Current Hypertension Reviews, 2019, *15*, 154-160

RESEARCH ARTICLE

Maternal Serum Uric Acid as a Predictor of Severity of Hypertensive Disorders of Pregnancy: A Prospective Cohort Study

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Abstract: ***Objective*:** To assess the relationship between maternal serum uric acid and severity of Hypertensive disorders of pregnancy in a rural tertiary care centre.

***Materials and Methods*:** Present study was conducted in Obstetrics and Gynaecology department of rural tertiary care centre of Northern India over seven months (October 2016-May 2017) on 110 women admitted with a Hypertensive disorder of pregnancy (Gestational hypertension, Pre-eclampsia, Eclampsia) at ≥34 weeks gestation. Maternal serum uric acid levels were compared in three groups in relation to disease severity, mode of delivery, maternal outcome.

***Results*:** Of total 110 women with a Hypertensive disorder of pregnancy; 35 (31.81%) had Gestational Hypertension, 49 (44.54%) preeclampsia and 26 (23.63%) had eclampsia. Mean±SD values for serum uric acid were 5.47±1.93 mg/dl in women with Gestational Hypertension; 6.72±2.15 mg/dl in Pre-eclampsia and 8.71±2.97 mg/dl in the eclamptic group. Of 110 women 34(97.14%) with gestational hypertension, 27(55.10%) with pre-eclampsia and one (3.85%) with eclampsia remained stable in post-partum period, 17 (34.69%) women with severe pre-eclampsia and 15 (57.69%) with eclampsia required intensive care in postpartum period and one (2.86%) women with gestational hypertension, five (10.20%) with pre-eclmapsia and ten (38.46%) with eclampsia required ventilator support and high dependency unit care. Of these 16 women with the severe disease, ten succumbed to death. Also, in women with serum uric acid,>6mg/dl, most common mode of delivery was a lower segment cesarean section (50.90%).

***Conclusion*:** Significant correlation was observed between maternal serum uric acid, disease severity and maternal outcome.

ARTICLE HISTORY

Received: July 15, 2018
Revised: November 02, 2018
Accepted: November 06, 2018

DOI:
10.2174/1573402114666181112141953

Keywords: Caesarean section, eclampsia, hypertension, pre-eclapmsia, uric acid, pregnancy.

1. INTRODUCTION

Worldwide Hypertensive disorder of pregnancy (HDP) is a major cause of maternal and perinatal morbidity and mortality [1-3] and complicates around 2-10% of all pregnancies [4]. According to latest figures; pre-eclampsia accounts for around 3–8% of all HDP [5] and together pre-eclampsia and eclampsia account for 10–15% of all maternal deaths occurring worldwide [6]. Furthermore, the incidence of preeclampsia in healthy nulliparous and multiparous women is 3-7% and 1-3% respectively [7, 8].

The most common reason for such a high maternal and perinatal morbidity and mortality associated with HDP is the unavailability of precise and specific test that can identify pregnant women at risk of developing HDP [9]. One such biochemical marker that can be used to assess the severity of HDP and its effect on the maternal and fetal outcome to a large extent is maternal serum uric acid level. The use of serum uric acid and its association with HDP and its severity was first reported in 1917 [10], and it is still considered as a marker of severity of HDP, as the disease severity was found to increase with increasing maternal serum uric acid levels [11, 12]. Also, it was found that in HDP the elevation of uric acid occurs before the onset of hypertension and or proteinuria [13, 14]. There are many reasons for raised serum uric acid levels in women with HDP, which include impaired clearance from kidneys, increased tissue breakdown, acidosis and increased activity of xanthine oxidase/dehydrogenase enzyme [14, 15]. The main reason behind impaired renal clearance of uric acid is reduced glomerular filtration rate, increased absorption and decreased secretion leading to rais-

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1875-6506/19 $58.00+.00

ing serum uric acid levels in women with HDP [14]. In the first trimester of normal pregnancy serum, uric acid levels usually decrease to 3 mg/dl or more, under the uricosuric effects of estrogen and also due to increase renal blood flow. This is followed by an increase in levels of uric acid in the third trimester, reaching up to the levels of 4-5 mg/dl at term [16]. However, pregnant women who are prone to develop HDP, show slightly higher levels of serum uric acid during their first trimester [16, 17]. Also, the degree of elevation of serum uric acid levels correlates with the severity of the disease and its outcome [16].

