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Original Article

Homocysteine: Association with preeclampsia and normotensive pregnancy

Singh Urmila [1], Gupta HP [2], Singh RK [3], Shukla Manju [4], Mehrotra Seema [5], Prasad Shweta [6]

[1] *Associate Professor,* [2] *Professor,* [3] *Professor & Head,* [4] *Professor,* [5] *Lecturer,* [6] *Senior Resident*

Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow.

Abstract

Objectives: To find out the changes in homocysteine levels that occur during normal pregnancy with PET and also to find out correlation between homocysteine concentration and PET. *Methods:* The study was conducted on 90 women, of whom 30 were controls which included normotensive non-pregnant women. Study group I consisted 30 pregnant normotensive women; study group II consisted 30 pregnant women with PET. Serum homocysteine was measured in all subjects using fluorescence polarization immunoassay. *Results:* Control group had the highest mean homocysteine levels, while the study group I had least mean homocysteine levels ($p<0.001$). Levels were significantly higher in subjects with BP >146/100 mm of Hg as compared to those with BP >140/90 and <146/100 ($p=0.017$). There was significant difference between the study groups I and II at same gestational age. *Conclusions:* Hyperhomocysteinemia was observed in pre-eclamptic females; it was also found that homocysteine levels were directly correlated with severity of preeclampsia.

Key words: Homocysteine, hyperhomocysteinemia, preeclampsia

Introduction

Homocysteine results from the demethylation of essential amino acid methionine consumed in the diet. Our body cannot store methionine so it is transported to the liver and demethylated to homocysteine for storage until needed. About 50% of it is remethylated back into methionine and the other 50% is transulfurated into cystathionine, a source of cysteine. The concentration of plasma homocysteine is regulated by several factors which include genetically determined metabolic enzyme alterations and environmental factors.

Elevated homocysteine levels confer an independent and incremental risk for vascular disease, direct endothelial toxicity, failure of nitric acid oxide release and platelet abnormalities. Homocysteine and hyperhomocysteinemia are relatively new concepts in obstetrics. Homocysteine may provide the missing link in the etiology of preeclampsia.

The present study was planned with the aim to know the concentration of homocysteine in preeclampsia and normotensive pregnant women, and find out the correlation between homocysteine concentration and preeclampsia.

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Correspondence :
Dr. Mehrotra Seema
1, Gautam Palli, Lucknow - 226 001
0522-2620966, 9335924300
email : mehrotra.seema@gmail.com

Methods

It was a cross sectional case control study. Ninety women were recruited, out of which 30 women were in control group which included normal healthy normotensive nonpregnant women. Sixty antenatal women with singleton pregnancy and gestational age 28-40 weeks were included in the study group. The study group was further divided into two subgroups; study group I included 30 normotensive pregnant women and study group II included 30 preeclamptic pregnant women. Preeclampsia was diagnosed by blood pressure ≥140/90 mm of Hg on more than two occasions and persistent proteinuria 30 mg/dl (>1+dipstick) in random urine samples. Women with diabetes mellitus, chronic hypertension, renal or liver disease, history of thromboembolism, neural tube defects, repeated miscarriage, abruptio placentae, preterm labor and delivery, anemia, history of smoking and history of prior significant medical illness were excluded from the study.

All the women were subjected to detailed history, examination and all were surveyed for the use of iron, folic acid, vitamins and any other drugs. Besides routine antenatal investigations in all pregnant women and special investigations in preeclamptic women, all the women of control and study groups were subjected to hemoglobin and general blood picture to rule out anemia and folic acid deficiency. Serum homocysteine was measured in all subjects.

For the measurement of homocysteine, 5 ml of blood sample was drawn from the antecubital vein and collected in the blood collecting tube. All the specimens were transported to the laboratory within 30 minutes of collection. Thereafter, specimens were centrifuged for 5-7 minutes at 3000 rpm. Then clear serum was transferred in a plastic vial and stored in refrigerator until analysis. Fluorescence polarization immunoassay was used for determining total homocysteine levels in blood using AXSYM machine and ABBOTT kit from ABBOTT Diagnostics, USA.

For the purpose of analysis, statistical package for social sciences version 10.0 has been used. Chi-square test, analysis of variance and student 't' test have been used for statistical analysis. For the purpose of this study 95% confidence level has been chosen and corresponding 'P' value < 0.05 has been taken as significant.

Results

A total of 90 women were included in this study. They were distributed in three different groups as discussed above. The mean age of women in the control group was 28.03±3.846 years, whereas in study groups I and II it was 25.06±2.803 and 25.67±3.406 years respectively. There was no statistically significant difference in the age of the three groups. Most of the women in all the groups were nulliparous and P1 + and were comparable to each other. All the three groups were well matched according to religion, socioeconomic status and dietary habit. Most of the women (>60%) of study groups I and II were 36-40 weeks of gestational age and two third of the antenatal women were booked.

Table 1 shows the homocysteine levels in different groups. Control group had the highest mean homocysteine levels (17.030±5.693 mmol/L) while study group I had least homocysteine levels (11.588±4.011 mmol/L). Significant difference were observed between control and study group I ($p<0.001$) as well as study group I and study group II ($p=0.007$).

Table 2 shows homocysteine levels in the study group II (PET) according to blood pressure. The homocysteine levels (16.698±4.182 mmol/L) of women whose blood pressure was ≥146/100 mm Hg were significantly higher than the homocysteine levels (13.076±3.573 mmol/L) of the women whose blood pressure was ≥140/90 and <146/100 mm of Hg ($p=0.017$). This shows that homocysteine levels are directly correlated with severity of preeclampsia.

