Original Research Article

Serum homocysteine and folate levels as a predictor of materno-fetal outcome in preeclamptic women

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Abstract

Aim and Background: This study was done to measure the serum homocysteine and serum folate levels and correlated with materno-fetal outcome in women with preeclampsia. **Materials and Methods:** This study was a prospective study which was conducted in department of obstetrics and gynaecology in : Deccan college of Medical Sciences., Hyderabad from November 2009 to October 2010. **Results:** The mean gestation of women in both the groups was 30.14±2.77 and 29.44±5.89 weeks in group A and group B respectively. Mean serum homocysteine levels in group A were higher when compared to that of group B, both at enrolment (9.59±2.57 vs 7.42±1.48), at delivery (16.22±4.89 vs 9.22±2.22) and statistical significant mean rise in homocysteine levels was observed in both the groups from enrolment to delivery. Women with abruption and neonatal death had mean homocysteine levels rise significantly. **Conclusion:** A reliable marker for predicting the preeclampsia severity and adverse pregnancy outcome is serum homocysteine which helps in reducing maternal and fetal morbidity and mortality, especially in women with early preeclampsia onset.

Key Words: Homocysteine, Pre-eclampsia, Maternal complications.

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INTRODUCTION

Worldwide, pre-eclampsia is a major contributor of maternal and perinatal mortality and along with other hypertensive disorders of pregnancy complicates 2-8% of pregnancies. Pre-eclampsia is defined as proteinuria and hypertension which is detected in the second half of pregnancy i.e. after 20 weeks of gestation[1]. Complications lead to maternal morbidity, mortality and adverse perinatal outcome and depends on severity of pre-eclampsia. The pre-eclampsia exact cause remains unclear. The pathogenic focus for all manifestations of pre-eclampsia is placenta.[2] Systemic vasospasm is one of the most striking physiologic changes in pre-eclampsia which is responsible for decreased perfusion of virtual organs. Homocysteine has three main metabolic fates namely to be re-methylated to methionine, to enter the cysteine biosynthetic pathway, or to be released into extracellular medium such as plasma and urine.[3] Homocysteine causes endothelial cell damage due to oxidative stress and is also considered as pre-eclampsia. Homocysteine is indirectly acting through its oxidation and concomitant production of reactive oxygen species which was suggested by an alternative hypothesis. Raised homocysteine levels is associated with folate deficiency which results in increased risk of vascular disease[4]. No evidence of lowering homocysteine by increased folate intake results in vascular disease risk diminution was observed. With respect to homocysteine metabolism, considerable genetic heterogeneity exists because of methylene tetrahydrofolate reductase polymorphins.[5] Between individuals and different intake levels, folate requirements may vary and also control hyperhomocysteinemia. Early preeclampsia prediction requires close surveillance and preventive strategies. Many studies have been done to predict preeclampsia but none have been effective in predicting preeclampsia onset. Therefore, this study was done to measure the serum homocysteine and serum folate levels and correlated with materno-fetal outcome in women with preeclampsia.

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MATERIALS AND METHODS

This study was a prospective study which was conducted in department of obstetrics and gynaecology in : Deccan college of Medical Sciences., Hyderabad from November 2009 to October 2010. Institutional Ethics committee approval was taken for the study. 150 women were selected in the study. Group A consisted of 75 women with preeclampsia and group B consisted of 75 normotensive pregnant women. Informed consent was taken from all the participants.

Inclusion criteria: Women with resting blood pressure of ≥ 140/90 mmHg on two occasions at least 7 hours apart and significant proteinuria in urine samples were included in the study. Subjects selected were having gestational age between 24-32 weeks and were singleton pregnant.