Hence, the proposed study was conducted with the mission of having information about the role of maternal serum uric acid in the prediction of severity of HDP and its effect on the overall outcome of pregnancy. The results of the proposed study will help in future in formulating policies for prevention of disease, its severity, and fatality with the existing resources to at least some extent.

2. MATERIALS AND METHODS

2.1. Aim

To study the relationship between maternal serum uric acid levels and severity of hypertensive disorders of pregnancy and overall pregnancy outcome in a rural tertiary care centre of Northern India.

2.2. Study Population

The present prospective cohort study was conducted over a period of seven months from October 2016 to May 2017 and included all pregnant women ≥34 weeks of gestation admitted in the Obstetrics and Gynaecology department of a rural tertiary care center of Northern India with the features of HDP as study subjects.

2.3. Exclusion Criteria

Pregnant women with a history of chronic hypertension, hyperuricemia, Type II diabetes mellitus, renal disease, liver pathology, cardiovascular illness, symptomatic infectious diseases, thyroid and other endocrine disorders, hydatidiform mole, malignancy, hematological disorders *etc*. were excluded from the study. Also, pregnant women with a history of smoking, alcohol or substance abuse were not considered.

2.4. Definitions

Hypertension during pregnancy is defined as diastolic blood pressure of 90 mm Hg or greater on two occasions more than 4 hours apart or a single diastolic blood pressure above 110 mm Hg [18].

Severe Hypertension during pregnancy is defined by systolic blood pressure ≥160 mm Hg and diastolic blood pressure ≥110mm Hg [19].

Gestational Hypertension: It is a clinical diagnosis defined by the new onset of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation in absence of proteinuria or new signs of end-organ dysfunction [20].

Pre-eclampsia was diagnosed in women who had a blood pressure of 140/90 mm Hg or more on two occasions each 6 hours apart associated with proteinuria of at least 300 mg per 24 hours or at least 1+ on dipstick testing. Severe pre-eclampsia was defined as a blood pressure of 160/110 mm Hg or above measured on two occasions each 6 hours apart [18, 20].

Eclampsia is a convulsive condition associated with pre-eclampsia [18].

2.5. Procedure

The present prospective cohort study was conducted in the Department of Obstetrics and Gynaecology of a rural tertiary care centre of Northern India over a period of seven months from October 2016 to May 2017 after proper Institutional Ethical Clearance and informed written consent from the participants. Every effort was made to keep the identity of participants undisclosed.

All pregnant women with gestational age 34 weeks or more admitted with the features of HDP in the department of obstetrics were enrolled in the study as cases. Patients were screened with detailed family and medical history and thorough clinical examination to determine their eligibility for inclusion in the study. The systolic and diastolic blood pressure of all the cases at the time of admission and after two hours of rest was carefully recorded. Then, four hourly blood pressure monitoring in every case was recorded. On admission, venous serum samples were collected from the patient's ante-cubital vein, before starting any treatment in plain tubes for serum uric acid level measurement by enzymatic color test using Uricase and Peroxidase enzymes. The analyser used was "SIEMENS Dimension clinical chemistry system" and the reagent used was Uricase- Bacterial (8IU/mL) for detection of serum uric acid. Urine samples were also collected for protein estimation at the same time. Urine protein was measured by dipstick and graded as Trace to 4+ (Trace,0.1gm/L;1+,0.3gm/L;2+,1gm/L;3+,3.0gm/L;4+, 10gm/L). Urine analysis was done in all subjects to measure the degree of proteinuria and to differentiate gestational hypertension from Pre-eclampsia. Reference levels of normal serum uric acid levels considered were [21]:

Unit	Non-pregnant Women	First Trimester	Second Trimester	Third Trimester
mg/dl	2.5-5.6	2-4.2	2.4-4.9	3.1-6.3

The participants were observed throughout their pregnancy for overall maternal outcomes.

