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Original Article

Correlation of Uric Acid Levels with Feto-Maternal Outcomes in Hypertensive Disorders in Pregnancy

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ABSTRACT

Objective: To explore the correlation between uric acid levels and feto-maternal outcomes in women with hypertensive disorders of pregnancy.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Obstetrics & Gynaecology Department, Combined Military Hospital, Rawalpindi Pakistan, from Feb to Aug 2021.

Methodology: In this cross-sectional study, 90 pregnant women with hypertensive disorders having greater than 26 weeks of gestation were included after seeking Ethical Committee approval. Selected parameters were noted on a structured proforma.

Results: Among the participants, 38(42.2%) had pregnancy-induced hypertension, 32(35.5%) had pre-eclampsia, 13(14.5%) had chronic hypertension with pre-eclampsia, and 7(7.8%) had eclampsia. Mean Uric acid levels ranged between 363.66±50.45 µmol/L and 451.86±120.62µmol/L, with a significant difference between PIH and eclampsia (p<0.001). Mode of delivery was a vaginal, primary cesarean section, and repeat cesarean section in 31(34.4%), 38(42.2%), and 21(23.4%) patients, respectively (p<0.001). Liquor was meconium stained in 49(54.4%) while clear in 41(45.6%) births, with (p<0.001). Early neonatal deaths 6(6.7%) participants had significantly higher uric acid levels than no NICU admission 22(24.4%). In maternal outcomes, 83 patients (92.2%) required routine post-operative care, while 7(7.8 %) went to the intensive care unit. Uric acid levels had a negative correlation with gestational age.

Conclusion: Maternal uric acid levels differ significantly in different hypertensive disorders of pregnancy and affect the mode of delivery and neonatal outcomes.

Keywords: Hypertensive Disorders in pregnancy, Neonatal outcomes, Uric acid levels.

How to Cite This Article: *Saleem U, Noman M, Yaqub U, Sohail A, Bashir K, Kaiani AS. Correlation of Uric Acid Levels with Feto-Maternal Outcomes in Hypertensive Disorders in Pregnancy. Pak Armed Forces Med J 2023; 73(1): 243-247. DOI: https://doi.org/10.51253/pafmj.v73i1.9140*

INTRODUCTION

In order to initiate the appropriate treatment to reduce the potential harm to the mother and fetus, it is important to properly diagnose and classify hypertensive disorders of pregnancy since these are the most prevalent medical disorder of pregnancy, affecting 6% to 8% of pregnancies in the United States.[1,2] Furthermore, as a result of rising obesity, nulliparity, advanced maternal age, and associated comorbidities like chronic hypertension, chronic renal disease, diabetes, multifetal gestation, and history of pree-clampsia and thrombophilia 5% to 10% of pregnancies are affected by Hypertensive disorders, indicating a 25% increase in incidence in the past 20 years.[3,4]

Due to the uricosuric effect of estrogen and the increase in renal blood flow, serum uric acid levels fall, often to 3µmol/L or below in the first trimester. Then, uric acid levels rise to 4–5µmol/L by term.[5] Increased serum uric acid levels during the first trimester, along with reduced urinary urate excretion, is a strong predictor of preeclampsia.[6] Therefore, keeping an eye on serum uric acid levels can aid in the early diagnosis of preeclampsia and prediction of feto-maternal complications.[7]

Recent research strongly implies that serum uric acid is a good biomarker for hypertensive diseases of pregnancies. It is also involved in the pathogenesis of maternal and fetal manifestations.[8] Uric acid has been shown to pass easily into the fetal circulation causing Inhibition of endothelial function and inducing systemic and glomerular hypertension in animals.[9] In addition, uric Acid may cause small for gestational age infants due to its fetal blocking angiogenesis by inhibiting VEGF-induced endothelial proliferation. It also plays a role in developing insulin resistance in pregnancy.[10]

Considering the relevant extensive research, our study aims to investigate the correlation of uric acid levels with disease severity and feto-maternal out-

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Received: 10 Aug 2022; revision received: 06 Sep 2022; accepted: 07 Sep 2022

comes. In addition, our research seeks to establish a definitive role played by serum uric acid levels in the pathogenesis of feto-maternal complications.

