After taking informed consent, a total of 200 antenatal patients who met the above criteria were enrolled. Group 1 (Control group) consisted of 100 normotensive antenatal patients with no history of raised BP and Group 2 consisted of 100 hypertensive patients, including gestational hypertension, pre-eclampsia and eclampsia. After admission, BP was recorded and repeat BP was taken after 4 hours. Serum venous samples were taken and sent for serum uric acid estimation. Urine samples were taken for urine protein estimation. The reference values for serum uric acid are 3.5 to 7.2 mg/dl for men and 2.6 to 6.0 mg/dl for women. Serum uric acid values were compared for various grades of hypertension, with maternal and fetal outcomes.

RESULTS

The majority of patients in both the groups were in the group were 25 to 27 years and were primigravida. Most were unbooked and studied till high school. The BMI ranged between 24 to 27 kg/m² in the case group and it was 24 to 26 kg/m²; this difference was significant. In the study, it was found that haemoglobin level was comparable in both groups. In this study, bilirubin and SGOT were significantly higher in the cases than controls (p <0.05). The mean bilirubin levels in cases were 0.74 ± 0.79 mg/dl and in controls were $0.57 \pm 0.27 \text{ mg/dl}$ and SGOT was 71.98 \pm 82.29 IU/L in cases and it was 50.40 \pm 44.32 IU/L in controls; their association with hypertensive disorder of pregnancy was significant. The mean value of platelets was 1.58 ± 0.68 lakhs/cumm in the case group and 1.85 ± 0.53 lakhs/cumm in the control group and this difference of platelets was found to be statistical significant (p <0.05). In the majority of the patients in the case group, urine albumin was 1+ and 31 patients had 2+/ more urine albumin. This difference of proteinuria between the groups was highly significant (p <0.001) (Table 2). Comparative analysis of blood pressures in both case & control groups shows statistical significance for all the parameters of blood pressure, SBP, DBP and MAP, which were more in the case group and were found to be significant(< 0.001)(Table 3). Table 4 shows that in the study, the minimum mean uric acid level in normotensive patients was 2.10 mg/dl, the maximum was 6.50 and the mean uric acid level was 4.20 mg/dl. In the hypertensive group, the minimum uric acid level was 2.60 and the maximum 20.30 mg/dl and the mean uric acid 6.87 mg/dl. All the serum uric acid values were higher in the hypertensive group.

Table 5 shows the relation of uric acid, blood pressure and urine proteinuria in normotensive and hypertensive groups and it was found that as the blood pressure (SBP and DBP) increases, the uric acid also increases significantly (p < 0.05).

In the study, maternal complications in the hypertensive group were studied with serum uric acid level and it was found that the various maternal complications were more common with raised uric acid. It was seen that proteinuria, oliguria, headache, and CNS symptoms were more common in the pre-eclampsia and eclampsia group, with a mean uric acid of 9.62 ± 3.96 mg/dl in the pre-eclampsia and 10.83 ± 3.06 mg/dl in the eclampsia group. One case of mortality was also seen in the eclampsia group, with a maximum uric acid of 20.30 mg/dl, but no significant difference in maternal outcome was noted for different parameters of the case

group (p > 0.05) except proteinuria and febrile morbidity (p < 0.05) (Table 6).

Table 7 shows that serum uric acid level was compared in patients with different grades of hypertension, controls and fetal outcome. It was found that 8 stillbirths occurred in the case group. In the gestational hypertensive group, 2 still births were seen, with a mean uric acid of 7.50 gm/dl, 4 out of 19 preeclamptic patients had still birth, 1 eclamptic patient had still birth, having the highest mean uric acid 14.30 \pm 6.64 mg/dl. All the fetal complications, IUGR, low APGAR at 1,5 mins, low birth weight and NICU admission were more in pre-eclampsia and eclampsia. But birth weight was found to be highly significant.

DISCUSSION

In our study, the majority of the studied patients were below the age of 25 years, i.e., 55.0% with a mean age of 26.67 ± 4.85 and 52.0% with a mean age of 26.19 ± 5.09 for cases and control groups, respectively. Similarly, the mean age of cases was 27 \pm 4.9 and 27.2 \pm 5.6 years as reported in Kooffrey ME et al., 13 and Sotunsa J et al., 14, respectively. Obagah L et al. 15 reported that the mean age of cases and controls was 28 ± 6.7 and 31 ± 6.5 years. In our study, most of the women were primigravida in both groups, i.e., 42% in the case group and 38% in the control group. The majority of the patients were unbooked, 87% in cases and 81% in the control group. Mahalakshmi G, Krishnaveni et al. 16 reported that in their study majority of patients were primigravida (77.45%) and 96.1% were un-booked cases, which is in concordance with our study result. Our study showed that the BMI was significantly

Table 2: Comparison of demographic, clinical, hematological and biochemical characteristics in both groups

