

Serum homocysteine in pre-eclampsia and eclampsia

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Abstract

Pre-eclampsia and eclampsia are common obstetrical problem causing adverse effects on pregnancy outcome. Large bodies of evidences suggest that hyperhomocysteinemia is a causal factor of pre-eclampsia/eclampsia. This study designed to explore the association between hyperhomocysteinemia and pre-eclampsia/eclampsia, the knowledge of which expected to be used for prevention of pre-eclampsia and eclampsia. In a case-control study serum homocysteine was measured in 136 controls (healthy pregnant), 84 pre-eclamptic and 120 eclamptic pregnant women. Serum homocysteine in patients with pre-eclampsia ($9.54 \pm 3.21 \mu\text{mol/L}$) and eclampsia ($10.57 \pm 3.39 \mu\text{mol/L}$) found to be significantly increased compared to controls ($6.86 \pm 2.47 \mu\text{mol/L}$)($p < 0.001$). Between pre-eclampsia and eclampsia, homocysteine found to be raised more in eclampsia compared to pre-eclampsia ($p < 0.03$). In conclusion, hyperhomocysteinemia is associated with pre-eclampsia as well as eclampsia, but in eclampsia the severity of homocysteine elevation is more compared to that in pre-eclampsia.

Introduction

Pre-eclampsia/eclampsia is the most common serious medical disorder of human pregnancy, which complicates approximately 5-7% of pregnancy^{1, 2}. Pre-eclampsia is a pregnancy specific, multisystem disorder that is characterized by the development of hypertension and proteinuria after 20 weeks of gestation². Edema is often seen but is not essential to make the diagnosis. If seizures occur as a complication of pre-eclampsia, the term eclampsia is used³. In addition to elevated blood pressure and proteinuria, impaired liver function, increased serum uric acid, decreased platelet count, and symptoms and signs, such as headache, visual disturbances, epigastric pain and pulmonary edema are considered particularly ominous⁴. Hypertension was reported to account for 15% of all antenatal hospitalizations for pregnancy complications⁵. Women who develop pre-eclampsia or eclampsia during pregnancy are at an increased risk of abruptio placentae, acute renal failure, cerebrovascular and cardiovascular complications, and maternal death^{6, 7}.

Pre-eclampsia is still regarded as “a disease of theories” and its etiology has remained poorly understood⁸. Although the specific cause remain unknown, endothelial dysfunction has been considered central in the pathophysiology of pre-eclampsia⁹.

Homocysteine is sulfur containing essential amino acid primarily derived from demethylation of dietary methionine required for the growth of cells and tissues in the human body¹⁰. In hyperhomocysteinemia, homocysteine undergoes auto-oxidation to produce reactive oxygen species (ROS), which inactivates nitric oxide and thrombomodulin leading to endothelial damage and endothelial dysfunction. Homocysteine also interferes with fibrinolytic system adding to the pathophysiology of eclampsia and pre-eclampsia¹¹.

In normal pregnancy serum homocysteine is normally decreased, due either to hemodilution incident to pregnancy or the relative deficiency during pregnancy¹². Maternal hyperhomocysteinemia has been associated with a number of pregnancy associated diseases such as pre-

eclampsia, placental abruption, recurrent pregnancy loss and neural tube defect in newborn¹³⁻¹⁷.

Bangladesh is a densely populated country. Like many other developing countries, we are facing various health related problems including high maternal mortality, which is 3.15 per 1,000 women¹⁸. The incidence of such mortality in developed countries has been reduced to 0.2-0.5% of all deliveries with a case fatality of 2%¹⁹. In Bangladesh, the incidence of pre-eclampsia and eclampsia are alarmingly high and about 16% of maternal deaths are associated with it²⁰. Intrauterine growth retardation, pre-term delivery, low birth weight, fetal death and neonatal death due to complication of pre-term delivery are common perinatal outcomes associated with pre-eclampsia²¹.

To decrease pre-eclampsia and eclampsia related mortality, appropriate prenatal care must be available to all women. Early detection, careful monitoring and treatment of pre-eclampsia are crucial in preventing mortality related to this disorder^{22, 23}.

It has been proposed that hyperhomocysteinemia may be associated with pre-eclampsia as the homocysteine mediated vascular changes are similar to those associated with pre-eclampsia^{24, 25}. With respect to hyperhomocysteinemia several studies found to be done in pre-eclampsia but very few studies so far have been done to explore the association between hyperhomocysteinemia and eclampsia. With the intention to reduce the maternal mortality by preventing pre-eclampsia/eclampsia through serial monitoring of serum homocysteine as a part of antenatal check-up in a developing country like Bangladesh, we have planned this study to explore the association between hyperhomocysteinemia and pre-eclampsia /eclampsia.

Materials and Methods

A case control study was conducted at the Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from January 2005 to December 2006. One hundred thirty six normotensive healthy pregnant women as control (Group I), 84 pregnant women with pre-eclampsia (Group II) and 120 pregnant women with eclampsia (Group III) were included in the study. Subjects were selected from the Department of Obstetrics and Gynecology, BSMMU, Dhaka Medical College and Sir Salimullah Medical College. Study subjects of each group were apparently matched with respect to maternal age,

gestational age and BMI. All study subjects were enrolled in the study after having their deliberate informed written consent. Ethical clearance was taken from the Ethical Committee of BSMMU and other concerned departments.