METHODOLOGY

The comparative cross-sectional study was conducted at the Department of Gynecology & Obstetrics, Combined Military Hospital, Rawalpindi Pakistan, from February to August 2021 after approval of the Institutional Review Board (Letter No- CMH RWP/242 /9th June 2021). The sample size was calculated using Net's sample size calculator taking 6% Population Proportion.[11] The subjects were enrolled through non-probability, consecutive technique.

Inclusion Criteria: Pregnant women with BP above 140/90mmHg, gestational age ≥26 weeks, proteinuria above 300mg/L in 24 hours, and urinary specimens with proteinuria above +1 in the dipstick were included.

Exclusion Criteria: Women with hyperuricemia without hypertension and those with major placenta previa or morbidly adherent placenta were excluded.

All participants underwent clinical examination, laboratory investigations (including complete blood counts), coagulation profile, ALT and uric acid levels. In addition, age, BMI, parity, gestational age, type of disorder, uric acid levels, maternal outcome, fetal outcome and liquor staining were noted on a structured proforma.

The data were analyzed using IBM SPSS-23.0. Quantitative variables were presented as mean and standard deviation. Qualitative variables were presented as frequency and percentage. An Independent t-test was utilized to assess the significant difference. Using Pearson Correlation, uric acid was also correlated with BMI, age, parity, and gestational age. Pearson's chi-square was utilized to assess the significant relationship between the variables. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

The mean age of the participants of this study was 29.04±5.20 years. The mean BMI was 28.21±1.41kg/m^2, the mean parity was 2.32±1.58 and the mean gestational age at diagnosis was 35.84±3.26 weeks. Among the participants, 38(42.2%) had pregnancy induced hypertension, 32(35.5%) had pre-eclampsia, 13(14.5%) had chronic hypertension with pre-eclampsia, and 7 (7.8%) had eclampsia.

Mode of delivery was a vaginal, primary cesarean section, and repeat cesarean section in 31(34.4%), 38 (42.2%), and 21(23.4%) patients, respectively, in maternal outcomes, 83(92.2%) required routine post operative care. In Fetal Outcome, 37(41.1%) patients had NICU >48 hours followed by No NICU 22(24.4%), NICU ≤48 hours 25(27.8%) and Early Neonatal Death 6(6.7%) (Table-I).

Table-I: Frequency of Maternal Outcomes, Fetal Outcomes, Mode of delivery and Liquor condition (n=90)

Variables	Frequency (%)
Mode of Delivery	
Vaginal	31(34.4%)
Primary C Section	38 (42.2%)
Elective Repeat C Section	21 (23.4%)
Maternal Outcome	
Ward Care	83 (92.2%)
Intensive care units	7 (7.8%)
Fetal Outcome	
No Neonatal Intensive care unit	22 (24.4%)
Neonatal Intensive care unit ≤ 48 hours	25 (27.8%)
Neonatal Intensive care unit > 48 hours	37 (41.1%)
Early Neonatal Death	6 (6.7%)
Liquor	
Meconium Stained	49 (54.4%)
Clear	41 (45.6%)

The mean of uric acid was found to be 393.62± 79.10µmol. Comparison of uric acid with Hypertensive Disorder, mode of delivery, Maternal Outcome, Fetal Outcome and Liquor was shown in Table-II.

Table-II: Comparison uric acid with Hypertensive Disorder, Mode of Delivery, Maternal Outcome, Fetal Outcome and Liquor (n=90)

	Uric Acid µmol/L (Mean±SD)	*p*-value
Hypertensive Disorder		
Pregnancy Induced Hypertension	363.66±50.45	<0.001*
Preeclampsia	405.16±77.32	
Chronic Hypertension with Preeclampsia	449.23±76.40	
Eclampsia	451.86±120.62	
Mode of Delivery		
Vaginal	385.77±83.19	<0.001*
Primary C Section	418.39±77.00	
Elective Repeat C Section	377.57±63.86	
Maternal Outcome		
Ward Care	393.06±72.26	0.054**
ICU Care	451.86±120.62	
Fetal Outcome		
No NICU	378.18±63.71	<0.001*
NICU ≤ 48 hours	367.36±46.91	
NICU > 48 hours	403.06±83.58	
ENND	534.67±21.57	
Liquor		
Meconium Stained	414.10±73.68	0.027**
Clear	377.95±78.73	

