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RESEARCH ARTICLE
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ASSOCIATION OF HYPERURICEMIA WITH PREECLAMPSIA IN SECOND TRIMESTER OF PREGNANCY

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Abstract

Background: Hypertension during pregnancy is a worldwide problem having serious consequences for the mother as well as the fetus. Uric acid is the end product of purine metabolism catalyzed by enzyme xanthine dehydrogenase/oxidase through several stimuli including ischemia. It is potent mediator of inflammation and through stimulation of inflammatory cytokines cause endothelial injury. Serum uric acid levels are proportional in women with pre-eclampsia.

Objective: To determine mean serum uric acid levels among pre-eclamptic women in the second trimester of pregnancy.

Material and methods:
Study Design: Descriptive cross-sectional

Setting: Pakistan Atomic Energy General Hospital Islamabad

Duration: 6 months from approval of synopsis i.e. 31-5-2018 to 1-12-2018

Data Collection Procedure: 100 indoor patients were included in the study. Data was collected using Performa which includes personal data of patients. 5ml of venous sample was taken from patients for quantification of serum uric acid level. Data was analyzed using version 21.0 of SPSS.

Results: The mean age of patients was 32.20±4.89years. The mean BMI of patients was 23.99±3.24kg/m^2. The mean gestational age of patients was 22.11±1.46weeks. The mean blood pressure of patients was 150.40±7.34mmHg. The mean uric acid level was 7.25±1.64mg/dl.

Conclusion: The average uric acid was high in females with preeclampsia and more than half of females had above-normal level of serum uric acid.

Keywords: Preeclampsia, serum uric acid, blood pressure, proteinuria, second trimester.

INTRODUCTION:

Pregnancy is a physiological state that is linked with many changes including biochemical, metabolic, hematological, and immunological, and diminution of these changes following few weeks after delivery. Hypertension during pregnancy is a worldwide problem having serious consequences for the mother as well as the fetus.[1]

Pre-eclampsia effects 3%-8% of all pregnancies, particularly in second and third trimester of pregnancy.[2]It is a multisystem disorder with cardinal features of hypertension, and proteinuria with or without edema. The complications of pre-eclampsia involve eclampsia, preterm labor, hemorrhage, residual hypertension, and recurrent pre-eclampsia. In complicated pre-eclampsia, the fetal outcome includes low birth weight fetuses, birth asphyxia, stillbirth, fetal demise, and early neonatal deaths.[3]Pre-eclampsia originates in early pregnancy, possibly through an exaggerated adaptation in the form of endothelial dysfunction.[4] Placental vasculature lacks autonomic innervations relying entirely upon locally produced or circulating substances for hemodynamic stability.[5]Placental insufficiency leads to a state of pre-eclampsia. Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks gestation and can present as late as 4-6 weeks postpartum.[6,7] It is clinically defined by hypertension and proteinuria, with or without pathologic edema.[8,9,10]

Uric acid was first recognized approximately 200 years ago, certain aspects of hyperuricemia are still not clearly understood.[11] For years, hyperuricemia has been well-known with or thought to be the same as gout, but uric acid has now been identified as a causative agent for a number of metabolic and hemodynamic abnormalities.[12,13,14]

Unlike allantoin, the more soluble end product of purine metabolism in lower animals, uric acid is a poorly soluble end product of purine metabolism in humans.[15] Human beings have higher levels of uric acid, in part, because of a deficiency of the hepatic enzyme uricase, and a lower fractional excretion of uric acid.[16] Approximately two-thirds of total body urate is produced endogenously, while the remaining one-third is accounted for by dietary purines.[17]The blood levels of uric acid are a function of the balance between the breakdown of purines and the rate of uric acid excretion.[18] Theoretically, alterations in this balance may account for hyperuricemia, although clinically defective elimination accounts for most cases of hyperuricemia.[19]

Uric acid in the blood is saturated at 6.4-6.8 mg/dL at ambient conditions, with the upper limit of solubility placed at 7 mg/dL.[20,21]Urate is freely filtered at the glomerulus, reabsorbed, secreted, and then again reabsorbed in the proximal tubule. The recent cloning of certain urate transporters will facilitate the understanding of specific mechanisms by which urate is handled in the kidney and small intestines.[22]

The primary substance involved in the optimization of placental perfusion is endothelial derived nitric oxide. Uric acid decreases NOS activity and increases the production of tranexamic acid, which is a vasoconstrictor and hypertensive agent.[23] Serum uric acid levels are proportional in women with pre-eclampsia, severity of proteinuria, maternal morbidity and fetal demise. As

discussed earlier, there is variability regarding the association of uric acid with pre-eclampsia.[24]A urate/anion exchanger has been identified in the brush-border membrane of the kidneys and is inhibited by an angiotensin II receptor blocker, losartan.[25] A human organic anion transporter has been found to be inhibited by both uricosuric drugs and antiuricosuric drugs,[26] while another urate transporter has been found to facilitate urate efflux out of the cells. These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate. Urate secretion does appear to correlate with the serum urate concentration because a small increase in the serum concentration results in a marked increase in urate excretion.[27]

The purpose of this study is to anticipate high risk pregnant women in order to avoid adverse pregnancy outcomes regarding mother and baby.

