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ORIGINAL ARTICLE

Serum Uric Acid, A Predictor of Fetal Outcome at Birth in Pre-eclampsia

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ABSTRACT

Objectives: To determine the association of serum uric acid levels with adverse fetal outcomes at birth among women with pre-eclampsia.

Study design: Prospective cohort study

Place and duration of study: Department of Gynaecology and Obstetrics, KRL Hospital Islamabad from April 2023 to September 2023.

Methodology: A total of 50 women with singleton pregnancy diagnosed with pre-eclampsia and having serum uric acid levels ≥5.5 mg/dL were included in Group-A, while another 50 women with same clinical characteristics and having serum uric acid levels <5.5 mg/dL were included in Group-B. Fetal outcomes at birth were assessed including low birth weight, preterm birth, APGAR score at 1 and 5 minutes, neonatal intensive care unit admission and stillbirth. Association between elevated serum uric acid levels and adverse fetal outcomes was evaluated by performing relative risk analysis with 95% confidence intervals, taking a p-value <0.05 as statistically significant.

Results: The mean age of women was 33.24±5.61 years in overall study population. Comparison of fetal outcomes revealed a significantly higher incidence of adverse fetal outcomes in Group A compared to Group B including the incidence of low birth weight (RR 1.87, 95% CI 1.14–3.05, p=0.01), preterm birth (RR 2.33, 95% CI 1.19–4.58, p=0.01), low APGAR scores at 1 min. (RR 2.29, 95% CI 1.03–5.07, p=0.03), and neonatal intensive care unit admissions (RR 4.50, 95% CI 1.02–19.79, p=0.03).

Conclusion: Elevated serum uric acid levels are strongly associated with adverse fetal outcomes in pre-eclamptic pregnancies.

Keywords: Newborn, Pre-eclampsia, Pregnancy outcome, Uric acid.

INTRODUCTION

Pre-eclampsia is a pregnancy-related hypertensive condition, characterized by new-onset hypertension and proteinuria typically developing after 20 weeks of gestation, and remains a leading cause of maternal and fetal adverse outcomes at global level.[1,2] The worldwide data show that approximately 2-8 % of pregnancies are complicated by pre-eclampsia, however, this presents a particular challenge in developing countries with compromised health budgets.

The incidence of pre-eclampsia is estimated to be seven times higher in developing countries than the developed ones. Out of 289,000 pregnancy-related deaths occurring globally during 2016, 99% were in the developing countries including Africa and South Asia.[2,3] The exact pathophysiology of pre-eclampsia is not clearly understood, however, it is said to be linked to placental dysfunction, endothelial damage, and a systemic inflammatory response triggered by placental ischemia.[4]

Among the various biochemical markers studied in pre-eclampsia, serum uric acid (SUA) has gained focused interest for its potential association with the severity of maternal disease and adverse fetal outcomes. Uric acid is a metabolic waste produced by the breakdown of purine as a byproduct and mostly eliminated by the kidneys. SUA level typically decreases due to increased renal clearance during pregnancy; however, in pre-eclamptic women, hyperuricemia is noticed due to impaired renal clearance and increased oxidative stress.[5]

The presence of endothelial dysfunction, vasoconstriction, and inflammation in hyperuricemic pre-eclamptic pregnancies is linked to maternal and fetal complications commonly observed in these women. Numerous studies have reported a strong correlation between raised SUA levels and adverse perinatal outcomes, however, the impact extends beyond maternal health, and significantly affects fetal outcomes in pre-eclamptic pregnancies combined with high SUA levels.[6] Adverse fetal outcomes are observed in these pregnancies in shape of low birth weight (LBW), intrauterine growth retardation (IUGR), preterm birth, low Apgar scores, and higher admissions in the neonatal intensive care units (NICU). The role of SUA in pre-eclampsia thereby become important for early risk stratification and timely management.[7]