Pre-eclampsia was diagnosed by a) pregnancy with gestational age >20 weeks, b) systolic blood pressure ≥ 140 mmHg, c) diastolic blood pressure ≥ 90 mm Hg recorded on two separate occasions 6 hours apart and d) 24-hour urinary protein ≥ 300 mg. Patients developing convulsion or coma superimposed on pre-eclampsia were regarded as eclampsia²⁶.

Pregnant women with possible confounding variables like pre-existing hypertension, cardiovascular disease, renal disease, diabetes mellitus or other endocrinopathies and antifolate drug (antiepileptic, methotrexate) therapy were excluded from the study.

Blood samples were collected with all aseptic precautions from all study subjects after an overnight fasting. Samples were centrifuged and serum was separated and stored at -35°C until analysis. Serum homocysteine level was measured by fluorescence polarization immunoassay (FPIA) run on Abbott's AxSYM platform²⁷.

Statistical analysis was performed using SPSS (version 12.00 for windows, software). To find out the statistical significance one way ANOVA test was done among groups and then Mann Whitney's U-test was done between the groups. $P < 0.05$ was considered statistically significant.

Results

Study revealed the mean serum homocysteine concentration in pre-eclampsia to be 9.54 ± 3.21 $\mu\text{mol/L}$ with the median value of 9.04 $\mu\text{mol/L}$ and that in eclampsia to be 10.57 ± 3.39 $\mu\text{mol/L}$ with the median value of 10.07 $\mu\text{mol/L}$. In control subjects mean homocysteine concentration was 6.86 ± 2.47 $\mu\text{mol/L}$ with the median value of 6.28 $\mu\text{mol/L}$.

Table I: Grouping of study subjects with age distribution and BMI

	Normal pregnancy (n=136)	Pre-eclampsia (n= 84)	Eclampsia (n=120)
Age (years)	25.84 \pm 5.43	24.00 \pm 4.14	25.83 \pm 5.69
Gestational age (weeks)	30.80 \pm 4.03	28.70 \pm 4.05	31.70 \pm 3.59
BMI	21.7 \pm 1.7	24.3 \pm 1.2	24.6 \pm 2.3

Data are mean \pm SD

Mann-Whitney U test shows that serum homocysteine concentration significantly increased in both pre-eclampsia and eclampsia compared to control. Homocysteine also found to be significantly raised in eclampsia compared to pre-eclampsia ($p < 0.03$).

Table II: Comparison of serum homocysteine concentration among different groups of study subjects

	Homocysteine ($\mu\text{mol/L}$)	F value*	P value
Normal pregnancy	6.86 \pm 2.47		
Pre-eclampsia	9.54 \pm 3.21	51.423	0.000
Eclampsia	10.57 \pm 3.39		
	Homocysteine (median) $\mu\text{mol/L}$	U value**	P value
Control vs. pre-eclampsia	6.28 vs. 9.04	2762	0.000
Control vs. eclampsia	6.28 vs. 10.07	2977	0.000
Pre-eclampsia vs. eclampsia	9.04 vs. 10.07	4132	0.029

*Level of significance reached by one way ANOVA test (two tailed);
**Level of significance reached by Mann-Whitney U test (two tailed)

Discussion

Serum homocysteine concentration in pre-eclampsia has been reported in a number of studies but the study of homocysteine in eclampsia is scanty. In line with this study, many studies abroad have demonstrated the relationship between hyperhomocysteinemia and pre-eclampsia^{25, 28, 29} while others have refuted an association¹¹. This relationship has been shown in early pregnancy³⁰, in second trimester³¹, and in the third trimester of pregnancy³². Cotter et al³⁰ in their study concluded that in early pregnancy increased homocysteine may be associated with a 4-fold increased risk for development of non severe pre-eclampsia. On the other hand, it has been suggested that mid-trimester plasma homocysteine concentrations in asymptomatic women are not predictive of the subsequent development of pre-eclampsia³³.

In consistent with our findings Gurbuz et al.²⁹ also found homocysteine concentration to be raised in pre-eclampsia and the level in eclampsia being higher than that in severe pre-eclampsia. So, serum homocysteine concentration tends to be positively correlated with the degree of severity of disease. However some study showed no significant difference of homocysteine concentration between pre-eclampsia and eclampsia^{27, 28, 34}, which might be due to smaller sample size.

Folate, vitamin B₁₂, vitamin B₆, and riboflavin are involved in the metabolism of homocysteine.³⁵

Elevated homocysteine is a marker of low B-vitamin status or decreased methylation capacity of cells^{36, 37}. So, vitamin B supplementation could have a role in preventing the elevation of homocysteine in pregnant women³⁵.

This study concludes that elevated homocysteine level is associated with pre-eclampsia and eclampsia and the higher homocysteine concentration in eclampsia compared to pre-eclampsia indicates its subtle association with the severity of disorder as well. So, maternal hyperhomocysteinemia seems to have causal role in the etiopathogenesis of pre-eclampsia /eclampsia. It needs more study to delineate the relationship between the serum homocysteine concentration and the severity of pre-eclampsia and eclampsia.

This study suggests the measurement of serum homocysteine in all pregnant women as a part of routine antenatal check-up and thereby monitoring and management of hyperhomocysteinemia in antenatal period taking into account the B-vitamin supplementation might help substantially to reduce the adverse pregnancy outcome.

Authors' contribution

MMH: Planning, research tool development, supervision and data analysis
TB: Data analysis and manuscript writing
MM: Field work and data collection
NAFI: Field work and data collection
MF: Field work and data collection

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