OBJECTIVE: To determine mean serum uric acid levels among pre-eclamptic women in the second trimester of pregnancy.
And to study the relationship of uric acid with the preeclampsia in 2nd trimester of pregnancy.

MATERIALS AND METHODS

Study Design: Descriptive cross-sectional
Setting: PAE General Hospital Islamabad
Duration:6 months from approval of synopsis i.e. 31-5-2018 to 1-12-2018
Sample Size: n = 100
Sampling Technique:
Non Probability consecutive

Sample selection:
Inclusion criteria:

- Age of female 20-40 years.
- Singleton pregnant females booked at PAEC General Hospital, Islamabad
- Gestational age >20 weeks
- Patients with pre-eclampsia [BP>140/90mmbHg and proteinuria 2+

Exclusion criteria:
Pregnant females with chronic hypertension, DM, Renal disease, multiple pregnancy or any other medications for raised uric acid.

Data Collection Procedure:
After obtaining institutional ethical committee approval, blood samples for the estimation of uric acid levels were collected from indoor patients. A written informed consent was taken from the patients. Data was collected using Performa that includes personal data of patients. Every patient was subjected to physical examination [B.P, edema and fundal height]. 5ml of venous sample was taken from patients under aseptic measures and send to the hospital lab for quantification of serum uric acid level, reports were verified by pathologist.

Data Analysis:

- Data was analyzed using version 21.0 of SPSS.
- Data obtained through Performa was summarized according to quantitative variables: age, parity, BP, BMI, and uric acid measured as meant±SD.
- Effect modifiers like age, parity, and BMI were controlled by stratification.
- Post stratification independent sample t-test was applied.
- P-value < 0.05 was significant.

RESULTS

The mean age of patients was 32.20±4.89years. Table 1
The mean BMI of patients was 23.99±3.24kg/m^2. Table 2
The mean gestational age of patients was 22.11±1.46weeks. Table 3

There were 9 (9%) primigravida (parity 0), 11 (11%) had parity 1 (primiparous), 36 (36%) had parity 2, 27 (27%) parity 3, 17 (17%) had parity 4. Fig 1
There were 9 (9%) primigravida, 11 (11%) were gravida 2, 32 (32%) were gravida 3, 28 (28%) were gravida 4, 17 (17%) were gravida 5 and 3 (3%) were gravida 6. Fig 2
The mean blood pressure of patients was 150.40±7.34mmHg. Table 4
The mean uric acid level was 7.25±1.64mg/dl. Table 5

Data was stratified for the age of patients. In patients aged 20-30 years, the mean uric acid level was 6.77±1.31mg/dl. In patients aged 31-40 years, the mean uric acid level was 7.54±1.76mg/dl. The difference was significant ($p<0.05$). Table 6
Data was stratified for the BMI of patients. In normal BMI patients, the mean uric acid level was 7.03±1.77mg/dl. In overweight & obese patients, the mean uric acid level was 7.34±1.59mg/dl. The difference was insignificant ($p>0.05$). Table 7

Data was stratified for parity of patients. In patients having parity 0-1, the mean uric acid level was 6.52±1.39mg/dl. In patients having parity 2-4, the mean uric acid level was 7.43±1.66mg/dl. The difference was significant ($p<0.05$). Table 8

Table 1 Descriptive Statistics of age of patients

Age (years)	n	100
	Mean	32.20
	SD	4.89
	Minimum	20
	Maximum	40

Table 2 Descriptive Statistics of BMI of patients

BMI (kg/m^2)	n	100
	Mean	23.99
	SD	3.24
	Minimum	18.5
	Maximum	29.9

Table 3 Descriptive Statistics of gestational age at presentation

Gestational Age (weeks)	n	100
	Mean	22.11
	SD	1.46
	Minimum	20
	Maximum	24

DISCUSSION

Preeclampsia is a serious pregnancy complication characterized by hypertension, proteinuria with or without pathological edema. According to some studies, serum uric acid lacks sensitivity and specificity as a diagnostic tool whereas another group of the researchers indicated uricemia as a predictor of preeclampsia in pregnant ladies.[28]

Uric acid is a terminal metabolite of the degradation of nucleotides, which increases their blood levels in patients with preeclampsia increasing its synthesis by damage and death of trophoblastic

cells and proliferation. Uricemia in preeclampsia likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption and decreased secretion.[29]

In our study, the mean uric acid level was 7.25±1.64mg/dl. In a study conducted at Obstetrics and Gynecology Department at Shivaji Hospital, uric acid was considered an important parameter in the pathogenesis of Pre-eclampsia showing mean 8.22+1.13.Pramanik et al., found that significantly high serum uric acid level [6.27±1.37 vs 4.27±0.61 mg/dl] in pre-eclamptic patients compared to their healthy counterparts. Results of the study indicated association of elevated serum uric acid level with preeclampsia which could be used as a biochemical indicator of preeclampsia in pregnant women.[30]

