

Original Research Article

Potential role of serum homocysteine and uric acid level as a predictive marker for pre-eclampsia

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ABSTRACT

Background: Hypertension is one of the common disorders during pregnancy and can cause severe health complications for both mother and developing fetus. Pre-eclampsia (PE) is a form of hypertensive disorder complicating pregnancy. This study was aimed to estimate serum uric acid and homocysteine level as a potential biomarker for prediction of preeclampsia.

Methods: 85 pre-eclamptic pregnant women and 50 normotensive pregnant women were recruited from department of Obstetrics and Gynecology, Star Hospital after obtaining the informed written consent. Blood samples were collected and analyzed for serum homocysteine and serum uric acid level.

Results: Serum uric acid and homocysteine levels were found to be significantly higher in pre-eclamptic cases than in controls (6.5 ± 0.7 mg/dl and 13.5 ± 5.4 μ mol/l in cases versus 4.3 ± 0.8 mg/dl and 10.1 ± 4.6 μ mol/l in healthy controls). Maximum sensitivity and specificity of serum uric acid was obtained at a cut-off of 5.5 mg/dl (sensitivity- 91% and Specificity- 88%) and serum homocysteine at 10.7 μ mol/l (sensitivity-67% and specificity-64%) respectively.

Conclusions: At optimum cut off value serum uric acid showed highest sensitivity and specificity for diagnosis of pre-eclampsia. Thus, serum uric acid level is better predictive marker compared to serum homocysteine level for pre-eclampsia.

Keywords: Pre-eclampsia, Hypertension, Uric acid, Homocysteine

INTRODUCTION

Preeclampsia is a complication of pregnancy characterized by hypertension and excretion of significant amount of protein in the urine.¹ It usually begins after 20 weeks of pregnancy in women who were normotensive in the past. Pre-eclampsia increases the risk of poor outcomes for both the mother and the infant. If left untreated, it may result in seizures leading to a life threatening condition known as eclampsia.² Global evidence indicates that preeclampsia is a leading but preventable cause of still births. It also causes an increased risk of perinatal morbidity and mortality.

Among pregnant women worldwide, 7–15% develops pre-eclampsia; approximately 1–2% will develop eclampsia. The Nepal Maternal Mortality and Morbidity study 2008/2009 revealed that 21% maternal death was due to eclampsia, which was increased from 14% in 1998.^{2,3}

Uric acid is an end product of purine metabolism. Studies have shown that uric acid can be considered as a pathogenic factor in Preeclampsia. Hyperuricemia prevailing in pre-eclampsia has been attributed to either a

decreased excretion or an increased production.⁴ Homocysteine is a naturally occurring amino acid produced in the body as a part of methylation process.⁵ The level of homocysteine in the plasma is being recognized as a risk factor for vascular disease having similar pathogenesis as preeclampsia; therefore hyperhomocysteinemia may exist in pre-eclampsia. Recent theory suggests vascular abnormality as a key factor in the development of preeclampsia.⁶

Numerous markers have been put forward till date for the prediction of preeclampsia with none of it with proven success. The process is still in continuity to detect this devastating condition of pregnancy at an early period to prevent further damage to the mother and the fetus. Thus, this study was intended to assess serum uric acid and homocysteine level and compare their values as a predictive marker for diagnosis of pre-eclampsia.

METHODS

This study was a hospital based cross-sectional study conducted at Star hospital, Sanepa, Lalitpur, Nepal from August 2017 to July 2018. Convenient sampling technique was used. Total of 135 study participants were included in the study; of which 85 were pre-eclamptic (PE) patients and 50 comprised of non-preeclamptic (non PE) healthy participants. Age and trimester matched healthy pregnant women visiting the Antenatal Outpatient Department (OPD) of Department of Obstetrics and Gynecology was enrolled as the control participants in the study. Ethical clearance was taken from Institutional review committee (IRC) of Pokhara University Research Committee (PURC). Written consent was taken from all the pre-eclamptic patients and healthy participants.

Inclusion criteria

Pregnant women with high BP (140/90 mm of Hg) and Proteinuria (>1+) by dipstick test were included as Pre-eclamptic

Exclusion criteria

Exclusion criteria were those having any chronic systemic diseases; renal dysfunction; liver dysfunction; Gout; history of drug or alcohol abuse; those who do not want to participate in the study.