Parameters Mea	n + SD/ Percentage	Case group (n=100)	Control group (n=100)	p-value
Age (years)		26.19 ± 5.09	26.67 ± 4.85	0.921
Gravida		Primigravida (38%)	Primigravida(42%)	>0.05
Antenatal bookin	g	Unbooked (85%)	Unbooked (81%)	
BMI (kg/m ²)		26.97 ± 1.19	24.20 ± 2.35	<0.001
Family history		10%	6%	0.297
Past history of pr	re-eclampsia	11%	2%	<0.05
Hemoglobin (g/d	1)	10.70 ± 1.57	10.84 ± 1.46	0.506
RBS (mg/dl)		94.37 ± 24.00	96.24 ± 13.35	0.497
Bilirubin (mg/dl)		0.74 ± 0.79	0.57 ± 0.27	<0.05
SGOT (IU/L)		71.98 ± 82.29	50.40 ± 44.32	<0.05
SGPT (IU/L)		61.50 ± 71.45	49.14 ± 46.11	0.148
SAP (IU/L)		168.39 ± 120.05	161.97 ± 106.37	0.689
Platelets (lakhs/d	cumm)	1.58 ± 0.68	1.85 ± 0.53	<0.05
Urine albumin	Nil	6	66	<0.001
	Trace	13	31	
	1+	50	2	
	2+ or more	31	1	

Table 3: Comparison of blood pressure in both groups

Parameters	Groups		
(Mean + SD) #	Case (100)	Control(100)	- p-value
SBP (mmHg)	149.24 ± 14.66	122.14 ± 9.20	<0.001
DBP (mmHg)	95.78 ± 8.23	78.74 ± 4.91	<0.001
MAP (mmHg)	113.60 ± 9.56	93.21 ± 5.44	<0.001

Table 4: Comparison of Serum uric acid values in normotensive antenatal women and Hypertensive antenatal women

Туре	Mean uric acid level	Std. Deviation	Minimum	Maximum
Hypertensive antenatal women	6.87	2.60	3.20	20.30
Normotensive antenatal women	4.20	0.83	2.10	6.50

higher in pre-eclampsia and eclampsia (27-29) kg/m 2 in cases than in the control group. This is supported by a study done by Lisa M *et al.*¹⁷ who also observed a rise in risk of hypertensive disorder of pregnancy from a BMI of 15 to 30 kg/m 2 , compared with women with a BMI of 21. The risk of pre-eclampsia doubled at a BMI of 30. Pallor, edema, icterus, temperature, and oliguria were present in significantly higher numbers in cases than controls (p <0.05).

In our study, the haematological and biochemical parameters were compared between cases and controls and it was found that serum uric acid, bilirubin and SGOT were significantly higher in cases than in controls (p < 0.05). The mean bilirubin levels in cases were 0.74 \pm 0.79 mg/dl and in controls, they were 0.57 \pm 0.27 mg/ dl and SGOT was 71.98 ± 82.29 IU/L in cases and it was 50.40 ± 44.32 IU/L in controls; their association with hypertensive disorder of pregnancy was significant. The mean value of platelets was 1.58 ± 0.68 lakhs/cumm in the case group and 1.85 ± 0.53 lakhs/cumm in the control group. The difference in mean was found to be statistically significant (p < 0.05). One such study done by Le TM et al. 17 showed that preeclamptic patients showed low bilirubin levels, which is in contrast with this study. The blood pressure in the maximum of the patients in our study group, i.e., 98, had BP > 140/90 mmHg with a mean uric acid level of 6.75 mg/dl, whereas subjects with BP< 140/90 mmHg had a mean uric acid of 4.89 mg/ dl. This shows that as the BP increases, the Serum uric acid values also increase simultaneously. In our study, the average urine albumin was 2+ and more in 31% patients with PIH, which is significant (p < 0.01). This is in accordance with a study conducted by Airoldi J & Weinstein L^{18} , who reported that proteinuria was present in 38% of patients with eclampsia. The average uric acid was lowest in normotensive (4.20 ± 0.83) and was highest in cases with eclampsia (9.75 ± 3.31) and the difference was statistically significant (p < 0.05). The patients with severe grades of hypertension have significantly higher levels of uric acid than normal or mild stages of hypertension (p < 0.05). Similar to our findings, Kumar N et al. ¹⁹ reported that the mean serum uric acid in gestational hypertensive

Table 5: Biostatistical correlation of age, S. uric acid, SBP, DBP and urinary protein for normotensive antenatal and hypertensive antenatal women

