

A Study of Serum Homocysteine Levels during Normal Pregnancy and Pre-eclampsia

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ABSTRACT

Elevated plasma homocysteine level is a risk factor for vascular problems, including atherosclerosis and arterial thrombosis. Hyperhomocysteinemia during pregnancy causes endothelial dysfunction as a result of increased oxidative stress. The ultimate results are vasculopathy and platelet dysfunction.

The aim of the study was to find the association of the homocysteine levels in pre-eclampsia and normal pregnancy and to know, if there exists any correlation between serum homocysteine levels and severity of PET.

Study design: Prospective case control study

Study place: Women attending antenatal OPD or admitted in antenatal ward of Department of Obstetrics and Gynecology, NKPSIMS.

Study duration: 1 March 2010 to 1 September 2010

Study population and sample size

Group 1: 30 pregnant normotensive healthy women, GA 28 to 42 weeks and fulfilling inclusion criteria.

Group 2: 30 pregnant women, GA 32 to 42 weeks with pre-eclamptic toxemia (mild and severe) and meeting inclusion criteria.

30 pre-eclamptic women were matched with 30 normotensive women of same gestational age.

Results: Mean level of homocysteine was significantly raised in pre-eclamptic women than in control group.

The rise in mean serum homocysteine level was more in women with severe PET as compared to those with mild PET, though not statistically significant.

The women in pre-eclamptic group having increased homocysteine levels showed increased incidence of IUGR, IUD, still birth and abruptio placenta and increased incidence of cesarean section.

Conclusion: It is concluded from our study that serum homocysteine levels were significantly elevated in women with PET compared with control group and strong correlation may exist between serum homocysteine levels and severity of pre-eclampsia.

Keywords: Hyperhomocysteinemia, PET, Severe PET.

INTRODUCTION

Elevated serum homocysteine level is a risk factor for vascular diseases. Hyperhomocysteinemia could result from a genetic defect on enzyme participating in homocysteine synthesis and metabolism or it could be because of deficiency of folic acid, vitamin B6, B12. The vascular changes induced by homocysteine are similar to those associated with PET and include endothelial dysfunction.

Homocysteine, a sulphur containing amino acid, is an immediate product of methionine metabolism. Methionine cannot be stored in liver and is demethylated to homocysteine for storage until needed. The concentration of plasma homocysteine is regulated by several factors, including genetically determined enzymes and environmental factors.

When proteins are metabolized, they are broken down into individual amino acids, including sulphur containing amino acid, methionine. Methionine is in turn broken down further in several steps to produce homocysteine, which once formed can be

removed from the body in only two ways. Firstly, it can be remade into methionine through a process known as remethylation. This requires FA and vitamin B12. Vitamin B12 functions as an essential cofactor. Secondly, homocysteine can be converted into amino acid cysteine through transsulphuration which again requires B12. So, if a person ingests lots of protein and there is not enough of FA and vitamin B12 to digest it, it can cause hyperhomocysteinemia. If FA, B6, B12 levels rise, it decreases homocysteine levels.

Homocysteine damages smooth muscle of the vessel wall, creating a scratch inside the vessel where plaque can build up. Homocysteine is critically important during pregnancy. High maternal homocysteine levels increase the chance of miscarriage as PET or placental abruptio. It can also lead to IUGR, LBW, prematurity and congenital malformations.

The present study was planned to know homocysteine levels in normal pregnancy and PET patients and to find out the correlation between severity of PET.

AIMS AND OBJECTIVES

Primary: To find correlation between serum homocysteine levels in normal pregnancy and pregnancy with pre-eclamptic toxemia in rural population based on tertiary care center.

Secondary: To know/correlate, if there exists any correlation between serum levels and severity of PET.

Study design: Prospective case control study

Study place: Department of Obstetrics and Gynecology, NKPSIMS

Study duration: 1 March 2010 to 1 September 2010

Study Population and Sample Size

Group I: 30 control

Group II: 30 study

Gestational age: 28 to 42 weeks

Inclusion Criteria

All women /patients: Booked antenatal women in the age group of 21 to 35 years and from lower socioeconomic GP (modified BG Prasad classification PCI 2009 < 485/month PCI).