Data collection technique

Socio-demographic characteristics included age, address, ethnicity, period of gestation, obstetric history including details of gravida and parity; past history, family history was taken and filled up on the proforma sheet.

Anthropometric measurement

Standard procedures were used to obtain weight and height.

Participant was made to stand against a wall on which measuring scale was inscribed. Height was measured by making the participant stand bare feet on a flat floor against the wall with feet parallel and heels, buttock, shoulders and occiput touching the wall with head held erect with eyes aligned horizontally and ears vertically without tilt. With the help of plastic scale the topmost portion of vertex will be identified on the wall.

A well calibrated weighing machine (KRUPS) was used to measure weight in Kg.

Blood sample collection:

3ml blood was drawn from antecubital vein into standard commercial evacuated tubes containing clot activator and serum separating gel from each participant under strict aseptic conditions with precautions against environmental contamination and allowed to clot for serum separation to measure biochemical parameters. The samples were separated using centrifuge and were stored at -20°C until analysis.

Principles and methods for estimation parameters

Serum homocysteine was measured by competitive immunoassay method.⁷ Serum uric acids was measured by enzymatic colorimetric test and reading was taken in semiautoanalyser.⁸

Validity and reliability

Tests were performed by following standard operating procedures according to the kit provided by the company. First machine was calibrated and subsequent controls were run. Tests were performed after verifying the result of control. Two levels of control were run for homocysteine; level 1 and level 2. The SD and CV were 0.238, 0.525 and 0.01%, 0.2% respectively. Two levels of control were run for Uric acid; level 1 and level 2. The SD and CV were 0.02, 0.03 and 0.48%, 0.32% respectively.

Data analysis and management

Data were entered in Microsoft Excel 2007 and then converted to statistical package for social science (SPSS) and analysed in version 16. Data were initially checked for normal distribution by Kolmogorov-Smirnov test. Descriptive statistics were used to analyze demographic parameters. Mean with standard deviations (SD) were computed for normally distributed data. Pearson's correlation and Student's T tests was applied to observe the inference. Receiver operating curve (ROC) analysis was computed to find sensitivity and specificity of the test.

RESULTS

This was hospital based comparative cross-sectional study comprised of total 135 participants. The mean age

of case and control were 27.1 ± 4.6 and 26.3 ± 4.5 yrs respectively. The mean gestational age of women with PE and non PE were 32.8 ± 4.9 and 29.4 ± 3.2 weeks respectively. The difference between them was statistically significant. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mm of hg was significantly higher in case than control group (147 ± 10 , 104 ± 10 and 100 ± 5 , 70 ± 10) respectively (Table 1).

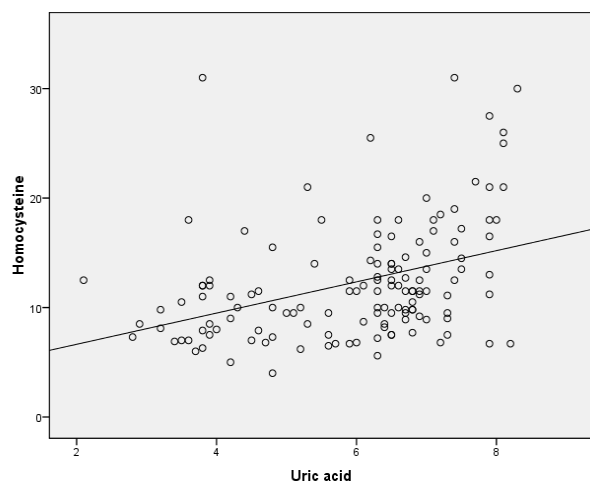


Figure 1: Correlation between homocysteine and uric acid in pre-eclamptic cases ($r=0.382$, $p=0.001$).

The mean uric acid values of case and control groups were 6.54 ± 0.72 mg/dl and 4.35 ± 0.88 mg/dl respectively. The difference between their mean values is statistically significant ($p=0.001$). The mean homocysteine value is significantly higher in case (13.55 ± 5.40 $\mu\text{mol/l}$) than control (10.17 ± 4.63 $\mu\text{mol/l}$) with p value 0.001. The

homocysteine and uric acid shows significant positive correlation ($r=0.254$, $p=0.001$). Pearson correlation test was applied to see the correlation between these variables (Figure 1).