2.6. Statistical Analysis

The data were validated and analyzed with the help of statistical software SPSS version 20. The unpaired t-test/Mann-Whitney Test was applied for comparing the mean uric acid levels with the maternal outcomes. Qualitative variables were correlated using Chi-Square test /Fisher's exact test and p-value < 0.05 was considered statistically significant.

3. RESULTS

Of total 110 pregnant women with HDP; 35 (31.81%) had Gestational Hypertension, 49 (44.54%) had pre-eclampsia and 26 (23.63%) eclampsia. Of the 49 women with pre-eclampsia, 31(63.26%) had mild disease and remaining 18 (36.73%) had severe disease. The socio-demographic features including the age of women, gravidity, and gestation of pregnancy are depicted in Table **1**. The mean±SD values for serum uric acid levels were 5.47±1.93 (Minimum to Maximum value: 2.4-11.5 mg/dl) in women with Gestational Hypertension; 6.72±2.15 (2.5-16.3 mg/dl) in women with Pre-eclampsia and 8.71±2.97 (3.6-13.9 mg/dl) in the eclamptic group.

Of 35 pregnant women with Gestational Hypertension, 20 (57.14%) patients at gestation >37 completed weeks were induced for labour using pharmacological agents (Tablet Misoprostol or Cerviprime gel), of which 17 (85%) delivered normally and remaining three (15%) were delivered by Lower Segment Caesarean Section (LSCS) (two for foetal distress and one for non-progress of labour), 3 (8.57%) patients were induced at gestation < 37 weeks (due to uncontrolled blood pressure and abnormal Doppler study), of which two (66.67%) had vaginal delivery and one (33.33%) was for Intra-uterine death (IUD), 11 (31.43%) patients went into spontaneous labour at gestation ≥37 completed weeks; of which eight (72.72%) delivered normally and three (27.27%) had LSCS (2 for previous LSCS in labour with scar tenderness and one for Twin gestation with first twin in breech presentation), the remaining one (2.86%) patient in first group was delivered by LSCS at gestation <37 weeks for scar tenderness and foetal tachycardia with labour pains. In group two of 49 women having pre-eclampsia; 16 (32.65%) patients were induced at gestation ≥37 completed weeks; of which 13 (81.25%) delivered normally and three (18.75%) were induced for IUD at term, 21 (42.86%) patients were induced at gestation <37 weeks (for uncontrolled blood pressure despite of drugs or for deteriorating maternal condition); of which eight (38.09%) delivered vaginally, four (19.05%) patients were delivered by LSCS (one for foetal distress, baby died after three days and remaining three for abruption placentae), eight (38.09%) patients were induced for IUD; of which two had Vaginal Birth After Caesarean (VBAC) and the remaining one (4.76%) foetus had fresh still birth. In this group ten (20.41%) patients went into spontaneous labor at gestation ≥37 weeks; of which nine (90%) patients were delivered by LSCS (8 for previous LSCS with poor bishop score/ scar tenderness and one for Abruptio placentae) and one (10%) with IUD delivered vaginally. The remaining two (4.08%) patients in this group had LSCS at <37 weeks without induction (one for previous LSCS with scar tenderness and one for IUD as the patient had previous 3 LSCS). In the last group of 26 women with eclampsia; eight (30.77%) were induced at ≥37 weeks; of which three (37.5%) delivered normally, three (37.5%) had LSCS for foetal distress and two (25%) were induced for IUD at term, 11 (42.31%) patients were induced at <37 weeks; of which six (54.54%) delivered vaginally (one baby died after three days), one (9.1%) by forceps (baby had fresh still birth), two (18.18%) were delivered by LSCS for foetal distress and two (18.18%) had IUD, the remaining seven (26.92%) patients in this group were delivered by LSCS at < 37 weeks, who presented with spontaneous onset of labour; of which four (57.14%) had LSCS for foetal distress and three (42.86%) had previous LSCS with poor bishop score. Table **2** shows primary and repeat caesarean sections in all the three groups.

