ORIGINAL ARTICLE

ANNALS OF PUNJAB MEDICAL COLLEGE

Serum Uric Acid Levels as a Predictor of Intrauterine Growth Retardation in Women with Pregnancy-Induced Hypertension

Sumbul Aijaz Gajani[1], Mehreen Yousaf Rana[2], Anaum Akhtar[3], Shoaibunissa Soomro[4], Raana Mazhar[5], Asma Ambreen[6]

1 *Senior Resident, Department of Gynecology & Obstetrics, Ziauddin University Hospital, Karachi Pakistan*
Select the study and wrote the first draft of manuscript

2 *Associate Professor, Department of Gynecology & Obstetrics, Ziauddin University Hospital, Karachi Pakistan*
Review literature and contribution in manuscript writing

3 *Senior Resident, Department of Gynecology & Obstetrics, Military Hospital, Rawalpindi, Pakistan*
Contribution in manuscript writing

4 *Associate Professor, Department of Gynecology & Obstetrics, Ghulam Muhammad Mahar Medical College, Sukkur Pakistan*
Review literature and contribution in manuscript writing

5 *Chief Consultant Gynecologist, Lady Aitcheson Hospital (KEMU), Lahore Pakistan*
Contribution in manuscript writing

6 *Lecturer, Department of Biochemistry, Liaquat University of Medical & Health Sciences, Jamshoro Pakistan*
Review the draft, formatting and analysis

CORRESPONDING AUTHOR
Dr. Sumbul Aijaz Gajani
Senior Resident, Department of Gynecology & Obstetrics, Ziauddin University Hospital, Karachi Pakistan
Email: sc.khairpur@gmail.com

Submitted for Publication: 25-02-2022
Accepted for Publication 29-08-2022

How to Cite: Gajani SA, Rana MY, Akhtar A, Soomro S, Mazhar R, Ambreen A. Serum Uric Acid Levels as a Predictor of Intrauterine Growth Retardation in Women with Pregnancy-Induced Hypertension. APMC 2022;16(3):156-161. **DOI: 10.29054/APMC/2022.1186**

ABSTRACT

Background: Hypertensive conditions during pregnancy are the most frequently occurring problems, with quite an increase in maternal, fetal, and neonatal rates of mortality and morbidity. Among women having pre-eclampsia/eclampsia or eclampsia, maternal serum uric acid content is a reliable indicator of prenatal consequences. **Objective:** To ascertain, whether serum uric acid is a suitable predictor in hypertensive pregnancies leading to intrauterine growth restriction (IUGR). **Study Design:** Descriptive cross-sectional study. **Settings:** The Ziauddin University and Hospital, Karachi Pakistan. **Duration:** July 2020 December 2020. **Methods:** A total of 170 women with singleton pregnancies beyond the 20th week, SBP≥140mmHg or DBP≥90mmHg were included in the study. Complete blood picture, serum uric acid, serum creatinine, Urea was carried out. Maternal investigations were taken on two separate occasions and the mean of the two readings was recorded. The uric acid level was categorized into mild-moderate and severe levels. The fetal assessment consisted of fetal growth scans, daily kick-count charts. Ultrasound Doppler was performed to assess for IUGR. Descriptive statistics were calculated. The Chi-square test was applied considering p-value ≤0.05 as significant. **Results:** The mean age was 31.41 ± 5.72 years. The mean BMI was 16.31 ± 1.91 Kg/m^2. Mean systolic blood pressure was 150.17 ± 6.90 mmHg while mean diastolic blood pressure was 101.25 ± 7.13 mmHg. Mean UA1 was 5.68 ± 0.47, mean UA2 was 5.74 ± 0.22, and mean UA3 was 5.77 ± 0.377. 87.1% were observed with Mild, 8.2% with moderate, and 4.7% with severe IUGR. 94.1% were found as mild, 3.5% as moderate, and 2.4% as severe. A significant association of uric acid levels with IUGR severity (p=<0.001) was observed. **Conclusion:** Serum uric acid was observed to be a valuable predictor in hypertensive pregnancies that lead to intrauterine growth restriction. A significant correlation was elevated between uric acid levels and adverse outcomes in pregnancies complicated by hypertension.