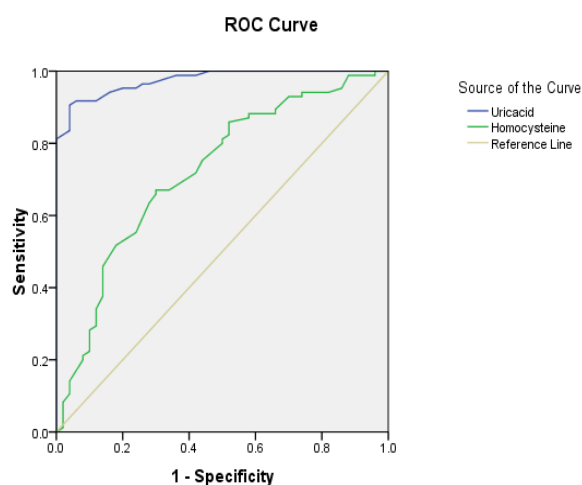


Figure 2: ROC curve analysis of homocysteine and uric acid.

Receiver operating curve (ROC) analysis was done to determine diagnostic efficacy of homocysteine and uric acid. Uric acid shows superior diagnostic efficacy as compared to homocysteine. The area under the curve for uric acid is 0.975 and for homocysteine is 0.722 respectively (Figure 2). From the curve we determine cut-off value for uric acid and homocysteine with maximum sensitivity and specificity. At cut off value of 5.5 mg/dl the sensitivity and specificity of serum uric acid is 91% and 88% respectively. Similarly at cut off value of 10.7 $\mu\text{mol/l}$ the sensitivity and specificity of serum homocysteine is 67% and 64% respectively (Table 2).

Table 1: Baseline parameters of the study.

Parameters	Case (n=85) Mean \pm SD	Control (n=50) Mean \pm SD	P value
Age (yrs)	27.1 ± 4.6	26.3 ± 4.5	0.327
Systolic BP (mm of Hg)	147 ± 10	104 ± 10	0.001
Diastolic BP (mm of Hg)	100 ± 5	70 ± 10	0.001
Homocysteine ($\mu\text{mol/l}$)	13.5 ± 5.4	10.1 ± 4.6	0.001
Uric acid (mg/dl)	6.5 ± 0.7	4.3 ± 0.8	0.001
BMI (kg/m^2)	27.7 ± 4	26.7 ± 4.3	0.474
Period of gestation (weeks)	32.8 ± 4.9	29.4 ± 3.2	0.001

Independent t-test was applied. P value <0.05 was considered statistically significant.

Table 2: Sensitivity, specificity and area under the curve from ROC analysis.

Test	Cut off	Sensitivity (%)	Specificity (%)	Area under the curve
Uric acid (mg/dl)	5.5	91	88	0.975
Homocysteine ($\mu\text{mol/l}$)	10.7	67	64	0.722

DISCUSSION

Preeclampsia is a hypertensive disorder complicating almost 1% of total pregnancies. Overall, high maternal age, obese patients are predisposed to higher risk of preeclampsia. The present study depicts that pre-eclampsia was diagnosed in both younger and middle aged women. Previous report have suggested that the rate of pre-eclampsia is significantly increased in women with age >28 years.⁹

Mean SBP and DBP in cases were higher than that of control group with the difference between the two groups being statistically significant. Mean BMI in case was higher than control group. BMI is one among the three risk factors for increased SBP and DBP, the other two being increased maternal age and gestational age. This was in accordance with several studies who showed that risk for developing hypertensive disease in pregnancy has been found to be increased in women with a high pre-pregnancy or baseline BMI.¹⁰⁻¹² A study published by Clausen et al showed that women with a high intake of energy early in the second trimester may have an increased risk of developing pre-eclampsia. Weight gain during pregnancy has not been associated with PE, but recently it has been associated with an increased risk of transient hypertension.¹³⁻¹⁵

The serum uric acid level is higher in cases (6.54 ± 0.72 mg/dl) than controls (4.35 ± 0.88 mg/dl) and the difference is highly significant (P value 0.001). Our finding is similar to study done Basar et al.⁴ In accordance to our study Zubaidh et al also shows mean serum uric acid (7.68 ± 0.79 mg/dl) of pre-eclamptic women was significantly higher than mean serum uric acid (4.18 ± 1.17) of normotensive control group.¹⁶

