

Association between High Serum Homocystine and Preeclampsia

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Abstract

Background: Hyperhomocysteinemia is an important biological marker for adverse outcome of pregnancy. **Objective:** The aim of the present study was to see the association of high serum homocystine with preeclampsia (PE). **Methodology:** This cross sectional study was carried out in the Department of Obstetrics and Gynaecology at Sir Salimullah Medical College & Mitford Hospital, Dhaka. All pregnant women with or without eclampsia admitted at the hospital were included in this study. Pregnant women with diabetes mellitus, chronic hypertension, multiple pregnancies, chronic renal disease and patients taking anti-folate drugs were excluded from this study. Fasting serum total homocystine (tHomocystine) concentration was estimated by Fluorescence Polarization Immunoassay (FPIA) method. **Result:** A total number of 50 PE patient [Severe PE (23) & Mild PE (27)] and 50 pregnant women without PE were selected purposively. Fasting serum total homocystine (tHomocystine) concentration was estimated by fluorescence polarization immunoassay (FPIA) method. Mean serum homocystine concentration in severe PE, mild PE and pregnant women without PE were 11.5 4.58 mol/L, 10.43 5.12 and 5.70 1.30 respectively. Serum homocystine was significantly increased in severe PE and mild PE in comparison to without PE group. However severe PE and mild PE group cases did not differ with respect to serum homocystine. **Conclusion:** Significant positive correlation was found between serum homocystine concentration and urinary total protein, uric acid level, systolic blood pressure and diastolic blood pressure. [J Shaheed Suhrawardy Med Coll, 2013;5(1):21-25]

Key words: Homocystine, preeclampsia, eclampsia, pregnancy

Received: December 2012; **Revised:** March 2013; **Accepted:** May 2013

Introduction

Preeclampsia is a pregnancy-specific condition that increases maternal and perinatal mortality and morbidity¹. If preeclampsia is not diagnosed or treated, it can progress to maternal multiorgan failure, coagulopathy and maternal and fetal death in severe form¹. It is widely accepted that preeclampsia starts with poor placental perfusion associated with defective trophoblast invasion²; however this is not sufficient to explain the disease. Widely accepted concept for the development of preeclampsia is the interaction of reduced placental perfusion with maternal factors².

Elevated circulating homocystine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive vascular disorders³. It is sulfur

containing essential amino acid required for the growth of cells and tissues in the human body. It is hypothesized that hyperhomocysteinemia might damage the vascular endothelium of the developing placenta by promoting oxidative stress, thereby increasing contractile response and the production of pro-coagulants and vasoconstrictor⁴. Plasma homocystine is normally lower throughout pregnancy than in the non-pregnant state⁵. Homocystine concentrations are directly correlated with albumin concentration, which decrease during pregnancy and decrease further in pregnant women taking folic acid supplements. Vollset et al⁶ reported that hyperhomocysteinemia may also be an important biological marker for adverse outcome of pregnancy and even possibly a cause of or a contributor to the complications of pregnancy. An increased risk of preeclampsia, premature

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Conflict of interest: Not declared

Financial Support: None

Contributions by authors: Dr. M. Ferdausi contributed from preparation of protocol to write up of the article. Prof. M. Khatun, Dr. A. Rahman & Z. Rahman have corrected the article. Dr. M. A. Yusuf has done the statistical work.

delivery, very low birth weight, neural tube defects and clubfoot occurs in those women who are suffering from hyperhomocysteinemia⁶.

Studies regarding homocysteine in Bangladesh are very rare. Two cross-sectional studies conducted by Zaher et al⁷ and Banu⁸ found positive association between homocysteine with all forms of coronary heart disease. Wahab⁹ showed that folic acid supplementation decreased fasting serum homocysteine concentration in coronary heart disease patients. Hyperhomocysteinemia is treatable by supplementation of vitamins like vitamin B6, B12 and folic acid. So, if hyperhomocysteinemia is detected in early pregnancy, homocysteine level can be decreased to normal value by vitamin supplementation and thus the occurrence of preeclampsia can be prevented in the population of this country.

Therefore, the present study was designed to see the association of elevated plasma homocysteine level with preeclampsia and especial attention can be given to this group of women during antenatal care for prevention of the pregnancy adverse outcomes.

