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Exploring The Mysteries Of Preeclampsia: Uric Acid's Vital Role In Prediction And Pathogenesis

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Abstract:
Background*: Preeclampsia is a complex pregnancy complication with an unclear pathophysiology. Predicting and managing it is crucial. Uric acid, a potential biomarker, has been investigated in this context. This study explores the relationship between uric acid levels and preeclampsia, focusing on individuals initially diagnosed with gestational hypertension (GHTN).*
Materials and Methods*: A prospective cohort study involving 152 pregnant women with GHTN was conducted at a tertiary hospital in Bangladesh. Patients were monitored throughout pregnancy. Uric acid levels, clinical data, and outcomes were collected and analyzed using statistical methods.*
Results*: Among the participants, 67% developed preeclampsia. Women who later developed preeclampsia were older, had higher BMIs, were more likely to be primiparous, had a history of miscarriages, and were diagnosed with GHTN earlier in their pregnancies. Uric acid levels at GHTN diagnosis and delivery were significantly higher in the preeclampsia group (5.2± 0.4 mg/dL). These levels remained elevated at the time of delivery, with the preeclampsia group registering 6.8± 0.9 mg/dL, while the non-preeclampsia group had 4.5± 0.8 mg/dL.*
Conclusion: *The study underscores the crucial role of uric acid as a potential predictor for preeclampsia in individuals with GHTN. Elevated uric acid levels were linked to an increased risk of preeclampsia, mirroring prior research on oxidative stress and placental ischemia. Identifying at-risk individuals can lead to timely interventions and improved outcomes for both mothers and infants.*
Key Word*: GHTN, Preeclampsia, Eclampsia, Uric acid.*

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I. Introduction

Preeclampsia is a formidable adversary of pregnancy. It unveils its clinical presence beyond the 20th week of gestation, or within the initial 4-6 weeks following childbirth, casting a shadow of heightened risk upon both mother and newborn.[1] Globally, this enigmatic condition afflicts an estimated 5-8% of all pregnancies, although its incidence traverses considerable geographical and definitional variance.[2]

The very essence of preeclampsia's pathophysiology remains shrouded in mystery, as it unfolds through incomplete invasion of trophoblasts and the turbulent disruption of spiral arteries. This unfortunate sequence of events culminates in ischemic placental injury, triggering the release of a myriad of mediators into the maternal bloodstream. Consequently, this initiates a cascade of distressing conditions, encompassing diffuse endothelial dysfunction, heightened vascular permeability, and the unwarranted activation of the coagulation cascade.[3]

For numerous individuals, the ultimate management strategy in cases of preeclampsia involves the termination of pregnancy. However, a substantial portion of expectant mothers embark on a journey characterized by meticulous vigilance. This journey entails the continuous monitoring of blood pressure, fetal well-being, and the implementation of preventive measures to mitigate the risk of seizures.[4] The ability to predict the onset and ramifications of preeclampsia assumes paramount significance, as it equips us with the means to identify those at the brink of peril and mitigate the impending threats to maternal and neonatal well-being, ultimately reducing mortality and morbidity rates.[5]

The pursuit of biomarkers with the capacity to anticipate the onset of preeclampsia and ascertain the most opportune timing for pregnancy termination has constituted a prominent area of research emphasis,[6] Notably, in this domain, there have been developments in biomarkers such as FMS-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), which hold promise in providing timely diagnostic information.[7] However, substantial deliberations persist regarding their appropriateness for broad-ranging screening applications.[8]

Amidst the intricate interplay of factors within this context, an unassuming molecule emerges into focus: uric acid. This molecule serves as the ultimate byproduct of purine metabolism, meticulously synthesized with the help of xanthine oxidase, and functions as a safeguard against the deleterious effects of free radicals.[9] In the course of normal pregnancies, a series of orchestrated events leads to a decline in uric acid levels, attributable to adjustments in blood volume and heightened uric acid clearance.[10]

However, the landscape of preeclampsia paints a contrasting narrative. Hypovolemia and the pervasive influence of angiotensin II conspire to induce a state of hyperuricemia.[11] Trophoblasts exhibit heightened activity, resulting in an increased production of uric acid. Yet, a competitive dynamic with lactate within the proximal tubules hampers the effective excretion of uric acid.[12]