Keywords: *Serum uric acid, PIH, Preeclampsia, Eclampsia.*

INTRODUCTION

Hypertensive conditions during pregnancy are the most frequently occurring problems, with quite an increase in maternal, fetal, and neonatal rates of mortality and morbidity.[1,2] The accurate etiology of preeclampsia remains undetermined.[3] There is limited information regarding why some women Globally, pregnancies affected due to hypertension ranges from about 10-17%,[4] while the report of preeclampsia is seen to be 2-8% worldwide.[5,6]

There have been limitations and inconsistencies in the previous results, except that steady results are showing a relationship between gestational hypertension and that leading to preeclampsia. Presumably, the kidney is expected to be affected by damage to endothelial cells in preeclampsia patients; therefore, evaluation of renal

function is important in the management of preeclampsia in pregnant women.[7] One of the typical findings in preeclampsia is hyperuricemia.[8] Uric acid (UA) is the final product of the purine metabolism pathway and is excreted from the kidney.[9] The link between increased serum UA and pregnancy with preeclampsia was first documented in 1917.[8] The reasons for an elevated serum UA in women with preeclampsia might be due to the low clearance level of UA secondary to reduced glomerular filtration volume, a high level of reabsorption, and declined secretion.[8]

In medical practice, in the monitoring of the severity of preeclampsia, serum UA evaluation is a regular part of the examination and helps in the management of these women. The active transportation of amino acids through the placenta involves multiple membrane transporters that have varying specificities for different types of amino acids. The A amino acid transporter system transports short side-chain amino acids that are neutral, from the maternal intervillous blood supply into the fetal circulation in a manner that relies on the presence of sodium. UA is recognized as an indicator of oxidative stress, renal failure, and tissue damage, which might be increased to a great extent in patients with preeclampsia due to hypoxia and ischemia of the placenta and elevated production levels of cytokines.[4]

Moreover, the elevation of UA is also considered to restrict fetal growth.[10] Literature shows that there is a positive correlation between elevated UA levels in urine (hyperuricemia) and pregnancy-induced hypertension (PIH).[11] Moreover, there are other difficulties for the mothers with preeclampsia that can cause dangerous outcomes for the fetus, involving fetal distress, intrauterine growth restriction (IUGR), preterm birth and perinatal mortality.[12] A sufficient nutritional supply to the growing fetus throughout gestation is required for proper fetal growth. The traditional view of preeclampsia care is that if hypertension is under control and the maternal state is stable, delivery should be attempted to end the illness process. This viewpoint is right in that delivery is the only way to stop the sickness from progressing. However, hypertension is simply one symptom of the underlying problem, and it can be unreliable as a predictor of illness severity. As a result, there is a 'fetal syndrome' (intrauterine growth retardation) and a maternal syndrome' (a systemic illness affecting both the mother and the child). Several studies have been reported in women with positive correlation, but several studies have evaluated several tests and parameters with mixed results. Serum UA from the maternal side was examined to be helpful in the disease prognosis and may exhibit the seriousness of the disorder.[13,14]

While others conveyed that UA levels though being considerably increased in preeclamptic women compared with pregnant women with normal blood pressure, did not come under the category of a good marker in the prognosis of maternal and fetal complications.[15] This study aims to ascertain, whether serum UA is a suitable predictor in hypertensive pregnancies leading to IUGR.

METHODS

This prospective longitudinal study was conducted at Ziauddin University and Hospital, Karachi, Pakistan, from July 2020 to December 2020. All pregnant women of age >18 years with raised blood pressure (Systolic ≥140 mmHg or Diastolic ≥90 mmHg, taken on two occasions, two hours apart, in a quiet atmosphere) attending the antenatal clinic with a singleton pregnancy beyond the 20th week of gestation and delivering between 32 and 37 weeks of gestation were included. Females with chronic hypertension, known cardiac diseases, nephropathy, acute or chronic hepatitis, or any endocrine disorders (Cushing syndrome, phaeochromocytoma) were excluded.

The females taking any medication (e.g., pyrazinamide, thiazide diuretics, salicylates, ethambutol, and cytotoxic agents) that increase serum UA levels were also excluded. After approval from the Ethical Review Committee of Ziauddin University, all the eligible women fulfilling the inclusion criteria were counselled and given detailed information about the protocol, and informed consent was taken. Investigations included a complete blood count (CBC), serum UA, serum creatinine, and urea, which were done with samples taken from the cubital fossa. Maternal (blood pressure, weight, routine lab investigations (CBC, blood sugars, urinalysis)) and fetal surveillance were continued throughout the pregnancy. Blood pressures were taken on two separate occasions, four hours apart, in a sitting position with a sphygmomanometer, and the mean of the two readings was recorded. Serum UA levels were seen and repeated according to the severity of the IUGR or the previous levels of UA. The UA level was categorized into mild, moderate, and severe. The fetal assessment consisted of fetal growth scans, daily kick-count charts (a piece of paper was given to women and they were asked to mark counts on every kick, 8 to 10 kicks per day would be satisfactory), and an ultrasound doppler was performed to assess for IUGR between 30 and 36 weeks of gestation. Mild to moderate cases were followed in the outpatient department, and severe cases were followed in inpatient care wards. The ultrasound doppler scan was repeated according to the severity of the previous scans.