Methodology

This cross-sectional study was conducted in the Department of Gynaecology and Obstetrics at Sir Sallimullah Medical College (SSMC) and Mitford Hospital (MH), Dhaka, Bangladesh from July 2004 to June 2006 for a period of two (2) years. All pregnant women with or without eclampsia admitted at the hospital were included in this study. Women with preeclampsia were divided into two groups named as mild and moderate preeclampsia. Mild pre-eclampsia was diagnosed by BP with $>140/90$ mm of Hg or $<160/110$ mm of Hg and proteinuria with >0.3 gm/24 hours urine. Severe pre-eclampsia was diagnosed by BP $>160/110$ mm of Hg and proteinuria with >2 gm/24 hours urine. Pregnant women without preeclampsia or any other uncomplicated pregnancies who were attending an outpatient department and or inpatient department of the study place were also selected. Pregnant women with diabetes mellitus, chronic hypertension, multiple pregnancies, chronic renal disease and patients taking anti-folate drugs were excluded from this study. Fasting serum total homocysteine (tHomocysteine) concentration was estimated by Fluorescence Polarization Immunoassay (FPIA) method. The reading was taken by the 'AxSYM system' (Abbott, USA) auto-analyzer. Urinary total protein, fasting blood sugar and serum creatinine were measured accordingly. Computer based statistical analysis were carried out with appropriate techniques and systems. All data were recorded systematically in preformed data collection form (questionnaire) and quantitative data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analysis was performed by using window based computer software devised with Statistical Packages for

Social Sciences (SPSS 17.0) (SPSS Inc, Chicago, IL, USA). 95% confidence limit was taken. Probability value <0.05 was considered as level of significance. The association between qualitative variables was measured by Chi-Square test. Student's t test has been performed to see the association between quantitative variables. Serum homocysteine concentration among severe PE, mild PE and without PE women was compared by ANOVA. The summarized data was interpreted accordingly and was then presented in the form of tables.

Results

A total number of 100 pregnant women were enrolled in this study of which 50 pregnant women were with preeclampsia and 50 pregnant women were normotensive. The mean age of the different study groups did not show any significant differences (without PE 25.84 ± 5.43 , mild PE 24.00 ± 4.14 and severe PE 25.83 ± 5.69 ; $p=ns$). Mean height of different study groups showed significant differences (mild PE= 158.4 ± 2.7 cm, severe PE 156.2 ± 3.4 cm and without PE 156.4 ± 2.8 cm; $p=0.01$). Women with more mean weight was found to suffer from more in PE than the lighter group (mild PE 61.1 ± 4.5 kg, severe PE 5.98 ± 6.5 kg and without PE 53.3 ± 4.7 kg; $p<0.001$). There were significant differences of BMI ($p<0.001$) between these groups. The mean BMI kg/m^2 of the different study groups were 21.7 ± 1.7 in without PE women, 24.3 ± 1.2 in mild PE and 24.6 ± 2.3 in severe PE. Gestational age showed significant difference ($p=0.02$). Mean gestational age in the without PE group was 30.8 ± 4.03 week, severe PE 31.7 ± 3.59 week and mild PE 28.7 ± 4.05 week. Mean systolic blood pressure in the different study groups were 108.2 ± 08.73 mm of Hg in without PE women, 163.9 ± 11.1 mm of Hg in severe PE and 139.6 ± 7.06 mm of Hg in mild group. Significant difference was found in this variable ($p<0.001$). Mean diastolic blood pressure (mm of Hg) in the women without PE group was 67.7 ± 7.09 mm (Hg), mild PE 96.3 ± 5.5 mm (Hg) and in severe PE 113.4 ± 84.87 mm (Hg). This variable also showed significant difference between the study groups ($p<0.001$). Significant differences were found between total platelet count and different types of study population ($p<0.001$), between total urinary protein and different types of study population ($p<0.001$). No significant differences were found between fasting blood sugar, uric acid, serum creatinine among different groups of study population. Mean Hb concentration in different study groups showed no significant differences ($p=NS$). Mean Hb concentration in between mild PE and severe PE were more or less same than the control group (Table 1).

The mean SD of serum homocysteine concentration was 11.5 ± 4.58 mol/L in severe PE, 10.43 ± 5.12 mol/L in mild PE and 5.70 ± 1.37 mol/L in without PE group. There were significant differences between different groups of study population. Serum homocysteine concentration among study subjects were compared by ANOVA which showed significant difference ($p<0.001$) among severe PE, mild PE and without PE group.