Uric acid, as it unfolds, emerges as a pivotal protagonist in the intricate narrative of preeclampsia. It appears to assume a central role by inhibiting nitric oxide production, interfering with the function of trophoblasts, and sowing the seeds of endothelial dysfunction.[13] Furthermore, it serves as an initiator in the generation of proinflammatory cytokines, including interleukin-1β.[14] The association between uric acid and preeclampsia has been recognized for a considerable duration, with uric acid having once occupied a position as a clinical diagnostic criterion.[15] While serum uric acid levels can be employed as a diagnostic indicator, especially in severe manifestations of preeclampsia, discussions regarding more economically viable diagnostic methodologies persist within the realm of medical research.[16]

A ray of potential hope materializes, as certain studies propose that uric acid might offer early indications of impending preeclampsia.[17] However, the narrative becomes more complicated with the call for additional research endeavors aimed at comprehending the precise role of uric acid in predictive models and identifying an optimal diagnostic threshold. Consequently, the current study endeavors to embark on a comprehensive exploration of the intricate relationship between serum uric acid levels and preeclampsia. It aspires to define a suitable predictive threshold, particularly among individuals contending with gestational hypertension (GHTN).

II. Material And Methods

Study Design: Prospective cohort study
Study Location: This was a tertiary care teaching hospital-based study done in the Department of Obstetrics & Gynaecology, at Combined Military Hospital (CMH)
Study Duration: Jan 2023 to July 2023.
Sample size: 152 patients.

Inclusion criteria:

1. Singleton Pregnancy: so that multiple fetuses do not confound the results.
2. Diagnosis of Gestational Hypertension (GHTN): as evidenced by systolic blood pressure (SBP) values exceeding 140 mm Hg and diastolic blood pressure (DBP) values surpassing 90 mm Hg.
3. Those who provided informed written consent.

Exclusion criteria:

4. History of Hyperuricemia.
5. Preexisting Cardiac or Hepatic Disorders.
6. Multiple Pregnancies.
7. History of Preeclampsia in Previous Pregnancies.
8. Unavailability for Follow-Up.

Data Collection: Initially, patient data were collected using a structured form. This information included age, body mass index (BMI) at the beginning of pregnancy, parity, history of miscarriages, smoking status, gestational age at the time of GHTN diagnosis, SBP, DBP, and BMI at the time of referral. Preeclampsia was defined as the sudden onset of hypertension (SBP > 140 mmHg and DBP > 90 mmHg) along with proteinuria exceeding 300 mg/24 hours after the 20th week of gestation. Eclampsia was considered if seizures occurred.[18] The study aimed to determine the incidence of preeclampsia or eclampsia and compare uric acid levels between individuals with and without preeclampsia. Subsequently, a 2 ml blood sample was obtained from each patient to measure the serum uric acid level through an enzyme-linked immunosorbent assay. Patients were then followed up until delivery without interfering with their treatment.

Upon delivery, blood samples were drawn to assess various parameters, including hemoglobin, hematocrit, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, lactate dehydrogenase, platelet count, and uric acid levels. Additionally, the usage of medications for GHTN, gestational age at the time of delivery, type of delivery, symptoms associated with preeclampsia and eclampsia (e.g., seizures, visual disturbances, oliguria, vaginal bleeding, headache, and right upper quadrant pain), and neonatal outcomes

[intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), hospitalization in the neonatal intensive care unit, and Apgar scores at 5 minutes were meticulously recorded.

Data Analysis: Statistical analysis was conducted using SPSS software (version 23.0). It commenced with the calculation of descriptive statistics, encompassing means, standard deviations, medians, interquartile ranges, frequencies, and percentages, providing a comprehensive overview of the dataset. Comparative analyses categorized participants into two groups - those with preeclampsia and those without. Independent samples t-tests and chi-squared tests were applied, with a predefined significance threshold of $p < 0.05$, ensuring the statistical significance of the findings. Correlation analyses probed associations between serum uric acid levels and relevant clinical and biochemical parameters. Logistic regression models were constructed to evaluate the predictive capacity of uric acid for preeclampsia, with odds ratios and confidence intervals computed.

