Original Article

Serum Uric Acid and Homocysteine Levels as Predictors of Preeclampsia in Young Pregnant Women

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ABSTRACT

Objective: To find out the role of serum uric acid and homocysteine levels as predictors of preeclampsia in young pregnant women.

Methodology: A cross-sectional study was carried out at Lahore General Hospital from a period of May 2017 to February 2018. A total of 35 consented preeclamptic women in the 2nd and 3rd trimester of pregnancy (preeclamptic pregnant group) with an age range of 21-28 years were included in the study. Thirty consented age-matched pregnant women with no history of any disease were taken as normotensive pregnant controls. Women with a blood pressure of 140/90 mmHg and proteinuria were considered as preeclamptic pregnant females. Questionnaires based on age, gestational period, parity, etc. were filled by both groups. Blood samples of both patients and controls were collected and analyzed for the serum levels of uric acid and homocysteine. Collected data was analyzed by Statistical Package for the Social Sciences (SPSS) version 20.

Results: Mean age of preeclamptic pregnant females was 35±6 years with a mean BMI of 30 kg/m^2. Their mean blood pressure was 143.55/93.87 mmHg. The majority of the pregnant women included in the study belonged to a poor socioeconomic class with a history of obstetrical complications like abortions in previous pregnancies. Significantly increased levels of serum uric acid and serum homocysteine were observed in the preeclamptic pregnant group as compared to the normotensive pregnant control group.

Conclusion: Levels of serum uric acid and homocysteine are raised in preeclamptic pregnant females. Estimation of maternal hyperuricemia and hyperhomocysteinemia can be a good parameter for assessing the prognosis and management of patients with pregnancy induced hypertensive disorders including preeclampsia. Furthermore, these serum markers may play an important role in understanding the etiology and pathogenesis of preeclampsia.

Keywords: *Hyperuricemia. Hyperhomocysteinemia. Preeclampsia.*

INTRODUCTION

Preeclampsia is a medical illness that is defined as a combination of pregnancy induced hypertension and proteinuria commonly observed in the second trimester after twenty weeks of pregnancy. It may provoke vascular and metabolic changes and increases the risk of cardiovascular diseases, diabetes mellitus, and various renal problems at later ages.[1] The sequelae of preeclampsia usually start after the 20th week of pregnancy in previously normotensive women. It can result in a poor outcome for both the infant and the mother. Negligence about preeclampsia during pregnancy can lead to a grave condition termed eclampsia, which greatly increases the risk of perinatal mortality.[2] Worldwide prevalence rate of preeclampsia is roughly 7 to 15% which may increase with increasing age. It can affect any organ of the body and leads to morbidity and mortality in both the mother and the fetus.[3]

Uric acid is a major end product of purine metabolism. It has been illustrated by many studies that uric acid may be taken as a pathogenic marker in cases of preeclampsia and hypertensive disorders of pregnancy. Normally, during early pregnancy, serum uric acid level falls to 3 mg/dl or even low because of uricosuric effects of estrogen produced by the placenta and increased blood flow to kidneys. However, in later pregnancy, normally, a rise in serum uric acid is seen.[4] Additionally, increased production of uric acid due to the breakdown of trophoblast fetal cells combined with reduced clearance of uric acid results in hyperuricemia in pregnant women with preeclampsia. The increased levels of serum uric acid alter the production of nitric oxide in cells of vascular endothelium causing endothelial dysfunction, the release of cytokine, ischemia, and inflammation.[5] It can be taken as a useful biomarker for diagnosis and also has a contributory role in the pathogenesis of fetal and maternal manifestations of hypertensive disorders. Uric acid blocks vascular endothelial growth factor (VEGF) induced endothelial proliferation and directly blocks fetal angiogenesis leading to intrauterine growth retardation, kidney dysfunction of the fetus, and trophoblastic invasion of the placenta.[6]

Homocysteine is a thiol-containing amino acid and an intermediary demethylated metabolic derivative of sulfur-containing essential amino acid methionine. It has been observed in various studies that raised serum homocysteine levels are associated with an increased risk of dysfunction of endothelial cells and injury to the vascular tissue leading to atherosclerosis and occlusion of vessels due to the thromboembolic phenomenon. Normally, during pregnancy, mean serum homocysteine level decreases with the gestational age due to physiological response of pregnancy, rise in estrogen levels, hemodilution due to increased plasma volume, and increased demand for methionine by both

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the mother and the fetus. Physiologically, homocysteine metabolizes by two pathways: one is remethylation to methionine and the other is the synthesis of cysteine. It needs folate as a substrate and vitamin B_{12} as a coenzyme for these reactions.[7] The elevated levels of serum homocysteine in women with preeclampsia exists in early pregnancy and remain high till delivery. A rise in serum homocysteine, an intermediary metabolite during pregnancy is associated with an increased risk of complications like abruption of the placenta, preeclampsia, restricted growth of the fetus, and even loss of pregnancy and reduced renal function.[8]

Hyperuricemia may occur in association with hyperhomocysteinemia due to the alteration in the metabolic pathways. Besides, the increased levels of both of these serum parameters may cause dysfunction of endothelium that result in preeclampsia. However, the degree to which serum uric acid and homocysteine independently affect the function of the kidney and increase the risk of preeclampsia is still not known.[5]

Several serum markers for early detection of preeclampsia have been suggested but have not yet been proven. There is a need for serum markers which may serve as early predictors of preeclampsia and may help to protect both the fetus and the mother from severe consequences. The present study was planned to assess the levels of serum uric acid and homocysteine in two groups namely, preeclamptic pregnant patients and the normotensive control group, and to analyze the role of these two serum markers as early predictors of preeclampsia.