*note: *One-way Anov, **Independent Sample T-Test)*

Among the hypertensive disorders, the intergroup analysis showed a significant difference in uric acid levels between pregnancy-induced hypertension and preeclampsia (p=0.033), pregnancy-induced hypertension and chronic hypertension with preeclampsia (p=0.002) and, pregnancy induced hypertension and pre-eclampsia (p=0.028). Among the delivery modes, the intergroup analysis showed significant intragroup differences in uric acid levels between elective and Primary C-sections. Among the fetal outcomes, the intergroup analysis showed the intra-group difference in uric acid levels between no NICU stay and Early Neonatal Death (p<0.001), NICU stay <48 hours and Early neonatal death (p<0.001), NICU stay >48 hours and Early Neonatal Death (p=0.017), NICU stay <48 hours and NICU > 48 hours (p=0.049) and, NICU Stay <48 hours and NICU stay >5 days (p=0.036). There was a positive correlation found between Uric Acid (µmol/L), age (r=0.064), BMI (0.072), Parity (r=0.070), and uric acid had a negative correlate with Gestational Age (p=-0.460) shown in Table-III.

Table-III: Pearson Correlation Between Uric Acid (µmol/L) levels and age, BMI, parity and Gestational Age (n=90)

Age	Pearson Correlation	0.064
	p-value	0.552
BMI	Pearson Correlation	0.072
	p-value	0.502
Parity	Pearson Correlation	0.070
	p-value	0.513
Gestational Age	Pearson Correlation	-0.460
	p-value	<0.001

Hypertensive Disorders had a significant association with mode of delivery (p<0.001), Maternal Outcomes (p<.001) & Fetal Outcomes (p=.001). In contrast, Hypertensive Disorders had an insignificant association with Liquor (p=.863), as shown in Table-IV.

Table-IV: Association of Hypertensive Disorders with Maternal Outcomes, Fetal Outcomes, Liquor Staining and Mode of Delivery (n=90)

Parameters	Pregnancy Induced Hypertension	Preeclampsia	Chronic Hypertension with Pre-eclampsia	Eclampsia	*p*-value
Mode of delivery					
Vaginal	17(44.7)	6(18.8)	8(61.5)	0(0.0)	<0.001
Primary C Section	8(21.1)	21(65.6)	3(23.1)	6(85.7)	
Elective Repeat C Section	13(34.2)	5(15.6)	2(15.4)	1(14.3)	
Maternal Outcome					
Ward Care	38(100.0)	32(100.0)	13(100.0)	0(0.0)	<0.001
ICU Care	0(0.0)	0(0.0)	0(0.0)	7(100.0)	
Fetal Outcome					
No NICU	14(36.8)	6(18.8)	2(15.4)	0(0.0)	0.001
NICU ≤48 hours	12(31.6)	10(31.3)	3(23.1)	0(0.0)	
NICU >48 hours	12(31.6)	12(37.5%)	6(30.8)	7(100.0)	
ENND	0(0.0)	4(12.5)	2(15.4)	0(0.0)	
Liquor					
Meconium Stained	20(52.6)	19(59.4)	7(53.8)	3(42.9)	0.863
Clear	18(47.4)	13(40.6)	6(46.2)	4(57.1)	

DISCUSSION

The current study observed that maternal uric acid levels considerably impact the hypertensive disorder developed and consequent fetal outcomes. When the patients having different hypertensive conditions were compared with each other, it showed that patients with pregnancy-induced hypertension, preeclampsia, chronic hypertension with preeclampsia and eclampsia had serum uric acid levels of 363.66±50.45 µmol/L, 405.16±77.32µmol/L, 449.23± 76.40µmol/L, 451.86±120.62µmol/L, respectively. In addition, our study shows notable intra-group differences among the hypertensive groups after post hoc analysis.

