

Elevated Serum Homocysteine Concentrations in Severe Preeclampsia and Eclampsia

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ABSTRACT

Background & objective: Preeclampsia, a pregnancy-specific syndrome, is a major cause of maternal and perinatal morbidity and mortality all over the world. Several studies have indicated that homocysteine concentrations are increased in women with preeclampsia. However, there is still conflicting evidence on the extent to which elevated maternal homocysteine contributes to this deadly complication of pregnancy. The present study was, therefore, intended to see the association between serum homocysteine and preeclampsia.

Methods: This cross-sectional study was carried out in the Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Dhaka over a period of 2 (two) years from July 2007 to June 2009. Pregnant women with gestational age ranging between 24 – 40 weeks having preeclampsia or eclampsia were considered as cases, while gestational age-matched pregnant women without preeclampsia and eclampsia were considered as controls. However, pregnancy with diabetes mellitus, known renal or hepatic disease, urinary tract infection, cardiovascular disease, and taking anti-epileptics were excluded from the study. A total of 100 pregnant women – 50 cases and 50 controls were selected for the study. Among the cases, 16 had mild preeclampsia, 17 had severe preeclampsia, and 17 had eclampsia.

Result: Two-thirds of the cases and 60% of the controls were in their 3rd decade of life with no significant difference between the study groups ($p = 0.651$). There was no significant difference between the groups in terms of gravidity and gestational age. However, the past history of PE demonstrated its more significant presence in the case group than that in the control group ($p = 0.030$). Out of 50 cases, 30(60%) had severe proteinuria (+++), 15(30%) had moderate proteinuria (++) and 5(10%) had mild proteinuria. The mean serum homocysteine level was significantly higher in mild PE ($7.2 \pm 1.2 \mu\text{mol/L}$) than that in normal pregnant women ($5.3 \pm 1.0 \mu\text{mol/L}$). The concentration of homocysteine increases with the increase in severity of preeclampsia ($p = 0.004$) and turning preeclampsia into eclampsia ($p = 0.027$). The data show as the grade of proteinuria increases progressively (from mild to severe) the concentrations of homocysteine level also increase progressively from $6.3 \pm 1.6 \mu\text{mol/L}$ in mild proteinuria to $11.4 \pm 3.7 \mu\text{mol/L}$ in severe proteinuria.

Conclusion: The serum homocysteine level is significantly elevated in mild PE than that in normal pregnant women. The concentration of homocysteine increases further with the increase in the severity of preeclampsia and in eclampsia.

Key words: Serum homocysteine, severity of preeclampsia, eclampsia etc.

INTRODUCTION:

Preeclampsia is a pregnancy-specific multisystem disorder of unknown etiology, characterized by the new onset of elevated blood pressure and proteinuria after 20 weeks of gestation. It is

considered severe if blood pressure and proteinuria are increased substantially or symptoms of end-organ damage occur. It complicates 5-7% of all pregnancies¹ and is a significant cause of maternal and perinatal mortality and morbidity. If not diagnosed or

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treated early, it can progress to maternal multiorgan failure, coagulopathy, and maternal and fetal death in severe form.^{2,3} In a baseline survey for the assessment of Emergency Obstetric Care Services in Bangladesh, 5% of the total obstetric admission in health facilities were due to preeclampsia and eclampsia.⁴

The pathophysiologic process of preeclampsia is poorly understood, but current concepts include endothelial dysfunction, inflammatory activation, oxidative stress, and some predisposing maternal factors. Endothelial dysfunction is hypothesized to be a central pathophysiological feature of preeclampsia, leading to altered vascular reactivity, loss of vascular integrity, and activation of coagulation cascade.⁵ Most recently homocysteine has been claimed as a factor for vascular endothelial cell injury in preeclampsia with all its consequences. Homocysteine is a sulfur-containing amino acid derived from the metabolic demethylation of dietary methionine, which is abundant in animal protein. It is eliminated from the body via conversion into – a) cystathionine by a reaction catalyzed by vitamin B6 and b) methionine catalyzed by vitamin B2 and folic acid as a cofactor.⁶