METHODOLOGY

This was a cross-sectional study and conducted at Lahore General Hospital from a period of May 2017 to February 2018. The study was ethically approved by the IRB committee of PGMI Institute Lahore. A convenient sampling technique was employed for the collection of data. The study population was divided into two groups. Thirty-five consented preeclamptic women in the 2nd and 3rd trimester of pregnancy with an age range between 21-28 years were taken as a preeclamptic pregnant group and thirty consented age-matched pregnant women with no history of any disease were taken as a normotensive pregnant control group. Preeclamptic pregnant females who were diagnosed at the time of admission and before the beginning of antihypertensive treatment were included in the study. Gestational age of women was estimated by the scan with preeclampsia in pregnancy index. Pregnant women with a blood pressure of 140/90 mmHg and 1+ proteinuria were considered as preeclamptic females. Pregnant women with any chronic problem like liver/renal dysfunction or a history of taking drugs were excluded from the study. The questionnaires based on age, gestational period, parity, etc., were filled by both the preeclamptic women and the controls.

Blood samples were collected from the antecubital veins of both groups. All the collected samples were sent to the laboratory within one hour of collection. These samples were subjected to centrifugation at 3000 rpm for 5-10 minutes and clear serum obtained was collected in a vial and stored at -2 to -8 degree centigrade. Elisa kit method was used to assess the serum homocysteine level. Serum uric acid level determination was done by the indirect equilibrium uricase method.

STATISTICAL ANALYSIS

Collected data was analyzed by Statistical Package for the Social Sciences (SPSS) version 20. Quantitative data was expressed as mean and standard deviation. Comparison of serum levels of uric acid and homocysteine between preeclamptic pregnant women and normotensive controls was performed by independent sample t-test. A p-value ≤0.05 was considered significant.

RESULTS

Demographic profiles of preeclamptic pregnant females were collected. It was observed that the mean age of pregnant females with preeclampsia was 35±6 years with a mean BMI of 30 kg/m^2. Their mean blood pressure was 143.55/93.87 mmHg. The average years of marriage were 3.11 years. Among the preeclamptic group, multigravidas were 11 with a parity of 3 while the rest were primiparas with a gestational age of 25 weeks. Most of the patients (85%) belonged to poor socioeconomic status and 14(40%) of the preeclamptic patients had a history of abortions.

Mean values of serum uric acid and homocysteine are shown in Table 1 & Figure 1. Serum levels of uric acid and homocysteine were compared in both the patients and the controls. It was observed that significantly

Table 1: Comparison of Serum Uric Acid and Homocysteine Levels in Study Subjects

Serum Markers	Pre-eclamptic Pregnant Females	Normotensive Pregnant Controls	p-value
Serum Uric acid (mg/dl)	6.16±1.54	3.68±0.67	0.001*
Serum Homocysteine (µmol/L)	20.09±3.45	6.35±2.39	0.05**

* Highly significant p-value=0.001 **Significant p-value=0.05

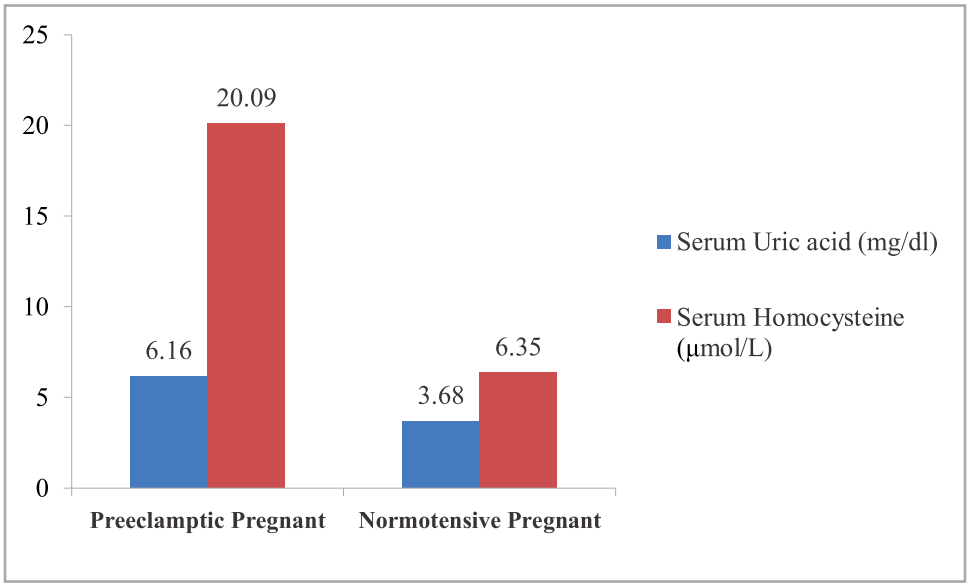

Figure 1: Comparison of Study Variables in Preeclamptic Pregnant Females and Controls