Exclusion criteria: women with chronic hypertension, twin or multifetal gestation, neural tube defects, diabetes mellitus, repeated miscarriages, abruptio placenta, smoking history, pre-existing renal disease, liver disease, medical illness, thromboembolism and severe anaemia. Participants were subjected to history and detailed examination. The subjects were not in labour and had no signs of infection. Subjects were on folic acid supplementation during course of pregnancy. At any time of day, maternal venous blood sample was collected in a sterile vial and kept at room temperature for 30 minutes and centrifuged at 3000 rpm for 10 minutes. The samples were light sensitive, so precautions were taken to prevent the deterioration. After centrifugation for 2 hours, 500 microliter sample was transferred into storage tube. Till the time of analysis, the serum aliquots were frozen at -20 degree celsius. Homocysteine is stable for at least 4 days at room temperature, after separation of serum from cells, and it is stable for several weeks at 0-8 degree Celsius and stable for several months or years at -20 degree Celsius. Homocysteine and folate were collected twice, once at enrolment and second at delivery. Statistical analysis was performed by using statistical package (SPSS 18.0). All values were expressed as mean and standard deviations. For comparing mean of groups, independent t-test was performed. Pearson's correlation coefficient was used to perform correlation analysis. 95% confidence interval was chosen and p value of <0.05 is considered as statistically significant.

RESULTS

There were similarities in maternal demographic characteristics between the groups. In the study group (Group A), the mean age of women was 24.36±4.51 years and in control group (Group B), the mean age of women was 23.87±3.66 years. The mean gestation of women in both the groups was 30.14±2.77 and 29.44±5.89 weeks. 60% of the cases were delivered before 32 weeks of gestation in group A, 40% at gestation of 33-36 weeks and 8% of the cases reached term. In group B, 93% of the cases were delivered at term. In group A, mean diastolic blood pressure was 99.21±8.95 and in group B, it was 67.14±5.98. In group A, mean 24 hour proteinemia was 1.49±0.47 gm/L and it was 0.11±0.88 gm/L in group B. Mean uric acid was 6.55±1.49 mg/dl in group A and 3.33±0.54 mg/dl in group B (pvalue-0.00). Triglyceride levels were 299±98.1 mg/dl in group A and in group B, it was 197.35±48.74 mg/dl.

Table 1: Homocysteine and folate levels in study groups

	Group A			Group B		
	Enrolment	Delivery	P value	Enrolment	Delivery	P value
Serum Homocysteine (µmol/L)	9.59±2.57	16.22±4.89	0.000	7.42±1.48	9.22±2.22	0.000
Serum Folate (ng/dl)	9.44±5.97	10.87±5.44	0.140	9.47±6.11	10.27±2.58	0.230

Table 1 shows that mean serum homocysteine levels in group A were higher when compared to that of group B, both at enrolment (9.59±2.57 vs 7.42±1.48), at delivery (16.22±4.89 vs 9.22±2.22) and statistical significant mean rise in homocysteine levels was observed in both the groups from enrolment to delivery. In serum folate levels, there was an insignificant difference in both the groups right from enrolment to delivery.

Table 2: Maternal complications with mean rise in homocysteine levels

	Group A (n=75), No., %		P value
Severe Hypertension (BP≥160/110)	Present	35 (46.6)	0.00
	Absent	40 (53.4)	
Deranged renal function (S.Cr. >1.2mg/dl)	Present	10 (13.3)	0.014
	Absent	65 (86.7)	
Deranged liver enzyme (AST>40µ/mL)	Present	10 (13.3)	0.02
	Absent	65 (86.7)	
Thrombocytopenia (<1.0 lac)	Present	11(14.7)	0.06
	Absent	64(85.3)	
Eclampsia	Present	12(16)	0.008
	Absent	63(84)	

Table 2 shows that it was observed that high mean rise in serum homocysteine levels in women developing complications like severe hypertension, deranged liver enzyme and thrombocytopenia and eclampsia was statistically significant.

Table 3: Comparison of maternal outcome with homocysteine rise

		Group A (n=75), No., %	P value
Abruption	Present	10 (13.3)	0.03
	Absent	65 (86.7)	
Pregnancy outcome	Full term live birth	05 (6.7)	0.00
	Preterm live birth	35 (46.6)	
	Perinatal death (IUD)	30(40)	
	Perinatal death (NND)	5(6.7)	

Table 3 shows that women with abruption and neonatal death had mean homocysteine levels rise significantly.