Homocysteine is found to be in low concentrations in all tissues under normal conditions but accumulates in tissues and plasma if those catalytic vitamins are depleted.⁷ Any drug, such as methotrexate, or nitrous oxide that reacts with folic acid, vitamin B12, B6 can cause hyperhomocysteinemia.⁸ Homocysteine by auto-oxidation generates superoxide and hydrogen peroxide, both of which damage the arterial endothelial lining or cause endothelial dysfunction. Such endothelial dysfunction results in decreased bioavailability of NO (Nitric Oxide), a vasodilator, antiplatelet aggregator anti-inflammatory, and inhibitor of smooth muscle cell growth.⁹ Thus, endothelial cell dysfunction appears to be a central feature of the pathophysiology of preeclampsia, leading to

altered vascular reactivity, activation of the coagulation cascade, and loss of vascular integrity.¹⁰ Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular diseases, such as atherosclerosis and occlusive vascular disorder.¹¹ The pathogenesis of endothelial dysfunction associated with homocysteine is related to endothelial dysfunction, smooth muscle proliferation, and abnormalities of coagulation. Elevated homocysteine is now recognized as an important risk factor for preeclampsia and eclampsia.⁷

Several studies have indicated that homocysteine concentrations are increased in women with preeclampsia.¹²⁻¹⁴ But there are a few reports concerning hyperhomocysteinemia in patients with eclampsia.^{15,16} So, the present study was designed to investigate whether there is an association between hyperhomocysteinemia and the severity of preeclampsia and eclampsia.⁷

METHODS:

This cross-sectional study was carried out in the Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Dhaka over a period of 2 (two) years from July 2007 to June 2009. Before commencing the study, ethical clearance was taken from the concerned authority of Dhaka Medical College Hospital, Dhaka. Pregnant women with gestational age ranging between 24-40 weeks having preeclampsia or eclampsia were considered as cases, while gestational age-matched pregnant women without preeclampsia and eclampsia were considered as controls. However, pregnancy with diabetes mellitus, known renal or hepatic disease, urinary tract infection, cardiovascular disease, and taking antifolate drugs (anti-epileptics) were excluded from the study. A total of 100 pregnant women-50 cases and 50 controls were selected for the study. Among the cases, 16 had mild preeclampsia, 17 had severe preeclampsia, and 17 had eclampsia. While preeclampsia or eclampsia was exposure variable, serum homocysteine was

outcome variable in this study. Data were processed and analyzed using SPSS (Statistical Package for Social Sciences) version 16.0. The test statistics used to analyze the data were Chi-square (χ^2) Test, Student's t-Test, and ANOVA Statistics. The level of significance was set at 5% and $p < 0.05$ was considered significant

RESULTS:

Table- II shows the age distribution between the groups. Two-thirds of the cases and 60% of the controls were in their 3rd decade of life (21-30 years) with mean ages of the cases and controls 24.6 ± 4.5 years and controls 25.0 ± 5.2 years respectively ($p=0.651$). The majority of the study subjects in either group belonged to a lower social class. There was no significant difference between the groups in terms of gravidity and gestational age. However, past history of PE demonstrated its significant presence in the case group than that in the control group ($p = 0.030$) (Table II). Out of 50 cases, 30(60%) had severe proteinuria (+++ on dipstick test), 15(30%) had moderate proteinuria (++) and 5(10%) had mild proteinuria (Table II).

Table III-IV shows the comparison of serum homocysteine levels among different study groups. The mean serum homocysteine level was significantly higher in mild PE (7.2 ± 1.2 $\mu\text{mol/L}$) than that in normal pregnant women (5.3 ± 1.0 $\mu\text{mol/L}$). The concentration of homocysteine increases with the increase in severity of preeclampsia ($p=0.004$) & turning preeclampsia into eclampsia ($p=0.027$).

Table V shows the association between serum homocysteine concentration and the degree of proteinuria in the case group. As the grade of proteinuria increases progressively (from mild to severe) the concentrations of homocysteine level also increase progressively from 6.3 ± 1.6 $\mu\text{mol/L}$ in mild proteinuria to 11.4 ± 3.7 $\mu\text{mol/L}$ in severe proteinuria. The mean birth weight of the neonates born to preeclamptic women was 2.08 ± 0.37 kg and that of the neonates born to normal

pregnant women was 3.20 ± 0.41 kg. The difference in birth weight between the two groups was statistically significant ($p < 0.05$).