The homocysteine levels of women of the study group II (PET) with blood pressure ≥146/100 mm of Hg (16.698±4.182 mmol/L) were significantly higher than that of normotensive pregnant women of the study group I (11.588±4.011) ($p=0.001$); but no significant difference was found in the homocysteine levels between study group I and study group II (PET) women with blood pressure ≥140/90 and <146/100 mm of Hg, as shown in Table 3.

In this study, pregnant women in study group I & II were between 28 and 40 weeks of gestational age. We did not find any significant difference in homocysteine levels at different gestational age in the same group.

Table 1: Homocysteine levels in different groups.

Group	Number of cases	Range of homocysteine levels	Mean homocysteine levels (µmol/L)	Standard deviation
Control	30	7.80-28.37	17.030	5.693
Study group I	30	5.39-18.50	11.588	4.011
Study group II	30	6.40-23.07	14.524	4.168
Comparison		**'t'**	**'p'**	
Control vs. Study group I		4.280	<0.001	
Control vs. Study group II		1.945	0.057	
Study group I vs. Study group II		2.780	0.007	

Table 2: Homocysteine levels in study group II (PET) according to blood pressure.

Group	Range	Homocysteine level
=140/90(n=18)	6.40-18.90	13.076±3.573
=146/100(n=12)	9.96-23.07	16.698±4.182
't' value		2.542
'p' value		0.017

Table 3: Homocysteine levels in hypertensive subjects of study group II and normal subjects of group I.

Group	Range	Homocysteine level
Study group II ≥140/90(n=18)	6.40-18.90	13.076±3.573
Study group II ≥146/100(n=12)	9.96-23.07	16.698±4.182
Study group I (n=30)	5.39-18.50	11.588±4.0119
Study group II ≥140/90 vs. Study group I	't' value = 1.294, p=0.202	
Study group II ≥146/90 vs. Study group I	't' value = 3.686, p=0.001	

Discussion

Preeclampsia is a leading cause of maternal and fetal abnormality. Although the exact, cause of preeclampsia is still unknown, we have learnt that in preeclampsia the basic pathology is endothelial dysfunction and intense vasospasm. Elevated plasma homocysteine concentration is an independent risk factor for peripheral vascular diseases and for coronary artery diseases.

For this study, total 90 women were recruited. In our study, the control group comprised of normal healthy normotensive nonpregnant women. Walker et al in their study of changes in homocysteine levels had also taken nonpregnant women as controls[1].

In the present study the mean homocysteine levels in control group was 17.030±5.693 mmol/L. The review article of Ueland et al[2] showed that the value between 5 and 15 mmol/L in fasting subjects are normal. In our

study, the mean homocysteine levels in study group I (normotensive pregnant) was 11.588±4.011 mmol/L, which is comparable to that reported by Kang[3], (9.39±13.03 mmol/L in normotensive pregnant women). The control group had highest mean homocysteine levels (17.030±5.693 mmol/L) and the study group I had the least mean homocysteine levels (11.586±4.011 mmol/L) and the difference between the two was statistically significant (p<0.001). Our findings are supported by the study of Walker et al[1] which shows that homocysteine levels were significantly lower in pregnancy as compared to nonpregnant control group (p<0.001). Levels of homocysteine are generally lower during pregnancy either due to physiological response to pregnancy, increase in estrogen, hemodilution or increased demand for methionine by both mother and the fetus [4].

On comparing the homocysteine level in the control group with that in the study group II (PET), no statistically significant difference was found. This shows that the decrease in homocysteine levels which occurs in normal pregnancy do not occur in preeclampsia. So it is possible that the increase in homocysteine concentration in preeclampsia is related to the defect in the mechanism that usually decreases homocysteine during normal pregnancy.

Powers et al[5] analyzed the homocysteine and folate levels in 21 women with preeclampsia and 33 women with normal uncomplicated pregnancies and found significantly higher homocysteine in preeclampsia than in normal pregnancy (p<0.04) and no difference was found in folate levels. Our study also showed a significant increase in homocysteine levels in preeclampsia than in normal pregnancy (p<0.001) which is comparable to the study of Powers et al (p<0.04). We could not measure folic acid and vitamin B12 in the study subjects because of cost effectiveness. However, normal general blood picture ruled out any folic acid deficiency.

The study of Hogg et al[6] also showed elevated homocysteine levels in women with PIH and PET at 37 weeks gestation.

Our study showed strong association between increased blood pressure and homocysteine levels. The homocysteine levels were significantly higher in subjects with ≥146/100 mm of Hg blood pressure (mean = 16.698± 4.18 mmol/L) than in subjects with blood pressure ≥140/90 mm of Hg and <146/100 mm of Hg (mean 13.067±3.513 mmol/L) (p=0.017). No statistical difference was found between study group I and study group II with blood pressure >146/100 mm of Hg (p=0.001). This suggests that homocysteine levels were directly correlated with severity of preeclampsia.

It is possible that with preeclampsia, there are elevated homocysteine level injuries and the vascular endothelium, which contribute 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 eventually results in preeclampsia.

Conclusion

Homocysteine concentration decreases during normal pregnancy, but this does not occur in preeclampsia. In PET, homocysteine levels further increase with severity of preeclampsia.

Elevated levels of homocysteine can be due to genetic or nutritional defect or a combination of both. Nutritional defects involve inadequate intake of folic acid or vitamin B12.

Further studies are required to know the cause of hyperhomocysteinemia (whether nutritional or genetic) observed in pregnant women with preeclampsia, which may help in pharmacological management of pregnant women at risk for PET.

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