Sure of gestational age (LMP or USG in 1st and early 2nd trimester).

Pregnant women with gestational age between 28 and 42 weeks.

Exclusion Criteria

DM/essential HT/RPL/diagnosed case of abruptio placenta/preterm labor/smoking/tobacco chewers/liver disease/severe anaemia/not willing to participate multifetal pregnancy/pregnancy with APL syndrome.

MATERIALS AND METHODS

Group I: 30 pregnant normotensive healthy women, GA 28 to 42 weeks with normal blood pressure and fulfilling inclusion criteria.

Group II: 30 pregnant women with pre-eclamptic toxemia, age 21 to 35 years, gestational age 28 to 42 weeks, with diagnosed PET by increase in BP 140/90 mm Hg on more than two occasions or systolic BP > 30 or diastolic BP > 15 mm Hg or MAP > 105 mm Hg with or without proteinuria.

The women who were fulfilling the inclusion criteria were grouped into two as mentioned. Detailed obstetric, medical, menstrual, treatment and dietary history were noted. The general

examination, systemic and obstetrics examination were done and they were subjected for routine investigations, like Hb, urine albumin and sugar, blood grouping and Rh typing, VDRL, HBsAg, HIV, USG. In the women of group II (with PET), special investigations were done apart from routine, i.e. blood urea, serum creatinine, serum uric acid, BT, CT, platelet count. Severity of PET was diagnosed depending on the clinical findings, i.e. BP > 160/90 with albuminuria and presence of warning symptoms. Serum homocysteine levels were done in all the patients.

Sample Collection

- Subjects were fasting for 4 to 5 hours.
- 5 ml venous blood from antecubital vein in coded bulbs/ bottles
- Sample immediately transferred to biochemistry department and centrifuged within 30 minutes
- Clear serum collected in coded bulbs and stored in refrigerator
- Homocysteine levels measured by ELISA method within 3 weeks of collection.

OBSERVATIONS AND RESULTS

Table 1 shows that women with pre-eclampsia were younger and more often primiparas.

Table 2 shows average of homocysteine levels in pregnant normotensive (group I) was lower as compare to nonpregnant women and it was significantly raised in patients of pre-eclamptic toxemia.

Table 3 shows that serum homocysteine levels remained unchanged in 43.33% of patients with normal BP whereas it decreased in 56.67% patients. As compared to this, patients with PET showed normal homocysteine levels in 13.3% patients and raised levels were seen in 86.67% patients. This is statistically highly significant.

Table 4 shows that rise in homocysteine level was more in women with severe PET as compared to those with mild PET, though not statistically significant. As the sample size was small, more studies with more no. of patients is required to established statistical significance.

Table 2		
Average homocysteine levels in nonpregnant, pregnant normotensive (group I) and pregnant women with PET (group II)		
Nonpregnant women	Group I	Group II
55.5 µmol/L	26.7 µmol/L	98.7 µmol/L

Table 1					
Age and parity distribution of the control group (GI) and study group (GII)					
		Group I (n = 30)		Group II (n = 30)	
		No. of patients	% of patients	No. of patients	% of patients
Age	21-30	24	80	21	70
	31-35	6	20	9	30
Parity	Primi	18	60	21	70
	1-3	12	40	9	30

Table 3 Association of homocysteine levels in normotensive pregnant women and pregnant women with PET

Group	Homocysteine levels			Total
	Normal	Increase	Decrease	
Normotensive pregnant women	13 (43.33%)	0	17 (56.67%)	30
Pregnant women with PET	4 (13.33%)	26 (86.67%)	0	30
Total	17	26	17	60

Chi-square 6.65, $p = 0.009$ (highly significant) and odds ratio = 4.97

Table 4 Association of rise in homocysteine levels in pregnant women with mild PET and severe PET

Group	Homocysteine levels		Total
	Normal	Increase	
Pregnant women with mild PET	4 (19.05%)	17 (80.95%)	21
Pregnant women with severe PET	0	9 (100%)	9
Total	4	26	30

Fisher exact test $p = 0.29$ (not significant)

Incidence of cesarean section was high in group II, out of 30 women of PET, 17 (57%) needed CS as compared to group I where four needed CS (10.9%).