Table I. Comparison of demographic and obstetric characteristics between groups

Characteristics	Group		p-value
	Case (n=50)	Control (n=50)	
Age# (years)			
≤ 20	10(20.0)	9 (18.0)	--
21 – 30	34(68.0)	30(60.0)	--
>30	6 12.0	11 22.0	--
Mean ± SD	24.6 ± 4.5	25.0 ± 5.2	0.651
Socio-economic status*			
Lower class	43(86.0)	35(70.0)	0.053
Middle class	7 (14.0)	15(30.0)	
Gravid*			
Primi	27 (54.0)	20 (40.0)	0.161
Multi	23 (46.0)	30 (60.0)	
Gestational age# (weeks)			
≤ 34	30 (60.0)	25 (50.0)	--
>34	20 (40.0)	25 (50.0)	--
Mean ± SD	33.7 ± 3.1	33.9 ± 5.0	0.847
Past history of PE*	7(14.0)	1(2.0)	0.030

*Data were analyzed using Chi-squared (χ^2) and were presented as n(%).

#Data were analyzed using Unpaired t-Test and were presented as mean ± SD.

Table II. Distribution of cases by proteinuria (n = 50)

Proteinuria	Frequency	Percentage
Mild	5	10.0
Moderate	15	30.0
Severe	30	60.0

Table III. Comparison of serum homocysteine concentration among different groups

Proteinuria	Normal (n=50)	Mild PE (n=16)	Severe PE (n=17)	Eclampsia (n=17)	F-value	p-value
Serum homocysteine ($\mu\text{mol/l}$)	5.3 ± 1.0	7.2 ± 1.2	10.2 ± 3.5	13.3 ± 4.3	50.97	0.001

Data were analyzed using ANOVA statistics and were presented as mean ± SD.

Table IV. Multiple comparisons made by posthoc Hochberg Test

Multiple comparisons	t-value	p-value
Normal Vs Mild PE	5.81	0.001
Normal Vs Severe PE	8.82	0.001
Normal Vs Eclampsia	12.29	0.001
Eclampsia Vs Mild PE	5.50	0.001
Severe PE Vs Eclampsia	2.32	0.027
Severe PE Vs Mild PE	3.22	0.004

Table V. Relationship between serum homocysteine concentration and proteinuria

Proteinuria	Serum homocysteine (µmol/L)	F-value	p-value
Mild	6.3±1.6		
Moderate	8.9±3.6	5.25	0.016*
Severe	11.4±3.7		

Data were analyzed using ANOVA statistics and were presented as mean ± SD.

DISCUSSION:

The purpose of the present study was to evaluate the serum level of homocysteine and its association with the severity of preeclampsia. The finding of the present study is strengthened by the fact that the case and control populations were similar in age, (mostly in their 3rd decade of life) gestational age, and gravidity. Among the cases 60% had severe proteinuria, 30% had moderate (++) proteinuria and rest 10% had mild proteinuria. An almost similar result was observed in Ferdous et al's study.¹⁷

The present study demonstrated that the mean serum homocysteine level was significantly higher in preeclampsia than that in the control group and that the mean serum homocysteine of preeclamptic women progressively increases with the severity of preeclampsia with the highest level of serum homocysteine being observed in eclamptic women. These results are fortified by the findings of other studies as well.^{10,13,14,16} This study also revealed a significant association between serum homocysteine concentration and proteinuria. Our study also showed that the newborn birth weight was significantly lower in cases (2.08 ± 0.37 kg) than that in controls (3.2 ± 0.41kg). This finding suggests that hyperhomocysteinemia could be a risk factor for low birth weight, which is consistent with the findings of Ingec et al.¹⁵

A meta-analysis demonstrated a strong association between elevated homocysteine and vascular occlusive disease,¹⁸ oxidative stress or endothelial cell dysfunction, and evidence of preeclampsia.¹⁹ The present study demonstrated a similar relationship between increased homocysteine levels proportionate to the severity of preeclampsia. Thus,

the elevated concentrations of homocysteine in preeclampsia may indicate that the patient is progressing to severe form preeclampsia or eclampsia.

CONCLUSION:

The study concluded that the serum homocysteine level is significantly higher in preeclampsia than that in normal pregnant women and that the serum homocysteine of preeclamptic women progressively increases with the severity of preeclampsia with the highest level of serum homocysteine being observed in eclamptic women. The elevated homocysteine concentration in preeclampsia and eclampsia might be a risk factor for low birth weight.

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