Study conducted by Shah et al announced that serum uric acid levels are significantly elevated in pre-eclampsia than normal pregnancy and there is high positive correlation with the disease severity as regards to hypertension and proteinuria.¹⁷ Uric acid clearance is key feature of pre-eclampsia. The serum level of uric acid rises as pre-eclampsia progresses; a level of >5.5 mg/dl is a strong indicator of the disease and a level >7.8 mg/dl is associated with significant maternal morbidity. During pregnancy serum uric acid initially falls by 25-30% due to effects of estrogen, expanded blood volume and increased glomerular filtration rate with subsequent rise to pre-pregnancy levels near term. The third trimester rise in uric acid may be related to an increase in fetal uric acid production or a decrease in clearance. Elevated serum uric acid levels due to decreased renal urate excretion are frequently found in women with pre-eclampsia. Beside the reduced clearance, hyperuricemia in pre-eclampsia may be due to increased uric acid production by trophoblast breakdown. Uric acid impairs nitric oxide generation in endothelial cell inducing endothelial dysfunction, cytokine release and ischemia. So pre-eclampsia is characterized by widespread endothelial

dysfunction and inflammation might be propagated by hyperuricemia.¹⁸

It has been noted that in established pre-eclampsia case, the diagnosis is usually clinically evident; uric acid measurement is of greater value where the diagnosis is in doubt. Low uric acid values indicate a good prognosis for the fetus. Rising or high values at this time indicate high risk cases which are better managed and treated in hospital.

The serum homocysteine level in case group (13.55 ± 5.40 μ mol/l) is found to be significantly high as compared to control group (10.17 ± 4.63 μ mol/l). The findings are comparable to that reported by Rajkovic et al and Laskowska et al.^{19,20}

Serum homocysteine concentration in pre-eclampsia has been reported in a number of studies. In consistent with our findings Hoque et al also found homocysteine concentration to be raised in pre-eclampsia.¹ In line with this study, many studies have demonstrated the relationship between hyperhomocysteinemia and pre-eclampsia.^{21,22}

Usually the homocysteine level gets decreased during pregnancy due to various factors. In second and third trimester total plasma homocysteine in maternal plasma is decreased by 50 percent than non-pregnant women. The decreased level with gestation may be either due to physiological response to pregnancy, increase in estrogen, hemodilution from increased plasma volume or increased demand for methionine by the mother and fetus.²³

Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive vascular disorders. It has been suggested that the adverse vascular effect of high homocysteine are mediated by oxidative inactivation of nitric oxide, a powerful endogenous vasodilator released from endothelium. Endothelial cell dysfunction is the most popularly hypothesized factor for pre-eclampsia. Therefore hyperhomocysteinemia during pregnancy may contribute to this condition.^{1,5}

So maternal hyperhomocysteinemia seems to have casual role in the etiopathogenesis of pre-eclampsia. It needs more study to delineate the relationship between serum homocysteine concentration and the severity of pre-eclampsia and eclampsia.

Besides the increased uric acid level in cases, a positive correlation is observed between serum uric acid and homocysteine. This support finding of Ingec et al.²⁴

At best cut off value the sensitivity, specificity and area under the curve were computed from ROC curve. At cut off value of 5.5 mg/dl the sensitivity and specificity of uric acid is 91% and 88% respectively. At cut off value of

10.7 µg/l the sensitivity and specificity homocysteine is 67% and 64% respectively (Table 4). However study done by Khurshid et al shows uric acid has sensitivity and specificity of 65% and 95% respectively, the sensitivity is lower than our study while specificity is high.⁷

Serum uric acid have high diagnostic efficacy than homocysteine at suitable cut off. Thus routine estimation of serum uric acid level can be valuable diagnostic marker to predict pre-eclampsia and severity of pre-eclampsia.

CONCLUSION

Hyperuricemia and hyperhomocystinemia can be used as biomarker for women at risk of pre-eclampsia. Our study demonstrates that at the best possible cut-off, serum uric acid exhibit better sensitivity and specificity compared to homocysteine for the effective prediction of preeclampsia.

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Conflict of interest: None declared

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