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All the information gathered by using pre-designed study proforma SPSS v 17.0 was used for the data analysis.

RESULTS

The mean age of the study subjects was 31.41 ± 5.72 years. The overall mean body mass index of the study subjects was 16.31 ± 1.91 Kg/m^2. The mean parity of the study subjects was 2.58 ± 1.76. The mean systolic blood pressure of study subjects was 150.17 ± 6.90 mmHg, while the mean diastolic blood pressure was 101.25 ± 7.13 mmHg. The mean gestational age was 29.64 ± 3.49 weeks, while the mean gestational age at delivery was 36.69 ± 0.72 weeks. Mean Doppler 1 was 32.20 ± 1.35, mean Doppler 2 was 34.36 ± 1.08, and mean Doppler 3 was 36.15 ± 0.74. The mean UA, UA1 was 5.68 ± 0.47, mean UA2 was 5.74 ± 0.22, and the mean UA3 was 5.77 ± 0.377. Further details can be seen in table 1.

Among 170 study subjects, the fetal weight of 14 (8.2%) patients was <2 kg, 94 (55.3%) were 2-2.4 kg and it was 2.4 kg among 62 (36.5%). Most of the study subjects 99 (58.2%) underwent SVD. A history of PIH in the family was observed in 83.5% of study subjects, while a history of PIH in previous pregnancies was observed in 61.2%. Among all study subjects, 28.8% were observed to have a history of addiction, while 40% were taking drugs for hypertension. All the details are elucidated in table 2.

Table 1: Baseline characteristics of all study patients (n=170)

	Mean ± SD	95% CI	Median (IQR)	Range	Minimum	Maximum
Age (years)	31.41 ± 5.72	30.54-32.28	32 (-9)	27	18	45
BMI* (kg/m^2)	16.31 ± 1.91	16.05-16.63	16 (-1.03)	11.5	10.37	21.87
Parity	2.58 ± 1.76	2.31-2.84	2 (-3)	9	0	9
SBP* (mmHg)	150.17 ± 6.90	149.12-151.22	150 (-5)	50	140	190
DBP* (mmHg)	101.25 ± 7.13	100.17-102.33	100 (-15)	30	90	120
Gestational age (weeks)	29.64 ± 3.49	29.11-30.17	29 (-5)	14	22	36
Gestational age at time of delivery (weeks)	36.69 ± 0.72	36.58-36.8	37 (0)	6	32	38
Doppler 1 (n=170)	32.20 ± 1.35	32-32.4	32 (-1)	6	30	36
Doppler 2 (n=166)	34.36 ± 1.08	34.2-34.53	34 (-1)	5	32	37
Doppler 3 (n=130)	36.15 ± 0.74	36.03-36.28	36 (-1)	3	34	37
UA1 (n=170)	5.68 ± 0.47	5.61-5.76	5.6 (0)	5	5	10
UA2 (n=166)	5.74 ± 0.22	5.71-5.77	5.7 (0)	2	5	7
UA3 (n=129)	5.77 ± 0.377	5.7-5.84	5.7 (0)	2	5	7

**BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, UA: uric acid*

Table 2: Clinical characteristics of the patients n=170

Variables		Frequency (n)	%
Mode of delivery	**EL. LSCS***	37	21.8%
	Em. LSCS*	34	20.0%
	SVD*	99	58.2%
Fetal weight	**>2.4 kg**	62	36.5%
	2-2.4 kg	94	55.30%
	<2 kg	14	8.2%
Patient's medical history	**Previous PIH history**	104	61.2%
	Family history of PIH	142	83.5%
	History of addiction	49	28.8%
	History of hypertension	68	40.0%
	NICU admission	91	53.5%

**lower uterine segment section (LSCS), *EL: elective, *Em: emergency, *spontaneous vaginal delivery (SVD), *PIH: pregnancy-induced hypertension, NICU: neonatal intensive care unit*

Table 3: Association between IUGR severity according to uric acid levels (n=170)

Uric acid levels	IUGR severity			P-Value
	Mild (n=148) 87.1%	**Moderate (n=14) 8.2%**	**Severe (n=8) 4.7%**	
Mild (n=160) 94.1%	148	11	1	<0.001*
Moderate (n=6) 3.5%	0	3	3	
Severe (n=4) 2.4%	0	0	4	