Of 110 women with HDP, 34(97.14%) in gestational hypertension group, 27(55.10%) with pre-eclampsia and one (3.85%) with eclampsia remained stable and healthy in their immediate post-partum period. Seventeen (34.69%) women

Table 1. Socio-demographic feature.

	Gestational Hypertension N=35	Pre-eclampsia N=49	Eclampsia N=26
Age (years)			
<-20-25	17 (48.57%)	20 (40.82%)	17 (65.38%)
26-30	13 (37.14%)	20 (40.82%)	7 (26.92%)
31-35	4 (88.57%)	9 (18.37%)	2 (7.69%)
36-40	1 (2.86%)	0 (0.0%)	0 (0.0%)
Gravidity			
Primigravida	10 (28.57%)	12 (24.49%)	17 (65.38%)
Multigravida	25 (71.43%)	37 (75.51%)	9 (34.61%)
Gestation (weeks)			
>34-<37	13 (37.14%)	23 (46.94%)	16 (61.54%)
≥37-<40	18 (51.43%)	24 (48.98%)	10 (38.46%)
≥40	4 (11.43%)	2 (4.08%)	0 (0.0%)

Table 2. Primary and repeat caesarean section in women with hypertensive disorders of pregnancy.

Caesarean Section (CS)	Gestational Hypertension N=35	Pre-eclampsia N=49	Eclampsia N=26	Total
Primary CS	05(14.29%) (5/35)	05(10.2%) (5/49)	09(34.62%) (9/26)	19(17.27%)
Repeat CS	02(5.71%) (2/35)	10(20.41%) (10/49)	03(11.54%) (3/26)	15(13.64%)
Total	07(20%)	15(30.61%)	12(46.15%)	34(30.63%)

Table 3. Maternal outcome in relation to serum uric acid levels.

	Gestational Hypertension				Pre-eclampsia				Eclampsia				Total			
Maternal status	HDP without morbidity	HDP with Morbidity/Mortality			HDP without morbidity	HDP with Morbidity/Mortality			HDP without morbidity	HDP with Morbidity/Mortality			HDP without morbidity	HDP with Morbidity/Mortality		
	N=34 (97.14%)	ICU[a] without ventilator N=0	HDU[b] on Ventilator N=1 (2.86%)		N=27 (55.10%)	ICU[a] without ventilator N=17 (34.69%)	HDU[b] on Ventilator N=5 (10.20%)		N=1 (3.85%)	ICU[a] without Ventilator N=15 (57.69%)	HDU[b] on Ventilator N=10 (38.46%)		N=62 (56.36%)	ICU[a] without ventilator N=32 (29.09%)	HDU[b] on Ventilator N=16 (14.54%)	
			Survived N=1	Deceased N=0			Survived N=2	Deceased N=3			Survived N=3	Deceased N=7			Survived N=6	Deceased N=10
S. Uric Acid (Min-Max)	5.3±1.65 (2.4-10.7)	11.5 ± 0 (11.5-11.5)			5.78±1.3 (2.5-8.5)	7.88±3.11 (3.7-16.3)			6.8 ± 0 (6.8-6.8)	8.79 ± 3 (3.6-13.9)			5.53±1.5 (2.4-10.7)	8.43±3.06 (3.6-16.3)		
P value	**0.092**				**0.004**				**0.463**				**<.0001**			
Chi-square test	**HDP without morbidity X^2= 3.0225, Critical value:5.99 P=0.22**								**HDP with Morbidity/Mortality X^2= 7.62, Critical value:5.99 P=0.022**							

a. ICU: Intensive Care Unit. b. HDU: High Dependency Unit.