	Case group	Name tanaina (n. 100)			
	Gestational Hypertensive (n = 77)	Pre-eclampsia (n = 19) Eclampsia (n = 4)		- Normotensive (n=100)	p-value
Age	26.90 ± 4.45	26.79 ± 6.29	21.75 ± 1.26	26.19 ± 5.09	0.206
Uric acid	6.22 ± 1.62	8.94 ± 4.01	9.75 ± 3.31	4.20 ± 0.83	<0.001
SBP	143.25 ± 7.37	165.47 ± 10.66	187.50 ± 22.17	122.14 ± 9.20	<0.001
DBP	92.57 ± 4.79	105.26 ± 7.23	112.50 ± 9.57	78.74 ± 4.91	<0.001

Table 6: Comparison of maternal outcome with serum uric acid level and various grades of hypertension in both groups

	Case group	Ma was a fa wa sii ya			
	Gestational hypertension (n = 77)	Pre-eclampsia (n = 19)	Eclampsia (n = 4)	— Normotensive (n = 100)	p-value
Proteinuria	6.63 ± 1.67	9.62 ± 3.96	10.83 ± 3.06	4.64 ± 0.93	<0.001
Oliguria	-	8.85 ± 2.40	10.40 ± 5.52		0.568
CNS symptom	6.60 ± 0.00	7.90 ± 0.70	10.83 ± 3.06		0.253
Headache	6.2 ± 1.97	8.7 ± 3.32	9.75 ± 3.31	3.55 ± 0.35	0.140
HELLP	11.47 ± 4.55	8.50 ± 2.16		_	0.862
Maternal mortality			9.1 ± 0.85		
Febrile morbidity	4.00 ± 0.00	8.35 ± 0.21			< 0.05

Table 7: Relationship of serum uric acid levels and fetal outcome in various grades of hypertensive group and control group

	Case Group	Normotensive			
	Gestational Hypertensive (n = 77)	Pre-eclampsia (n = 19)	Eclampsia (n = 4)	(n = 100)	p-value
Still birth/IUD	7.50 ± 0.17	10.47 ± 3.87	14.30 ± 6.64	4.95 ± 0.07	0.104
Low APGAR at 1 minute	7.36 ± 0.45	9.50 ± 3.41	12.00 ± 3.25	4.95 ± 0.07	0.073
Low APGAR at 5 minutes	7.50 ± 0.17	10.47 ± 3.87	14.30 ± 6.64	4.95 ± 0.07	0.104
Low birth weight (<2.5 kg)	6.31 ± 1.15	11.05 ± 4.82	9.10 ± 0.85	4.39 ± 1.17	<0.001
NICU admission	7.15 ± 0.78	10.02 ± 5.79	9.70 ± 4.45	3.90 ± 1.17	0.719

antenatal women with healthy fetuses was 5.16 ± 1.74 mg/dl and with distressed fetuses was 6.52 ± 2.31 mg/dl, in pre-eclampsia it was 5.3 ± 1.44 and 7.29 ± 2.63 mg/dl and in eclamptic women 5.7 ± 0.0 mg/dl and

 8.83 ± 2.96 mg/dl, respectively, which also supports our study. Maternal complications like Antepartum eclampsia, HELLP syndrome, and post-partum eclampsia were present in significantly higher numbers in cases than controls (p < 0.05). Caesarean deliveries, HELLP syndrome, and post-partum eclampsia were higher where the uric acid level was above 6.5 (p <0.05). Similar to our findings, Saldanha CL et al.20 reported that the maternal complications during the antepartum and postpartum period were higher when serum uric acid levels (SUA) were ≥5 mg/dl. Many more studies were done, which also support our study. In our study, it was noted that NICU admission stillbirths were significantly higher in number in cases (p < 0.05) than in controls. APGAR at 1 and 5 minutes and birth weight were significantly lower in cases than in controls (p < 0.05). Hypertensive antenatal women with low birth weight (<2.5 kg) babies show significantly higher uric acid levels (p <0.05). Stillbirth, NICU admission, was significantly higher in cases with uric acid levels above 6.5 Babies had low APGAR at 1 and 5 minutes and low birth weight in patients with uric acid above 6.5 (p <0.05). It was supported by a study done by Saldahana et al. 20 where et al. complications like prematurity, low birth weight, low APGAR, and NICU admission were more common in cases with SUA > 5 mg/ dl. Similar results, like stillbirth, low APGAR, low birth weight, etc, were shown in a study conducted by Singh et al. In our study, there is an increasing trend of adverse neonatal and maternal outcomes with high serum uric acid levels. This may indicate that when uric acid is high, there is a higher chance of progression of gestational hypertension and development of pre-eclampsia and eclampsia.

CONCLUSION

In this study, it was found that there is a significantly greater rise in serum uric acid in hypertensive antenatal patients in comparison to normotensive patients. The rise

in serum uric acid is found to correlate with the degree of hypertension. This study also concludes that estimation of serum uric acid levels helps in prognosticating the maternal and perinatal morbidity and mortality. Serum uric acid level can be used as a cost-effective and widely available biochemical marker in antenatal patients with hypertensive disorders of pregnancy.

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