There is, however, varying understandings among clinicians on the role of SUA, whether as a routine biochemical marker or strongly associated with adverse fetal outcomes in pre-eclamptic women. Identifying SUA as a reliable biochemical marker for fetal outcomes can assist in timely interventions, thereby reducing perinatal complications.[8]

Most of the large scale data and meta-analysis on this topic covers the Western and high-income countries, where the population characteristics and healthcare systems differ significantly, whereas, the relationship between SUA and fetal outcomes is found to vary on the basis of genetics, environment and sociodemographic factors. The high burden of pre-eclampsia and its complications in Pakistan underscores the importance of working on this subject in our local population.[9,10]

This study was therefore planned to determine the association of SUA levels with adverse fetal outcomes at birth among women with pre-eclampsia presenting at KRL hospital Islamabad. The results of this research will help to provide valuable insights for obstetric care and improve fetal outcomes in cases of pre-eclampsia in our local patients.

METHODOLOGY

This prospective cohort study was performed at the Department of Gynaecology and Obstetrics, KRL Hospital Islamabad from April 2023 to September 2023 over a period of 6 months after getting approval from ethical committee of the hospital (Ref ERC:KRL-HI-PUB-ERC/2023/78).

The sample size was calculated as per following details:

alpha = 5% (two-sided), power = 90%.
p1 (LBW in pre-eclamptic women with hyperuricemia) = 52.38%
p2 (LBW in pre-eclamptic women with normal SUA) = 14.66%.[11]
Estimated sample size was n1 = 31, n2 = 31, we however included 50 patients in each group.

A total of 50 women with singleton pregnancy diagnosed with pre-eclampsia having serum uric acid levels ≥5.5 mg/dL were included in Group-A, while another 50 women with singleton pregnancy diagnosed with pre-eclampsia and having SUA levels <5.5 mg/dL were included in Group-B using consecutive sampling.

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The exclusion criteria was set as women with multiple pregnancies, gestational diabetes, chronic conditions affecting uric acid metabolism (gout, chronic kidney disease), use of uric acid-lowering medications, pre-existing renal disease or chronic hypertension, and cases with incomplete follow-up or missing data.

Written consent was received from the women prior their inclusion in this study.

Pre-eclampsia was declared when patients had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg that occurred after 20 weeks of gestation in a previously normotensive woman, accompanied by proteinuria (declared at ≥300 mg per 24-hour urine collection or protein/creatinine ratio ≥0.3) or, evidence of systemic organ dysfunction in the cases where proteinuria was absent.[12]

All the baseline demographic details, obstetric history like parity and gravidity were recorded for each patient. Blood pressure was measured and laboratory investigations were performed including SUA, serum creatinine, liver function tests, and complete blood count.

Fetal outcomes at birth were assessed and recorded, including LBW (when birth weight <2500 gm), preterm birth (gestational age at delivery <37 weeks), APGAR score was evaluated at 1 and 5 minutes (A score <7 was considered low), need for NICU admission and the occurrence of stillbirth.

Data was analyzed using SPSS 26. Quantitative variables, including age, gestational age, SUA levels, and birth weight (grams), were expressed as mean and standard deviation while the categorical variables such as hyperuricemia, mode of delivery, and LBW were presented as frequencies and percentages. Independent t-tests were used to compare continuous variables, while categorical data were analyzed using the chi-square test. To evaluate the association between elevated SUA and adverse fetal outcomes, relative risk (RR) analysis with 95% confidence intervals (CI) was performed taking a p-value of <0.05 statistically significant.

RESULTS

The mean age of women was 33.24±5.61 years in overall study population. The details of maternal age, BMI, gestational age at the time of diagnosis and other related clinical findings are shared and compared between the two study groups in Table-I.