increased levels of serum uric acid and serum homocysteine were observed in patients as compared to the control group with a p-value of 0.001 and 0.05 respectively (Table 1).

DISCUSSION

Preeclampsia is a term used for the disorder related to blood pressure seen during pregnancy. It occurs at around 20 weeks of gestation. It has been observed by Kunwar et al., that preeclampsia is responsible for complicating 1% of all pregnancies.[9] According to Yelikar et al., pre-eclampsia affects 5-7% of all pregnancies and is mostly found in obese and elderly pregnant females.[10] Preeclampsia remains a great public health issue in both developing and the developed countries. Preeclampsia, still, is considered a major contributing factor of maternal and perinatal morbidity as the course of illness and its exact etiology remains unknown till today. Although endothelial dysfunction and associated vasospasm are considered as major contributing factors, however, recently other causes have also been suggested in this regard. The most important among those are hyperuricemia and hyperhomocysteinemia that have gained a lot of attention in the recent past and much work is currently been done to explore the role of these two serum markers in preeclampsia.[11]

Homocysteine is an intermediate metabolite of methionine, an essential amino acid and it has been postulated to be responsible for the production of oxidative stress and endothelial injury which may lead to preeclampsia. In a recent study by Kunwar et al., it has been observed that concentrations of both homocysteine and uric acid were elevated significantly in maternal plasma in patients with preeclampsia which was in accordance with our results.[9] Other studies also supported the hypothesis that preeclampsia may be associated with a higher concentration of homocysteine in maternal blood.[12,13] Until now, the exact etiology of raised serum homocysteine and uric acid levels in preeclampsia has not been figured out. A study conducted by Shahbazian et al., stated that by measuring the levels of serum homocysteine, folic acid, and vitamin B_{12}, women at risk for preeclampsia could be screened, but they failed to prove that use of folic acid and vitamin B_{12} in pregnant women could decrease the level of serum homocysteine.[14] Holmes et al., also supported this school of thought and suggested that continued folic acid supplementation during pregnancy lowers the risk of high homocysteine concentration in maternal serum during the third trimester.[15]

Our results are consistent with the results of a study by Noori et al., and another study by Maru et al., where a significant relationship was found between raised homocysteine and severity of preeclampsia.[12,16] The hypothesis was further strengthened by another study by Sun et al., which showed that hyper-homocysteinemia was caused by endothelial disruption of arteries that may lead to placental infarction or abruption resulting in repeated miscarriages, fetal growth retardation, and neurological dysfunctions.[17] All these observations and results were concluded by another study held in Pakistan that showed a significantly increased homocysteine levels were seen in preeclampsia in the second and third trimester of pregnancy.[18] In our present study, raised serum uric acid levels were significantly correlated with the preeclamptic pregnant patients. A study conducted by Yadav et al., concluded that serum uric acid and serum creatinine level increase significantly in preeclampsia

in comparison to the controls.[19] A study held in India in 2019 concluded that increased uric acid levels can affect fetal health and have adverse effects on fetal outcome.[20] Another study observed that an increase in serum uric acid level is a major cause for pregnancy induced hypertension and uric acid can be used as a marker to predict the severity of this condition.[21] All the above mentioned studies and their results are comparable with the results found in our present study, strengthening and supporting the correlation of increased serum uric acid and homocysteine levels with preeclampsia. Further research is needed to describe the relationship between serum concentrations of uric acid and homocysteine, and the severity of preeclampsia.

CONCLUSION

Levels of serum uric acid and homocysteine are raised in preeclamptic in pregnant females. Estimation of maternal hyperuricemia and hyperhomocysteinemia can be a good parameter for assessing the prognosis and management of patients with pregnancy induced hypertensive disorders including preeclampsia. Furthermore, these serum markers may play an important role in understanding the etiology and pathogenesis of preeclampsia.

LIMITATIONS AND RECOMMENDATIONS

The limitations of our study were the small sample size and median gestational age difference of preeclamptic pregnant females and normotensive pregnant controls. It is recommended that homocysteine and uric acid levels in early pregnancy and even before conception should be done to decrease the incidence and complications of preeclampsia. It is also recommended that supportive supplementations of folic acid, vitamin B_{12}, and B_6 can be tried to minimize the disorders related to amino acid metabolism, especially methionine, involved in the formation of homocysteine and uric acid as intermediates.

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