The incidence of IUGR 14 (42%), IUD two (6.66%) was more with severe PET. Severe IUGR was seen in four out of 10 women with severe PET with raised Sr HCY level and LBW were 14 (42%) with raised Sr HCY level.

DISCUSSION

Dr Kilmer McCully in 1960 described the importance of homocysteine to human health. Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity. Incidence of PET in 8 to 10%, though exact cause of PET is not known, the basic pathology is endothelial dysfunction and intense vasospasm.⁵ Homocysteine is critically important during pregnancy. High maternal homocysteine level (hyperhomocysteinemia) causes endothelial damage and dysfunction, platelet dysfunction, thrombus formation and smooth muscle proliferation. Probably, this causes increased incidence of PET, miscarriage, IUGR, placenta abruption, LBW, etc. Also hyperhomocysteinemia causes increased oxidative stress, thereby causing endothelial dysfunction and PET (pre-eclamptic toxemia).

V Singh, H Gupta et al¹ studied homocysteine levels during normal pregnancy, PET and correlation between HCY level and severity of PET and concluded that hyperhomocysteinemia was observed in patients of PET, and the HCY levels were directly correlating with the severity of PET and p -value < 0.017 and was highly significant.¹ A similar study concluded that serum homocysteine levels were high in pts of PET, p -value was < 0.01 .² Another study concluded that pregnant women with high homocysteine levels have 7.7 fold more risk of PET compared to normal p -value was < 0.001 .^{3,12} Another study concluded that serum homocysteine levels were significantly elevated in patients of PET.⁴ Homocysteine levels were

significantly high in patients with PET with value < 0.014 .⁶ R Noto, S Neri et al⁷ concluded that high-risk level of HCY confined pregnant women belong to high-risk groups for vascular damage but not on development of PET. Hoang Y, Lvoz et al⁸ studied 59 patients of PET in China and compared them with normal and concluded that there was significant difference of Sr HCY levels in two groups with p -value 0.05. Cottar M, Mulley A et al⁹ also found that high serum HCY levels in patients of PET, Wand I, Truding BJ et al¹⁰ studied and concluded that Sr HCY levels were high in pts of PET as compared to normotensive women. Georgios M, Alexis P, Areti H et al¹¹ studied Sr HCY levels FA and B12 levels in pregnancy with PET and concluded that hyperhomocysteinemia appears to be more common among pre-eclamptic gravid than normal control suggesting the endothelial cell damage. Our study where we selected patients of pre-eclampsia without previous history of PET in previous pregnancy, confirms these findings with significantly elevated levels of serum homocysteine in pre-eclamptic patients (group I) 98.7 $\mu\text{mol/L}$, compared to women with normal blood pressure of same gestational age (group II) 26.7 $\mu\text{mol/L}$ showing p -value of (0.009) which was highly significant. There was also some correlation between Sr HCY and severity of PET. The incidence of fetal and maternal complications were high in study group (PET) as compared to control group, like IUGR 14 (42%), IUD two (6.66%), still birth (3.1%), abruptio placenta two (6.66%). Similar findings were also noted by Georgios M, Alexis P, Areti H et al in their study.

CONCLUSION

Hyperhomocysteinemia appears to be more common among pregnant women with pre-eclamptic toxemia when compared to normotensive pregnant women of same gestational age suggesting that endothelial cell damage in these patients may be mediated by hyperhomocysteinemia. It is concluded that in

our study homocysteine levels are significantly high in patients with pre-eclampsia compare with control group. The severity of PET and increased HCY levels were correlated. There were more fetal complications noted in the study group with high Sr HCY levels as compare to control group. But the limitation of the study was the serum folic acid, and B12 levels were not done in the patients. More studies in more number of patients are needed. The present study concluded that serum homocysteine levels were significantly high in women with pre-eclamptic toxemia and more fetal complications were noted in these patients suggesting strong correlation of hyperhomocysteinemia and pre-eclamptic toxemia.

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