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Homocysteine as a prognostic indicator for women with pregnancy-induced hypertension-A proportional study of homocysteine levels in normal versus pre-eclamptic women.

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ABSTRACT… Objective: To find the probable role of Homocysteine as a prognostic indicator for women with Pregnancy-Induced Hypertension and comparison of Homocysteine Levels in Normal Versus pre-eclamptic women. **Study Design:** Cross Sectional Comparative study. **Setting:** Gynecology Unit of Lahore General Hospital, Lahore. **Period:** May 2017 to Oct 2017. **Material & Methods:** Thirty four consented pre-eclamptic pregnant women with age range 29 to 35 years were included in the study. 20 age matched pregnant women with no history of any clinical problem were taken as controls. A questionnaire based on age, obstetric details including detail of gravida, family history etc was filled by both subjects and controls. Anthropometric parameters were noted based on height and weight. Blood sample of both patients and controls was drawn for estimation of blood urea, serum creatinine, and homocysteine. **Results:** Mean age of women was 31 year with BMI 27.0 Kg/m^2. Levels of serum homocysteine were significantly more women with pre-eclampsia in comparison with cases of controls. However the values of blood urea and serum creatinine were insignificantly high in pre-eclamptic women in comparison with their controls. **Conclusion:** Serum homocysteine as a biomarker may help to find out its additive importance in the prediction of pre-eclampsia and the severity of its related complications.

Key words: Hyperhomocysteinemia, Hyperuricemia, Pre-Eclampsia.

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INTRODUCTION

Preeclampsia is labeled by hypertension and urinary protein excretion typically start after 20 weeks in pregnant women and may increases the risk of poor consequences for mother / infant and some time may results eclampsia.[1] Globally the incidence of pre-eclampsia was 7–15%. However, in under developed countries like in Pakistan is 9.3%, in India 10.3% and in Nigeria, the incidence rate is 10.2%.[2]

Factors associated with preeclampsia including history of preeclampsia, nulliparity, chronic hypertension, age ≥ 35 years, pregestational diabetes mellitus, history of chronic kidney disease and environmental features.[3]

Preeclampsia may be a cause of liver and kidney damage. It is proposed that renal injury may be due to high values of uric acid and contribute in the pathogenesis of Preeclampsia.[4] The condition of hyperuricemia in pre-eclampsia is mostly due to high production of uric acid. Its high levels are considered as early indicator of kidney damage in women with pre-eclampsia and may be a reason of fetal death. However, the function of uric acid as a likely reason of poor effects both mother and fetus is remain controversial.[5]

Homocysteine is a metabolite of methionine metabolism and related with the chances of development of placenta-arbitrated complications, preeclampsia, abruption of placenta, restriction of growth of fetus and miscarriages. All conditions have been related to abnormal vasculature of placenta.[6] Hyperhomocysteinemia (Hcy) is a risk feature for vascular diseases and endothelial dysfunction may be related with pathogenesis

of pre-eclampsia.[7] The levels of Hcy were estimated in pregnant women relative to the high chances of adverse outcomes of pregnancy like pre-eclampsia, pre-term infants, frequent abortions, under-weight infants, or restriction of intrauterine growth.[8] Impairment of One-*carbon metabolism* is found in many pathologies and anomalies like neural tube defect, cardiovascular problems etc. Polymorphisms in genes related to 1 carbon metabolism, as well as various modifiable lifestyle and behavioral factors are associated with elevated homocysteine and in-turn may enhance the risk of neural tube defect. However, the association of homocysteine with pre-eclampsia is controversial.[9,10]

Role of homocysteine with uric acid is proposed by a study. It is stated that high level of homocysteine causes a damage of vascular system of organ of mother and fetus and increase the levels of uric acid and reduced the values of magnesium and it may affect renal and vascular systems, thereby annoying the process resulting in increased morbidity and mortality of mother / fetus. It is therefore said that vascular abnormality is a major factor in development of problem of preeclampsia.[11]

Number of markers are suggested for early indication of preeclampsia but none these are proved. Studies are still carried out to find out the early markers for prevention of mother and fetus from consequences of eclampsia. This study was therefore carried out to find the probable role of serum homocysteine level as a predictive marker for pre-eclampsia.

MATERIAL & METHODS

Cross sectional comparative study was conducted at Lahore General Hospital Lahore for a period of May 2017-oct 2017. Thirty four consented pre-eclamptic pregnant women with age range 29 to 35 years were included in the study. 20 age matched pregnant women with no history of any clinical problem were taken as controls. Diagnostic standards for preeclampsia was based on recently high blood pressure (140 mm Hg / higher systolic and 90 mm Hg / higher diastolic taken with an interval of six hours along with proteinuria (300 mg / 24 hour urine) at 20th weeks of gestation.[12] Patients having any systemic problem / diseases like liver, renal dysfunction were excluded from the study. A questionnaire based on age, obstetric details including detail of gravida, family history etc was filled by both subjects and controls. Anthropometric parameters were noted based on height and weight. About 3ml blood was taken from both patients and controls for estimation of blood urea, serum creatinine, and homocysteine using auto-analyzer and ELISA respectively. This research was approved by Ethical committee of institution.

Data was analyzed by SPSS 20. Study variables were expressed as mean ± SD. Student's 't' tests was used to compare the variables between patients and controls. $P < 0.05$ is taken as significant.

RESULTS

Demographic profile of Preeclamptic women and control group is tabulated as Table-I. It was observed that mean age of pre-eclamptic women and control was 30 and 31 years respectively. Their blood pressure was 144.65/96.07 mmHg. Gestational age was 25 week in both groups. Poor class was more in control groups than patients group. Dietary habits are vegetable + meat. Obstetric complication including abortion and cesarean were observed in patients. Gestational age, socioeconomic class and dietary habits are quite similar in PCOS women and control groups.