IUGR: intrauterine growth restriction

Out of the total study subjects, 91 (53.5%) were referred to the NICU. In our study, 87.1% of study subjects had mild, 8.2% had moderate, and 4.7% had severe IUGR. As far as the UA is concerned, 94.1% were found to be mild, 3.5% as moderate, and 2.4% as severe, as mentioned in table 4. The results showed that there was a significant association between UA levels and IUGR severity (p=<0.001). Table.3

DISCUSSION

Uric acid (UA) is the final product after the breakdown of nucleotides. Pre-eclampsia is a type of hypertension that is unique to and confined to pregnancy. There is very limited knowledge about the approximate threats that are related to the development of preeclampsia in those patients who are present with the initial diagnosis of gestational hypertension. Antihypertensive drugs as a treatment protocol have their demerits. Therefore, these medicines should only be prescribed if the symptoms are severe or the condition is worsening, though this could result in unfavourable outcomes. The odds of developing preeclampsia are decreased in patients with late-onset of gestational hypertension, partially because of the short duration of labour. Current practice is in favour of elective delivery in terms of hypertensive pregnancies to avoid the risk of developing preeclampsia.

The development of preeclampsia is not connected with maternal obesity and a history of preeclampsia. The facts should be interpreted with extreme care because the number of patients with such risk factors is very few (hence, wide confidence intervals CI). In the present study, we found a significant association of UA levels with intrauterine growth restriction (IUGR) severity. Furthermore, there was a significant association seen for the patients with age ≤ 30 years, patients aged > 30 years, patients with parity ≤3 and >3. This research proves that serum UA can be found as a suitable predictor to indicate chances leading to IUGR in women with pregnancy-induced hypertension and thus can be used as a prognostic detector for future pregnancies. There were studies done with similar results showcasing the positive relation of serum UA concerning IUGR as an outcome in preeclamptic patients. A study conducted in Nigeria had a majority (94%) of patients with the gestational age of at least 34 weeks being associated significantly between serum UA levels and preeclampsia, IUGR as well as birth asphyxia.[16]

In similarity with the previously mentioned research, the mean gestational age at the time of delivery in our study was 36.69. Another research found renal function tests affected patients suffering from IUGR and abnormal cysteine C levels.[7] Hyperuricemia was seen associated with preeclampsia and found a significant association with the IUGR in a study conducted in August 2020 and September 2020.[8,17] A lot of studies were supporting the narrative of UA level as a great prognostic guide like Priya *et al*.[18] Hussain *et al*,[19] Tejal *et al*,[20] Kristin *et al*,[21] all these studies were linked with eclamptic and preeclamptic women with the diagnosis of adverse fetal outcomes. Le *et al* found in a prospective study that increased serum UA levels in preeclamptic women can lead to preterm IUGR and fetal death.[12]

Moreno Santillan *et al*. also associated raised UA tests with preeclamptic patients resulting in severe fetal outcomes.[22] Some studies gave contrary results like Williams and Galerneau found UA levels, not a good predictor,[23] Khaliq *et al* demonstrated that in such scenarios there are various discrepancies found suggesting UA is not a good predictor.[24] Many studies

have found confounding factors resulting in these opposite results. There are a few recommendations that future researchers should keep in mind. We performed a longitudinal study, of more cohort research, which should be done to draw an association. In recent times, increased UA levels as early as 1st trimester of pregnancy is found to be associated with preeclampsia

CONCLUSION

Serum uric acid has been observed to be a valuable predictor in hypertensive pregnancies that lead to intrauterine growth restriction. A significant correlation was found between elevated uric acid levels and adverse outcomes in pregnancies complicated by hypertension. Therefore, monitoring serum uric acid levels in hypertensive pregnancies can help identify patients at higher risk of developing intrauterine growth restriction and other complications, allowing for timely intervention and better management. It is important for healthcare professionals to recognize the significance of serum uric acid as a predictor in hypertensive pregnancies in order to provide the best possible care to their patients.

LIMITATIONS

There were a few limitations in our study which cannot be overshadowed. Due to the study population being taken from a tertiary care hospital, it might have represented more gestational hypertensive patients.

SUGGESTIONS / RECOMMENDATIONS

While there is some evidence to suggest that serum uric acid levels could predict IUGR in women with PIH, more research needs to be conducted to confirm this association. Large-scale studies with diverse populations and more rigorous study designs will be required to strengthen the evidence base.

CONFLICT OF INTEREST / DISCLOSURE

None.

ACKNOWLEDGEMENTS

The authors are expressing gratitude to everyone who contributed to the writing of their research article, especially their research team, whose hard work and dedication were crucial in shaping the direction and content of the research.

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