Ethical Considerations: Informed consent was obtained from all participants, with a focus on transparency regarding study objectives, procedures, and potential risks and benefits. Patient confidentiality was rigorously maintained, and stringent data security measures were in place. The study protocol was approved by the institutional Ethical Review Board (IRB approval number: 1508), ensuring adherence to ethical guidelines. The welfare and safety of pregnant individuals were prioritized, with monitoring for any emergent health issues and the option for participant withdrawal if health was jeopardized. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

III. Result

A total of 152 patients were assessed for the study. All patients were followed up throughout the pregnancy period. **Table no1:** presents the demographic clinical data of the participants. Preeclampsia or eclampsia were observed in 103 (67%) of the 152 subjects in our study. Table 1 provides an overview of the patient characteristics. The individuals affected by preeclampsia or eclampsia were characterized by older age, a higher body mass index (BMI), primiparity with a history of miscarriage, and a notably lower gestational age at the time of diagnosis of gestational hypertension (GHTN) ($P<0.05$). However, there were no significant differences in baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the two groups ($P > 0.05$). Furthermore, the utilization of hypertension medications in the preeclampsia/eclampsia group was notably higher ($P < 0.001$).

Table no 1: Demographic clinical data of the participants.

Parameters	**GHTN followed by Preeclampsia/ eclampsia**		**P value**
	No (n= 49)	**Yes (n= 103)**	
Age (years)	27±3.4	29±3.6	0.001
BMI (kg/m^2)	26.2±3.5	28±2.7	0.002
History of abortion	11/49 (22%)	62/103 (60%)	<0.001
Primiparous	19/49 (38%)	74/103 (71%)	0.003
Gestational age at diagnosis of GHTN (in weeks)	29±3	26±44	<0.001
Systolic BP in mm Hg	142±5	143±4	0.295
Diastolic BP in mm Hg	93±3	95±4	0.122
On anti-hypertensive medication therapy	23/49(46%)	84/103 (81%)	<0.001

Table no2: presents the serum uric acid levels of the patients. Notably, both at the point of gestational hypertension (GHTN) diagnosis and at the time of delivery, the uric acid levels were considerably elevated in patients with preeclampsia/eclampsia, as compared to the rest ($P < 0.001$). Remarkably, the preeclampsia/eclampsia group exhibited a significantly higher rate of uric acid increase during pregnancy ($P < 0.001$).

Table no2 : Uric acid levels

Parameters	**GHTN followed by Preeclampsia/ eclampsia**		**P value**
	No (n= 33)	**Yes (n= 119)**	
Uric acid level at the time of diagnosis of GHTN, mg/dL	4.3±0.5	5.2±0.4	<0.001
Uric acid level at the time of delivery, mg/dL	4.5±0.8	6.8±0.9	<0.001
Uric acid level increase during pregnancy	0.03±0.3	1.5±0.3	<0.001

IV. Discussion

Our study revealed that 67% of gestational hypertension (GHTN) patients progressed to preeclampsia/eclampsia. Notably, the preeclampsia/eclampsia group exhibited significantly elevated serum uric acid levels both at GHTN diagnosis and delivery. Uric acid, a recognized biomarker for oxidative stress, placental ischemia, and kidney damage, plays a pivotal role in the context of hyperuricemia triggered by preeclampsia via the activation of xanthine oxidase .[19] This condition is characterized by higher uric acid levels, as supported by studies such as Wu et al., where GHTN patients later developing preeclampsia displayed notably elevated mean uric acid levels compared to those who did not (5.06 mg/dL vs. 4.59 mg/dL).[20]

Bellomo and colleagues further observed that among pregnant women diagnosed with gestational hypertension (GHTN), those with elevated uric acid levels experienced a remarkable ninefold increase in the risk of developing preeclampsia. Additionally, their study indicated that the initial uric acid assay exhibits acceptable sensitivity in predicting the progression to preeclampsia.[21] Our own research aligns with these findings, demonstrating that elevated serum uric acid levels at the time of GHTN diagnosis in women already diagnosed with GHTN can be indicative of increased susceptibility to preeclampsia.