Serum uric acid levels at the initial presentation of gestational hypertension were significantly higher comparing patients who later progressed to preeclampsia vs. those who did not (5.06 ± 0.78 vs. 4.59 ± 1.01 mg/dl, $P< 0.01$), whereas the levels of other routinely available lab test biomarkers were very similar.[31]

According to Mustaphi et al, mean uric acid levels in normotensive women in the antenatal period were 4.65±0.33 and in mild PIH were 5.42±0.55 respectively. Level of serum uric acid in mild PIH was significantly higher than normotensive women. In severe PIH, the mean serum uric acid levels were 6.65±0.60 in antepartum which was significantly more than controlgroup and mild PIH group women.[32]

Elevated uric acid concentrations were first noted in preeclamptic women in the late 1800s. Since that time numerous reports have demonstrated a relationship between uric acid concentrations and severity of disease.[33]Hyperuricemia was present in 16% of women with gestational hypertension without proteinuria and 75% of women with clinically diagnosed PE. Pregnancy hypertension with hyperuricemia was associated with an excess of these adverse fetal outcomes. The increased frequency of preterm birth and growth restriction was present in hypertensive women with elevated concentration of uric acid even in the absence of proteinuria.[34]

In our study, the mean age of patients was 32.20±4.89years. Data was stratified for age of patients. In patiens aged 20-30years, the mean uric acid level was 6.77±1.31mg/dl. In patiens aged 31-40years, the mean uric acid level was 7.54±1.76mg/dl. The difference was signficant ($p<0.05$).

In our study, the mean BMI of patients was 23.99±3.24kg/m^2. Data was stratified for BMI of patients. In normal BMI patiens, the mean uric acid level was 7.03±1.77mg/dl. In overweight & obese patiens, the mean uric acid level was 7.34±1.59mg/dl. The difference was insignficant ($p>0.05$).

In our study, there were 9 (9%) primigravida (parity 0), 11 (11%) had parity 1 (primiparous), 36 (36%) had parity 2, 27 (27%) parity 3, 17 (17%) had parity 4. Data was stratified for parity of patients. In patiens having parity 0-1, the mean uric acid level was 6.52±1.39mg/dl. In patiens having parity 2-4, the mean uric acid level was 7.43±1.66mg/dl. The difference was signficant ($p<0.05$).

Zinc and magnesium are important nutrients with anti-inflammatory properties. Chinese studies have linked low dietary levels to hyperuricemia in men. A study by Xie et al in 2697 men and 2471 women indicated that dietary zinc intake was inversely associated with hyperuricemia in middle-aged and older males, but not in females.Wang et al reported that in 5168 subjects, dietary magnesium intake was inversely associated with hyperuricemia, independent of some major confounding factors, but only in males.

CONCLUSION

The average uric acid was high in females with preeclampsia and more than half females had above normal level of serum uric acid. So in future we will recommend the females to screen for serum uric acid level in order to predict the development of preeclampsia in later pregnancy. So that females can be prevented from hazardous complication of pregnancy.

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DECLARATION OF ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH

Student's Name:	**Nosheen Amjad**
Student's ID:	**3001-MSFND-F21**
Title of Research:	**Effect of Qurut (fermented dairy product) in treating nausea and Vomiting during Pregnancy**

1. I declare that I have reviewed Ethical Principles and Guidelines for the Protection of Human Subjects of Research (or other internationally recognized equivalent and the relevant institutional (IRB) policies and procedures for the protection of human subjects.
2. I understand and hereby accept the responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this Agreement.
3. I will comply with all other applicable federal, international, state, and local laws, regulations, and policies that may provide additional protection for human subjects participating in research conducted under this agreement.
4. I will abide by all determinations of the Institutional Review Board (IRB) and will accept the final authority and decisions of the IRB, including but not limited to directives to terminate participation in designated research activities.
5. I will complete any educational training required by the Institution and/or the IRB prior to initiating research.
6. I will report promptly to the IRB any proposed changes in the research. I will not initiate changes in the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.
7. I will report immediately to the IRB any unanticipated problems involving risks to subjects or others in research.
8. I, when responsible for enrolling subjects, will obtain, document, and maintain records of informed consent for each such subject or each subject's legally authorized representative as required and stipulated by the IRB.
9. I acknowledge and agree to cooperate in the IRB's responsibility for initial and continuing review, record keeping, reporting, and certification for the research referenced above. I will provide all information requested by the IRB in a timely fashion.
10. I will not enroll subjects in research prior to its review and approval by the IRB.
11. Emergency medical care may be delivered without IRB review and approval to the extent permitted under applicable federal regulations and state law.
12. I acknowledge that I am primarily responsible for safeguarding the rights and welfare of each research subject, and that the subject's rights and welfare must take precedence over the goals and requirements of the research.

For IRB Use:

- ☐ I recommend that the Research Proposal be revised.
- ☑ I recommend that the Research Proposal be accepted & forwarded to BASR.
- ☐ I recommend that Research Proposal be accepted & forwarded to BASR with minor amendments

Chairperson IRB: _____ Nur International University Lahore

Member DGC: _____

Head of the Department _____

Manager Research Operations (ORIC): _____