Table 1: General Characteristics of the study groups

| Variables | Mild PE Mean ± SD (n=23) | Severe PE Mean ± SD (n=27) | Without PE Mean ± SD (n=50) | p value |
|-----------------------------------|--------------------------------|----------------------------------|-----------------------------------|---------|
| Maternal age(years) | 24.00 ± 4.14 | 25.83 ± 5.69 | 25.84 ± 5.43 | NS |
| Height(cm) | 158.4 ± 2.7 | 156.2 ± 3.4 | 156.4 ± 2.8 | 0.01 |
| Weight (kg) | 61.1 ± 4.5 | 59.8 ± 6.5 | 53.3 ± 4.7 | <0.001 |
| BMI(kg/m ²) | 24.3 ± 1.2 | 24.6 ± 2.3 | 21.7 ± 1.7 | <0.001 |
| Monthly income(taka) | 6611 ± 2450 | 7636 ± 4445 | 10560 ± 4768 | < 0.001 |
| Gestational age(months) | 28.7 ± 4.05 | 31.7 ± 3.59 | 30.8 ± 4.03 | 0.02 |
| Systolic BP(mmHg) | 139.6 ± 7.06 | 163.9 ± 11.1 | 108.2 ± 8.73 | < 0.001 |
| Diastolic BP(mmHg) | 96.3 ± 5.5 | 113.48 ± 4.87 | 67.7 ± 7.09 | < 0.001 |
| Haemoglobin (g/dl) | 10.7 ± 0.56 | 10.6 ± 0.54 | 10.4 ± 0.73 | NS |
| Platelets (1000/mm ³) | 187.5 ± 37.4 | 167.6 ± 36.24 | 206.0 ± 32.2 | < 0.001 |
| Serum creatinine(mg/dl) | 1.38 ± 1.33 | 1.21 ± 0.17 | 1.06 ± 1.01 | NS |
| FBS(mmol/l) | 5.67 ± 0.82 | 5.82 ± 1.1 | 5.32 ± 0.76 | NS |
| Serum uric acid(mg/dl) | 5.87 ± 2.01 | 6.13 ± 1.17 | 3.7 ± 0.42 | <0.001 |
| UTP (g/24 hour) | 0.57 ± 1.26 | 4.68 ± 2.81 | 0.09 ± 0.06 | < 0.001 |

*BP= Blood pressure; UTP= Urinary total protein; ANOVA was done to see the association; *p value <0.05 was taken as significant.

Table 2: Comparison of Serum Homocysteine level among Study groups

| Study Groups | Hcy (mol/L) (Mean ± SD) | p value |
|--------------|----------------------------|---------|
| Mild PE | 10.43 ± 5.12 | |
| Severe PE | 11.5 ± 4.58 | <0.001 |
| Without PE | 5.70 ± 1.37 | |

* ANOVA was done to see the association

* Hcy = Homocysteine

Positive correlation was noticed ($r=0.472$; $p<0.001$) between serum homocysteine and BMI; between serum homocysteine and urinary total protein ($r=0.278$; $p=0.005$); between serum homocysteine and uric acid level ($r=0.478$; $p=0.001$); between serum homocysteine and platelet count ($r=0.326$; $p=0.001$); between serum homocysteine and systolic blood pressure ($r=0.528$; $p<0.001$) and between serum homocysteine and diastolic blood pressure ($r=0.579$; $p<0.001$) (Table 3).

Table 3: Correlation of Serum Homocysteine with Biochemical Parameters

| Variables | r | p value |
|------------------------------|-------|---------|
| UTP (gm/ 24 hr urine) | 0.278 | 0.005 |
| Uric Acid (mg/dl) | 0.478 | < 0.001 |
| TPC (X1000/mm ³) | 0.326 | 0.001 |
| Systolic BP (mm of Hg) | 0.528 | < 0.001 |
| Diastolic BP (mm of Hg) | 0.579 | < 0.001 |

*r=correlation coefficient; BP=Blood pressure; TPC= Total Plate count; UTP= urinary total protein

Discussion

An elevated plasma homocysteine level is associated with a variety of vascular disorders; however it is not clear whether

the association is causal or an effect of the disease process. A meta-analysis demonstrated a relationship between homocysteine and coronary artery disease, cerebro-vascular disease, and peripheral vascular disease¹⁰. The risk of coronary artery disease is seen to increase across a range of homocysteine values. Welch et al⁴ suggested that it was a positive association between homocysteine and ischemic heart disease & showed that increase in homocysteine of 5 mol/L, the rate of ischemic heart disease risk increased by 84.0%. Similarly this study demonstrated a relationship between increased homocysteine and development of preeclampsia.