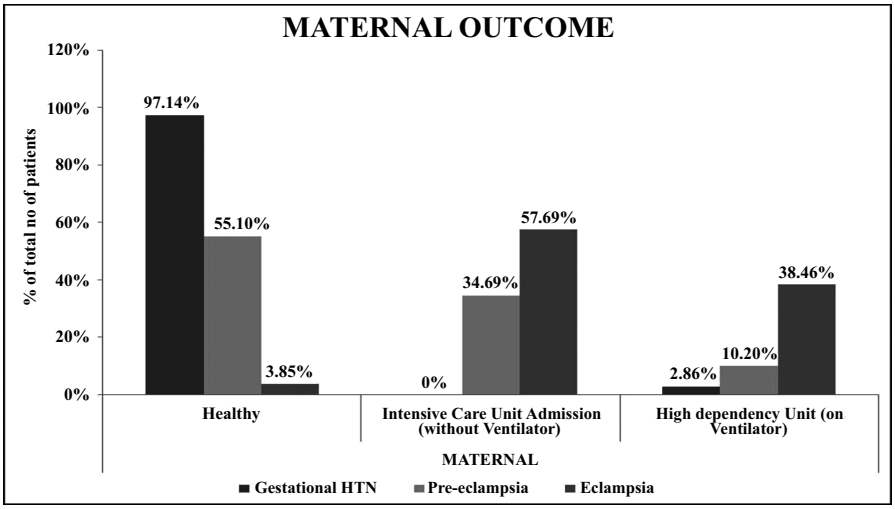

Fig. (1). Correlation of Maternal Serum Uric Acid with Maternal Outcome in Women with Hypertensive Disorders of Pregnancy.

with severe pre-eclampsia and 15 (57.69%) women with eclampsia required intensive care in immediate postpartum period and one (2.86%) women with gestational hypertension, five (10.20%) with pre-eclmapsia and ten (38.46%) with eclampsia required ventilator support and high dependency unit (HDU) care for management of critical maternal condition. Of these 16 women with the severe disease, ten could not be revived and succumbed to death. The relation between maternal serum uric acid levels and severity of disease and the maternal outcome is depicted in Table **3**, Fig. **1**.

4. 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 outcome. In women with severe pre-eclampsia and eclampsia, the mean serum uric acid levels were 7.88±3.11 and 8.79 ± 3 respectively, which was highly significant. Similar results were reported by various other studies which demonstrated a strong correlation between elevated maternal serum uric acid levels and adverse maternal outcomes [11, 13, 16, 22]. Another similar study reported that the serum uric acid levels in women with eclampsia and severe pre-eclampsia were significantly higher than that of normal pregnant woman (7.07 ± 0.22 mg/dl and 7.04 ± 0.17 mg/dl *vs* 4.48 ± 0.76 mg/dl respectively, (p value <0.05), while there was no significant difference in serum uric acid levels of normal pregnant woman and women with mild pre-eclampsia (4.48 ± 0.76 mg/dl *vs* 5.05 ± 1 mg/dl, (p value <0.05), indicating strong association of maternal serum uric acid levels with severity of disease [23]. A recent study has also reported a strong correlation between increasing maternal serum uric acid and severity of Pre-eclampsia [12].

Regarding the socio-demographic features observed in the present study, it was found that the mean age of presentation in Gestational hypertension, Pre-eclampsia, and Eclampsia groups were 26.51 ± 3.82 years, 27.14 ± 3.64 years and 24.73 ± 4.01 years respectively, with maximum cases of pre-eclampsia and eclampsia occurring in women of 20-25 years of age group. This is similar to the results of various other studies which have reported that the highest incidence of HDP was found in women of age group 21-25 years [24, 25]. In our study, we have also observed that the women with severe pre-eclampsia belonged to 22-35 years of age group and in eclampsia 19-32 years.

Furthermore, in our study, it was found that eclampsia was more commonly observed in primigravida (65.38%) as compared to multigravida (34.61%), whereas pre-eclampsia and gestational hypertension was more prevalent in multigravida as compared to primigravida. This was similar to the results of a recent study which reported that majority of patient with eclampsia were primigravida (62.26%) of age group 21 to 25 years (43.39%) [26]. Similar results were reported by various other studies also which found that eclampsia is more common in primigravida as compared to multigravida patients [27, 28].