Numerous studies have emphasized the significance of uric acid in the prognosis of preeclampsia.[22] However, the establishment of a specific uric acid level as a definitive predictive threshold remains elusive. Various investigations have reported differing thresholds, with some suggesting levels of 5.6 mg/dL and 6 mg/dL around week 38,[23] while others have proposed lower values.[24] It is essential to acknowledge the variability in findings and interpretations across different studies. While the majority of research considers uric acid a valuable predictor of hypertensive disorders during pregnancy,[23] some studies have reported its limitations in predicting maternal and fetal outcomes.[25] This divergence of results underscores the complexity of the relationship between uric acid and preeclampsia and highlights the need for further research and standardization in this domain. Additionally, some studies have not detected a significant difference in serum uric acid levels between pregnant women with preeclampsia and those with normal pregnancies.[26]

In a comprehensive meta-analysis conducted by Bellos and colleagues in 2020, the predictive potential of uric acid for preeclampsia was investigated. Their findings highlighted a consistent association between preeclampsia and elevated uric acid levels across the first to third trimesters of pregnancy. Notably, they also identified a correlation between laboratory conditions, such as hemolysis, elevated liver enzymes, and low-platelet syndrome, and higher uric acid levels. The sensitivity of uric acid in predicting adverse perinatal outcomes ranged from 67.3% to 82.7%, while its specificity varied from 70.7% to 47.7%. This meta-analysis concluded that uric acid can serve as a predictive tool for preeclampsia and its severity. However, it was emphasized that further studies are essential to refine our understanding and establish more precise thresholds.[17]

The guidance of the American College of Obstetricians and Gynecologists (ACOG) has also delved into the relationship between biomarkers, including uric acid, and adverse pregnancy outcomes in preeclampsia patients.[27] Nevertheless, our present study contributes valuable insights by demonstrating that uric acid levels exceeding 5.2 mg/dL at the time of gestational hypertension (GHTN) diagnosis can be indicative of an elevated risk for subsequent preeclampsia. This finding, while aligning with existing research, underscores the practical application of uric acid as a predictive marker in clinical settings.

V. Limitations

Limitations of our study include its single-center nature, which may limit the generalizability of our findings to broader populations. Additionally, the sample size, although substantial, may not fully encompass the diverse range of factors influencing preeclampsia. The study's reliance on serum uric acid levels as a predictive marker for preeclampsia, while supported by existing literature, is a limitation in itself, as it may not encompass the entirety of the complex pathophysiology of preeclampsia. Future research should aim to incorporate a broader range of biomarkers and clinical parameters to enhance predictive accuracy. Finally, our study focused primarily on the predictive potential of uric acid, but further investigations should delve into the mechanistic aspects of uric acid's role in the pathogenesis of preeclampsia to gain a more comprehensive understanding of this complex condition.

VI. Conclusion

In summary, our study highlights the significant role of uric acid as a potential predictor for preeclampsia among pregnant women initially diagnosed with gestational hypertension. Elevated serum uric acid levels at the time of gestational hypertension diagnosis were strongly associated with an increased risk of developing preeclampsia or eclampsia. This finding aligns with previous research emphasizing uric acid as a biomarker for oxidative stress, placental ischemia, and kidney damage, all contributing to the pathogenesis of preeclampsia.

Future research should incorporate a broader range of biomarkers and clinical parameters for improved predictive accuracy. Preeclampsia remains a significant obstetric challenge, and reliable predictive markers are

crucial for minimizing its impact. Our findings emphasize the practical applicability of uric acid as a predictive tool in clinical settings. Early identification of individuals at risk of preeclampsia can facilitate timely interventions to protect maternal and neonatal well-being. We hope our study contributes to this ongoing effort and encourages further research to unravel the intricate relationship between uric acid and preeclampsia pathogenesis, ultimately improving care and outcomes for expectant mothers and their infants.

DECLARATIONS

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