A North Indian study involving 110 women at more than 34 weeks of gestation showed similar results. Uric acid levels in women with gestational hypertension were 5.47±1.93mg/L, 6.72±2.15mg/dL in pre-eclampsia, and 8.71±2.97mg/dL in eclampsia. Thirty-four patients with gestational hypertension, 27 with pre-eclampsia and one with eclampsia. Remained stable in the post-partum period 17 patients with severe pre-eclampsia, 15 with eclampsia and one with gestational hypertension needed ICU care. Out of these, 5 with pre-eclampsia and 10 with eclampsia required ventilator support.[7]

Another study assessed uric acid levels in pre-eclamptic women and normal controls, reported uric acid levels to be significantly higher in patients with pre-eclampsia (3.21±072µmol/L vs 7.65±081µmol/L, p=0.001).[12]

Regarding maternal outcomes, our study reports that patients who had developed eclampsia always ended up in the ICU. At the same time, those with pre-eclampsia, pregnancy induced hypertension and chronic hypertension with preeclampsia were nursed in the ward (p=<0.001). However, there was no significant difference between the uric acid levels of both groups.

The results of previous study showed that increased risk of preterm birth (OR 6.367, 95% CI 3.009–13.084) was associated with high uric acid level (≥393 µmol/L), along with low Apgar scores, intrauterine growth restriction (OR 7.188, 95% CI 3.592–14.382), and neonatal death (OR 7.818, 95% CI 1.614–37.867).[6] Another Indian study reported similar findings by quoting the difference in gestational age at delivery between preeclamptic women and normal controls (35.8±2.42 vs 38.1±1.63, p=0.040).[13] The findings were similar to our study, considering a significant negative Pearson correlation between uric acid levels and gestational age at delivery. This means the higher the uric acid level, the earlier the delivery. Hence premature delivery was linked to high uric acid levels in the current study. Adding further, neonatal death was also associated with increased uric acid levels. This was shown by comparing uric acid levels in the fetal outcomes. No NICU stay, NICU stays <48 hours, NICU stay >48 hours, NICU stay >5 days, and early neonatal death reported maternal uric acid levels of 378.18± 63.71 µmol/L, 367.36±46.91 µmol/L, 403.06± 83.58 µmol/L, 484.00±0.00 µmol/L, 534.67±21.57 µmol/L (p= <0.001). In a post-hoc analysis, neonates who had early neonatal death had significantly higher maternal uric acid compared to neonates who did not stay in the NICU and those who stayed in the NICU for <48 hours, >48 hours and <5 days (p=<0.05). A previous study correlated raised serum uric acid with the adverse neonatal outcome based on the APGAR score. It was found that raised maternal uric acid (>6µmol/L) resulted in a neonatal APGAR score of less than 7(75% vs 4.3%, p<0.001). The lower APGAR score is associated with poor neonatal outcomes.[14] Another study conducted reported similar findings, that neonatal outcomes are adversely affected by maternal uric acid levels.[15]

A study in China also reported that higher maternal uric acid levels lead to adverse maternal outcomes. The odds ratio of adverse pregnancy outcomes with serum uric acid levels >357µmol/L was 1.258, p<0.05.[11] This is similar to the findings of the current study, as stated above. Two other studies reported similar findings.[16,17]

Regarding the mode of delivery, the current study argues that serum uric acid levels and hypertensive disorders determine the mode of delivery. This is in coherence with earlier studies. A study conducted reported that the higher the uric acid levels, the higher the chance of having a cesarean section (33% versus 12%; p=0.007). Like our study, it also reported a negative correlation between uric acid levels and the gestational age of the mother (rho=−0.456; p<0.001) and a positive association between admission into the neonatal ward and uric acid levels (p<0.001).[18] Considering this, research is now being conducted to assess the optimal cut-off values of uric acid in predicting maternal and fetal complications.[17,18] The current study also suggests that optimal values should be calculated in prospective studies, which can help develop guidelines for better managing pregnant women.

ACKNOWLEDGEMENTS

We would like to thank Sultan Muhammad Fateh and Eman Azhar Kayani.

CONCLUSION

Serum uric acid levels significantly vary among the different hypertensive disorders of pregnancy, the highest among patients with chronic hypertension with pre-eclampsia. Maternal serum uric acid levels are higher among neonates who suffer from early neonatal death while low in neonates who do not get admitted to the neonatal ICU. Moreover, Uric acid levels affect the liquor staining as well as the mode of delivery of the mother. Patients with eclampsia are more likely to get admitted to ICU than those with pre-eclampsia, pregnancy-induced hypertension and chronic hypertension with preeclampsia.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

US & MN: Study design, drafting the manuscript, critical review, approval of the final version to be published.

UY & AS: Conception, drafting the manuscript, approval of the final version to be published.

KB & ASK: Data acquisition, data analysis, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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