In our study maximum cases of eclampsia and severe pre-eclampsia presented at gestation <37 completed weeks, whereas most of the patients with gestational hypertension and mild pre-eclampsia presented at or near term. Similar results were reported by other studies also which found that in women with severe HDP the gestational age was significantly lesser than that of normal pregnant women ($p < 0.001$) [29-31]. Similar results were obtained in another study also which found that the rate of preterm delivery was higher in women with pre-eclampsia and eclampsia, as compared to women with gestational hypertension (44.23% in pre-eclampsia group; 30.77% in eclampsia group and 25% in gestational hypertension group respectively) [32].

In the present study, it was observed that 34.62% (9/26) women with eclampsia underwent emergency primary caesarean section for fetal distress, in pre-eclampsia group, though the caesarean section was done in 30.61% (15/49) cases, but only 10.2% (5/49) women had primary caesarean section, rest 20.41% (10/49) caesarean sections were repeat sections. In women with gestational hypertension 14.29% (5/35) cases had primary section. Similar results were reported by a recent study where the most common mode of delivery for women with severe HDP was LSCS (62.26%) [26]. This was supported by various other studies which found that the induction of labor or cesarean section rates among women with severe HDP was 5 times higher than that of normotensive women [33, 34]. In our study, 75.51% of women with pre-eclampsia and 73.07% with eclampsia were induced either at term or at <37 weeks of gestation. Similar results were reported by another study which observed an increased rate of interventions like induction of labor, increased instrumental and cesarean deliveries in pregnancies complicated by severe preeclampsia and eclampsia [35]. Another similar study reported that the fetal birth weight was also significantly lower in pre-eclamptic women as compared to normal pregnant women (2.61±0.53 kg vs 2.98 ±0.36 kg) [31].

The present study also observed a significant correlation between poor perinatal outcome and maternal serum uric acid levels. This was supported by various studies which found that high maternal serum uric acid levels were associated with low birth weight and delivery by cesarean section. They found that pregnant women with high serum uric acid (≥ 5.88 mg/dl) were at over 2.93 times the risk of having a cesarean section and poor neonatal outcomes as compared to the pregnant women with low serum uric acid levels [10, 36]. Furthermore, it was observed by a similar study that high maternal serum uric acid levels were significantly associated with adverse perinatal outcome [32].

Moreover, in our study all the patients with eclampsia reported in emergency hours with no previous history of any antenatal check-up and presented with advanced features of HDP, hence the morbidity and mortality were very high. Furthermore, our Institution is a rural tertiary care centre and therefore we receive sick and complicated cases from rural areas, this further explains the high mortality rates in eclampsia patients. The results of present study were supported by many other studies which have reported that the case fatality rate for eclampsia was as high as 17.7 % in many regions of India [37, 38]. Another study reported that the Eclampsia accounted for 43.35% of total maternal deaths, with a case fatality of 4.960%, indicating that Eclampsia is still one of the major causes of maternal mortality in India and is mainly due to unsupervised pregnancies and deliveries [39]. In our 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 [11, 40], as well as a useful indicator of overall maternal and fetal outcome [10, 41].

CONCLUSION

The present study observed that maternal serum uric acid levels show a significant correlation with the severity of HDP. A direct correlation was also observed with the adverse maternal and fetal outcome as well as with increased rate of interventions during labor 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.

LIMITATIONS

The present study was conducted for a shorter duration and with a smaller sample size. In future we can plan of conducting a study for longer duration and with more sample size and also use this as base information we can plan of finding some other tests that can help in early detection of HDP, so that we can prevent the progress and severity of disease and hence can save many more maternal and foetal lives in future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Department of Obstetrics and Gynaecology of a rural tertiary care centre of Northern India.

HUMAN AND ANIMAL RIGHTS

No animal were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki <http://www.wma.net/policiespost/wmadeclaration-ofhelsinki-ethicalprinciples-> for-medicalresearch-involvinghuman-subjects/>principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

An informed written consent was obtained from the participants.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

I thank Dr. Namit Kant Singh for his expert advice and support.

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