Fetal outcomes were compared between the two groups, revealing a significantly higher incidence of adverse neonatal outcomes in Group A compared to Group B. Group A demonstrated statistically significant increased LBW, preterm birth, low APGAR scores at 1 minute, and higher NICU admissions. These findings indicated a strong association between elevated maternal SUA levels and compromised fetal health. The relative risk analysis and corresponding p-values substantiate the critical role of hyperuricemia as a potential prognostic marker for adverse fetal outcomes in pre-eclamptic pregnancies as detailed in Table-II.

Table 1: Demographics and clinical findings. n=100

Demographics and clinical findings	Group A (n=50)	Group B (n=50)	p-value
Age (Mean±SD) years	33.62±5.2	32.86±6.01	0.5
BMI (Mean±SD) Kg/m^2	28.34±2.41	27.64±2.22	0.13
Primigravida n (%)	23 (46)	19 (38)	0.52
Gestational age at Diagnosis (Mean±SD) Weeks	32.66±2.81	31.96±3.1	0.24
Diastolic blood pressure (Mean±SD) mm HG	98.9±4.46	100.02±4.79	0.23
Systolic blood pressure (Mean±SD) mm HG	153.88±6.5	154.86±5.86	0.43
Proteinuria (Mean±SD) mg /24 hours	581.66±157.61	551.68±122.47	0.29
Serum Uric Acid (Mean±SD) mg/dL	6.97±0.89	4.06±0.57	<0.0001

Table-II: Fetal outcomes in association to SUA Levels in women with pre-eclampsia. n=100

Fetal outcomes	Group A (n=50)	Group B (n=50)	Relative risk (95% CI)	p-value
Low birth weight <2500 g n (%)	28 (56)	15 (30)	1.87 (1.14 - 3.046)	0.01
Pre-term birth <37 weeks n (%)	21 (42)	9 (19)	2.33 (1.19 - 4.58)	0.01
APGAR <7 at 1 min n (%)	16 (32)	7 (14)	2.29 (1.03 - 5.07)	0.03
APGAR <7 at 5 min n (%)	10 (20)	3 (6)	3.33 (0.98 - 11.40)	0.06
NICU admission n (%)	9 (18)	2 (4)	4.5 (1.02 - 19.79)	0.03
Stillbirth n (%)	4 (8)	1 (2)	4 (0.46 to 34.55)	0.17

DISCUSSION

We compared the fetal outcomes between the groups, Group A (women diagnosed with pre-eclampsia and having SUA levels ≥5.5 mg/dL) and Group B (women diagnosed with pre-eclampsia and having SUA levels <5.5 mg/dL) revealing a significantly higher incidence of adverse neonatal outcomes in Group A compared to Group B. Group A demonstrated statistically higher incidence of LBW (RR 1.87, 95% CI 1.14–3.05, p=0.01), preterm birth (RR 2.33, 95% CI 1.19–4.58, p=0.01), low APGAR scores at 1 min. (RR 2.29, 95% CI 1.03–5.07, p=0.03), and NICU admissions (RR 4.50, 95% CI 1.02–19.79, p=0.03). Although stillbirth was more frequent in the Group A, the difference was not statistically significant. These findings indicated a strong association between elevated maternal SUA levels and compromised fetal health. The relative risk analysis and corresponding p-values substantiate the critical role of hyperuricemia as a potential prognostic marker for adverse fetal outcomes.

Different studies have investigated the association between elevated SUA levels and fetal outcomes using varying methodologies and cutoff values. A cross-sectional study by Shaheen S et al. aimed to determine the impact of hyperuricemia on fetal outcomes in 200 pre-eclamptic women. Hyperuricemia was found to significantly increase the risk of LBW (52.38% vs. 14.66%, p=0.000) and preterm birth (52.38% vs. 20.69%, p=0.000), suggesting that elevated SUA is associated with adverse fetal outcomes. [11]

Naz T et al. assessed the association of hyperuricemia with mortality in pre-eclamptic females. Maternal death occurred in 16 cases, while perinatal mortality was recorded in 15 cases in women with hyperuricemia. A significantly elevated adverse outcomes was confirmed in group with high SUA showing a 3.25 times greater perinatal and 1.93 times greater maternal risk of mortality.[13]