In this study it has been measured serum Hcy concentration in 50 diagnosed PE patients and 50 uncomplicated pregnancies. The mean serum Hcy level found to be significantly high ($P<0.001$) in PE cases compared to non PE group. This finding conforms to other similar studies done by Cotter et al¹¹, Lopez-Quesada et al¹², Walker et al¹⁵, Refsum et al¹³, Rajkovic et al¹³. Currently reported two studies by Mignini et al¹⁴ and Ingec et al¹⁵ showed serum homocysteine concentration in patients with PE were higher than those with uncomplicated pregnancy which were similar to this present study. Mean serum homocysteine concentrations in women with severe PE were significantly higher than those in without PE subject (11.5 ± 4.58 mol/L versus 5.70 ± 1.37 mol/L). Similar studies were done by Cotter et al¹¹ and Ingec et al¹⁵ and found similar results¹¹⁻¹⁵. Mean serum homocysteine concentrations in women with mild PE were significantly higher than those in without PE group (10.43 ± 5.12 versus 5.70 ± 1.37 mol/L). These results were consistent with the result of Cotter et al¹¹; however this findings differ from Ingec et al¹⁵ who demonstrated that plasma homocysteine is not increased in mild PE. No significant difference was detected in the serum levels of hemoglobin and creatinine among all groups. These findings were similar with the findings of Ingec et al¹⁵. Uric acid and proteinuria were higher in PE group than without PE group

($p < 0.001$) however, platelet count was lower in cases than without PE group ($p < 0.001$); These findings were consistent with the findings of Ingec et al¹⁵.

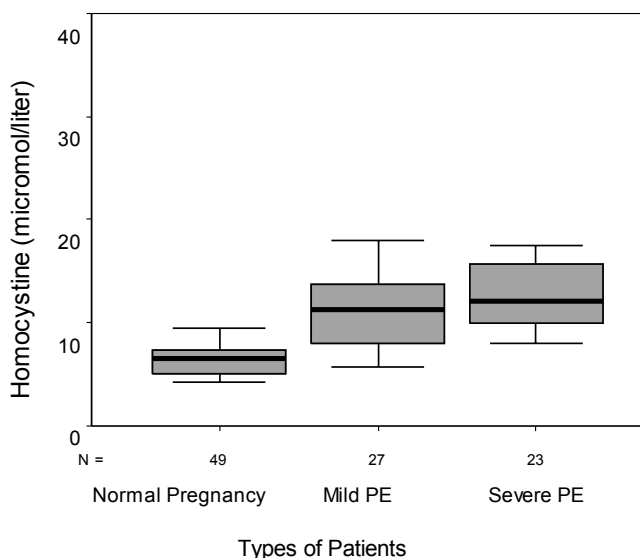


Figure 1: Box Plot of Hcy Concentration among Types of Patients (In the box plot, there are no outliers; the whiskers are not equal which indicates that the data is not normally distributed. Within the box, the midline is not in the centre which indicates that the data is not normal)

In this study, the mean BMI of PE group was higher than without PE group ($p < 0.001$). When it was measured height and weight between the women with and without PE, there was found a significant difference of weight ($P < 0.001$).

The study was also revealed significant positive correlation between serum Hcy concentration and proteinuria ($r=0.278$; $p=0.0050$), serum Hcy concentration and uric acid ($r=0.478$; $p < 0.001$). These findings were similar to Ingec et al¹⁵. This study also observed significant negative correlation between serum Hcy concentration and platelet count ($r = 0.326$; $p=0.001$). These findings were consistent with the findings of Ingec et al¹⁵. There was also positive correlation between serum Hcy with systolic blood pressure ($r=0.528$; $p < 0.001$) and serum Hcy concentration with diastolic blood pressure ($r=0.579$; $p < 0.001$).

It is known that serum homocysteine level increase with age¹⁷ and plasma homocysteine level decrease throughout pregnancy¹⁸; however the study population provided blood samples at a similar gestational age. Women with or without PE groups were not matched for parity. In this study parity was not associated with the homocysteine level. A possible confounder in any analysis of PE is the presence of different ethnic groups, though in the present study all population was of Asiatic origin. In the present study fasting level of homocysteine was studied. Therefore, this is able to exclude a possible effect of dietary factors on homocysteine values¹⁹.

It is possible that, elevated homocysteine concentration injures the vascular endothelium in preeclampsia; thereby it contributes to the pathogenesis of preeclampsia. In addition, vascular endothelium in pregnant women may be more sensitive to injury; therefore moderate elevation in homocysteine levels may lead to endothelial injury with

subsequent activation of various factors that result eventually in preeclampsia. The great limitation of the study is that multivariate linear regression was not done to adjust the other confounder and odd ratio is not calculated to measure the risk assessment of hcy level with PE.

Conclusion

Serum homocysteine was significantly increased in severe PE and mild PE in comparison to without PE groups. However severe PE and mild PE groups did not differ with respect to serum homocysteine. BMI has got an effect to increase homocysteine especially due to weight of the patients; thus a heavy woman with high BMI is at risk of developing PE. Further cohort or case-control studies with large sample should be carried out to evaluate the association of serum homocysteine with PE.

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