Comparison of the levels of uric acid, homocysteine, blood urea and serum creatinine in patients with controls with age 29-35 yrs is tabulated as Table-II. It is observed that significant increased level of serum uric acid and serum homocysteine was observed in patients compare to control group with p value <0.05 and 0.001 respectively. On the other, level of blood urea, and serum creatinine were non significantly decreased in patients as compared to control group.

Characteristics	Pre-eclamptic women (34 cases)	Control (20 cases)
Mean age (yrs)	31.44±2.66	30.00±1.49
BMI (Kg/m^2)	27.42±1.70	24.83±1.70
Blood Pressure (mm Hg)	144.65/96.07 3.08±4.01	124.65/70.55 6.53±5.41
Gestational age (yrs)	25.50±0.82	24.90±0.88
Socioeconomic status	09 Poor class 05 Middle class	08 Poor class 02 Middle class
Dietary habits	03 vegetarian 03 vegetable + chicken 07 vegetable + Meat	03 vegetarian 03 vegetable + chicken 04 vegetable + Meat
Obs complications	04 Abortions 04 PE/CS	-

Table-I. Demographic profile of pre-eclamptic women.

Variables	Pre-eclamptic women with age range 29-35 years	Controls with age range 29-35 years
Serum homocysteine (μmol/L)	20.18±2.94**	8.29±2.33
Blood Urea (mg/dl	31.43±7.86	25.00±4.57
Serum creatinine (mg/dl)	1.10±0.18	0.69±0.15

Table-II. Comparison of the levels of homocysteine, blood urea and serum creatinine in patients with controls with age 29-35 years.

*P<0.05 = Significant difference
**P< 0.001 = highly significant difference

DISCUSSION

Pre-eclampsia is a problem of pregnancy that is related with morbidity and mortality of both mother and fetus. Disease is associated with onset of hypertension along with proteinuria results in dysfunction of liver, kidney and brain. Dysfunction of endothelium in mother due to factors circulate in fetus from the placenta is a trademark of pre-eclampsia.[13]

According to our study high blood pressure was observed in pre-eclamptic women at 20th week of gestation. However, a study stated that in start of pregnancy, there is low value of high blood pressure and it is not a predictor of pre-eclampsia. Nevertheless, hypertension that was treated to control blood pressure is highly related with the development of preeclampsia results in adverse effect on both mother and infant. Study also found that high BMI and back history of preeclampsia were not related with the development of preeclampsia.[14]

Our study group has an age range of 29-35 years. They have high BMI and obstetric complications. We agreed with a study who demonstrated that preeclampsia is a recurrent syndrome and may be related with high maternal age. Study observed that women with increasing age are more prone to develop pre-eclampsia as compare to younger one. They are at more risk of obstetric complication with high values of BMI. Study also found that these women may high a high occurrence of chronic hypertension and diabetes and may increase the chances of pre-term and low body weight at birth. It is proposed that this may be associated with aging of blood vessels of uterus.[15,16,17]

Our study in-line with a study, who found that in pre-eclamptic women, hypertension, proteinuria, high values of serum uric acid /creatinine are related with fetal problems such as preterm and low birth weight at the time of delivery.[18] Additionally a study stated that GFR or glomerular filtration rate increases 40 - 50% above the baseline values in the period of pregnancy. Thus, normal values of circulating creatinine (in our

study it is slightly raised) may mirror significant insufficiency of kidney in pregnancy.[4]

Additionally, a study proposed that hyperuricemia is commonly seen in early stage of pregnant women. Study found that the value of serum uric acid was high at 10th week of pregnancy as glomerular endotheliosis may justify the reduced clearance of uric acid. It is noted that hyperhomocysteinemia may cause the abnormal invasion of trophoblast in condition of pre-eclampsia. Study concluded that it may have an important function in the development of disease and may be a good predicator of fetal and mother outcomes.[19]

Another study found that high values of uric acid, mostly due to high urate tubular reabsorption, enthused by the hypovolemia and by the act of angiotensin II.[20] Impairment of excretion of uric acid is also due to competition of lactate in the proximal convoluted tubule, while its synthesis is exaggerated by the high turnover of trophoblast.[21]

We observed significantly high levels of homocysteine in a group of pre-ecalamptic women. A study is in line with our study and proposed that cortisol and estrogen in the period of pregnancy may mediate concentration of homocysteine.[22] The increased values of homocysteine may reduce the expression of many antioxidant, which may alters the bioavailability of strong vasodilator nitric oxide, This alter availability of nitric oxide may be involve in homocysteine facilitated vascular damage and due to the reduction of antioxidant, the cells are more sensitizes for ROS or reactive oxygen species.[23] On the other hand uricosuric effect of estrogen reduced the values of uric acid up to 3 mg/ ml. it is noted that the values of uric acid increase at 3rd trimester of pregnancy and this may relate with the reduction of excretion of urates.[24]

Sample size was small. More studies are needed to find the additional markers in combinations of serum homocysteine with other early predictors of preeclampsia like placental growth factor and endoglin in forecasting the development of preeclampsia and poor outcomes of both mother and fetus. This may help the clinicians in proper managing the gestational hypertension.

CONCLUSION

Serum homocysteine along with serum uric acid as a biomarker may help to find out its additive importance in the prediction of pre-eclampsia and the severity of its related complications.

No conflict of Interest.

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3	Kiran Namoos	Analysis and interpretation of data.	
4	Iram Fayyaz	Drafting of article.	
5	Huma Ashraf	Critical revision of article for important intellectual.	
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