Some other researchers have corroborated these findings across different populations using slightly higher SUA thresholds. Lakahn H et al. examined fetal outcomes in pre-eclamptic women with SUA levels >6 mg/dL and strongly linked it with adverse fetal outcomes. Among 130 cases, IUGR was recorded in 28.5%, preterm birth in 26%, low Apgar scores in 19.2% and intrauterine death in 14.6% of cases.[14]

Le TM et al. worked on the predictive value of maternal SUA levels in fetal/neonatal complications in pre-eclampsia/eclampsia. By keeping a cutoff of 393 µmol/L, SUA showed 64.4% sensitivity and 79.5% specificity. Elevated levels significantly increased risks of preterm birth (OR 6.367), low Apgar scores, IUGR, and neonatal death, concluding the uric acid as a strong prognostic marker.[16] Corominas AI et al. evaluated diagnostic utility of uric acid levels in predicting pre-eclampsia. Among 1,293 pregnant women, 40 developed pre-eclampsia. Uric acid ratio (UAr) >1.5 was observed in all pre-eclampsia cases, with ROC area 0.918. UAr <1.5 had a

99.5% negative predictive value, making it a valuable, low-cost exclusion tool for pre-eclampsia screening.[16]

Collectively, these investigations demonstrate a consistent pattern linking elevated maternal SUA with poorer fetal outcomes across diverse populations and methodological approaches.

Beyond its association with adverse fetal outcomes, hyperuricemia has also been associated with increased severity of pre-eclampsia itself, highlighting its broader clinical significance. The direct association between increasing levels of SUA and severe pre-eclampsia was established by Ugwuanyi RU et al. in 102 pregnant women. Women with pre-eclampsia had significantly high SUA levels versus the controls (6.08 ± 0.49 mg/dL vs. 5.20 ± 0.19; P < 0.01). Moreover, elevated SUA levels (>6 mg/dL) were found to be 4 times more likely to have severe pre-eclampsia (P=0.02, OR = 4.00, 95% CI = 1.225–13.056), 66 times more likely to have APGAR score <7 in the first minute (P < 0.01, OR = 66.00, 95% CI = 6.991–623.128), and 3 times more likely to have lower BW (P=0.04, OR = 3.400, 95% CI = 1.073–10.775) than those having normal SUA levels.[17] This evidence was further reinforced by Sudjai D et al. who suggested that elevated SUA is directly associated with increased pre-eclampsia severity as its levels exceeding 7 mg/dL are correlated with renal involvement, while uric acid of 5–7 and >7 mg/dL independently predicted preterm birth (OR 2.67, 95% CI 1.59–4.49 and OR 4.89, 95% CI 2.75–8.68, respectively. These raised levels also cause greater risks of respiratory distress syndrome and NICU admissions.[18]

The results of our study and studies discussed above reinforce strong association of SUA and adverse fetal outcomes and emphasize the need for close monitoring and early interventions in pregnancies complicated by pre-eclampsia.

Our study is limited by its single-center design, small sample size and lack of long-term neonatal follow-up. Future multicenter research covering these points will add up in this useful data on the role of SUA levels in determining fetal outcomes among women diagnosed with pre-eclampsia.

CONCLUSION

Elevated SUA levels are strongly associated with adverse fetal outcomes in pre-eclamptic pregnancies, including increased risks of LBW, preterm birth, poor APGAR scores, and higher NICU admissions. These findings highlight the complex relationship between maternal SUA and fetal health. Further research is crucial to develop targeted interventions for improving perinatal outcomes in these high-risk pregnancies.

Authors Contribution
Conceptualization, Data collection: NA, LK.
Methodology: NA, LK.
Formal analysis: NJ, SJ.
Writing, review and editing: LK, HR, IM.
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