Table 4: Comparison of fetal outcome with homocysteine levels rise

			Group A (n=75), No., %	P value
Birth weight	ELBW (<1Kg)		24 (32)	0.006
	VLBW (1-1.49 Kg)		35 (46.7)	
	LBW (1.5-2.49 Kg)		16 (21.3)	
APGAR at 1 minute	<7		15	0.42
	>7		29	
APGAR at 5 minutes	<7		5	0.20
	>7		36	
Perinatal death	Yes	IUD	25 (33.3)	0.007
		NND	06 (8)	
	No		44 (58.7)	

Table 4 shows that in between mean homocysteine levels rise and birth weight, significant negative correlation was observed. While in babies with low APGAR score, insignificant negative relation was observed. This shows that all the above parameters had higher mean homocysteine rise statistically significant.

DISCUSSION

In the present study, the mean gestation of women in both the groups was 30.14±2.77 and 29.44±5.89 weeks in group A and in group B. This was similar to the mean gestation of women in Md. Hoque *et al* study[6]. As the samples were taken prior to preeclampsia onset, there was difference in mean gestation at enrolment in Cotter *et al* study[7]. Acilmis *et al* and Powers *et al* study results were comparable to the present study. Triglyceride levels were 299±98.1 mg/dl in group A and in group B, it was 197.35±48.74 mg/dl in the present study and it was similar to Md.Hoque *et al* study[6], cotter *et al*[7], Acilmis *et al*[8], Powers *et al*[9] studies. Mean homocysteine levels at enrolment in both the groups in the present study was comparable to studies which were conducted by Md.Hoque *et al* study[6], cotter *et al*[7] and Powers *et al*[9] studies. In Ingec *et al*[10], Singh *et al*[11] studies, mean homocysteine levels were higher. Mean homocysteine levels were significantly higher in Group A as compared to Group B both at enrolment and delivery ($p < 0.05$). Women with higher rise in mean homocysteine levels were associated with an increased risk of adverse maternal complications ($p < 0.05$). Mean rise in homocysteine levels were significantly higher in women who developed abruption and perinatal death ($p < 0.05$) while no correlation was found with the mean change in serum folate levels ($p > 0.05$) in Namitha Jain *et al*[12] study. Hogg *et al*[13] suggested that if levels of HC were measured in early gestation, they might have found elevated plasma HC concentration both in early pregnancy and at time of delivery in cases with early onset severe disease. Leeda *et al*[14], gave folic acid and Vit B6 supplementation to 14 patients with a previous history of hyperhomocysteinemia and severe preeclampsia/ HELLP syndrome in previous pregnancy and found that although half patients developed preeclampsia, but the outcome was much better. This suggests that hyperhomocysteinemia can be due to genetic or nutritional defect or both. Study by Hoque *et al*[6] and Ingec *et al*[10] have reported higher plasma levels of homocysteine in women with eclampsia than women with mild preeclampsia group and control subjects. Similar results were obtained in the present study. In study by Makedos *et al* on 26 cases, delivery by caesarean was seen in 75%, abruption in 7% and intrauterine deaths in 7% of the cases.[15] While in present study, delivery by caesarean occurred in 27%, abruption in 19% and intrauterine deaths in 35%. Mean age of enrolment was 34±6.0 weeks in study by Makedos *et al*[15] while in present study it was 30.06±1.33 weeks. In the present study, mean homocysteine levels rise and birth weight,

significant negative correlation was observed. While in babies with low apgar score, insignificant negative relation was observed. This shows that all the above parameters had higher mean homocysteine rise statistically significant. Low birth weight babies were also observed in studies by Powers *et al* and Makedos *et al.*[15]

CONCLUSION

A reliable marker for predicting the preeclampsia severity and adverse pregnancy outcome is serum homocysteine which helps in reducing maternal and fetal morbidity and mortality, especially in women with early preeclampsia onset.

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