VOLUME-7, ISSUE-6, JUNE-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Gynecology

ESTIMATION OF ROLE OF SERUM HOMOCYSTEINE AND SERUM FOLATE IN PREECLAMPTIC WOMEN AT TERM PREGNANCY

Dr. Mohini Paul MBBS, MD Senior Specialist Obstetrics And Gynecology Kasturba Hospital New Delhi

Dr. Annu Dabla* MBBS Obstetrics And Gynecology Kasturba Hospital New Delhi *Corresponding Author

ABSTRACT

Elevated plasma homocysteine and decreased serum folate level has been implicated in vascular changes and endothelial dysfunction caused by lipid peroxidation and formation of free radicles similar to those seen in preeclampsia. The aim of this study was to determine the levels of serum homocysteine in preeclamptic patients at term, to determine the levels of serum folate in preeclamptic patients at term and to study correlation between serum folate levels and serum homocysteine in preeclamptic patients at term.

Study design Prospective case control study of 50 preeclamptic patients that were age, parity and BMI matched with 50 controls of same gestational age. The preeclamptics were further divided into mild , 38 and severe preeclampsia , 12.

Results Mean levels of serum homocysteine were significantly elevated in the preeclamptic than in control group (9.45±2.68µmol/l v/s 4.99 ± 0.96µmol/l respectively). Mean levels of serum folate were significantly reduced in the preeclamptic patients (9.28 ± 1.96ng/ml v/s 15.48 ± 2.47ng/ml). An inverse but statistically insignificant relation appeared between low serum folate and elevated serum homocysteine levels in the preeclamptic patients.

Conclusion From the present study it was concluded that serum homocysteine levels were significantly elevated in patients with preeclampsia and serum folate levels were significantly decreased when compared to control group. An inverse correlation was seen between serum folate levels and serum homocysteine levels in preeclamptic patients.

KEYWORDS : Preeclampsia, Homocysteine, Folate

Introduction

Preeclampsia is a pregnancy specific syndrome that can affect virtually every organ system . It affects about 5 to 10% of all pregnancies worldwide, and is one of the leading causes of maternal and infant morbidity and mortality. [1,2]

Maternal hyperhomocysteinemia has been associated with preeclampsia in several studies. [3-4] Homocysteine-mediated vascular changes are similar to those associated with preeclampsia probably caused by lipid peroxidation and formation of free radicals causing endothelial dysfunction . [5-6] Thus hyperhomocysteinemia may lead to preeclampsia by causing similar pathogenetic changes in the uteroplacental microcirculation. The concentration of plasma homocysteine is regulated by genetically determined metabolic enzyme alterations and environmental factors. Levels of maternal serum homocysteine normally decrease with gestation, due to a physiological response to the pregnancy, increase in estrogen, hemodilution from increased plasma volume, and increased demand for methionine by both the mother and fetus . [7]

Folate plays a central role in homocysteine metabolism. If it is not present in adequate amount to support the metabolic changes ,then the natural decrease of homocysteine might not occur and hyperhomocysteinemia can develop. Folate defeciency might thus confer a greater risk of preeclampsia on the mother.

Hyperhomocysteinemia appears to cause endothelial dysfunction through direct toxic and oxidative stress mechanisms. It can damage the decidual blood vessels and result in faulty placentation with its consequences as in preeclampsia.

Folate contributes to cell division and growth, and folate metabolism is involved in a large number of physiological and pathophysiological processes in human development. Sufficient supply of folate is therefore particularly important during pregnancy. In recent years, there has been a growing body of evidence suggesting that folate deficiency is associated with PE, and folic acid supplementation may reduce the risk of developing PE in certain populations.

Material and methods

50 patients with severe preeclampsia that were age , parity and BMI matched with 50 normal antenatal patients at term period of gestation were studied prospectively in obstetrics and gynaecology department of Kasturba hospital . Serum levels of homocysteine and folate were compared in preeclamptic patients and controls. After taking informed written consent of patients, sampling was done as soon as possible after the diagnosis of preeclampsia was made.Venous blood samples after 8 hours of fasting were collected from preeclamptic patients and normal patients at time of enrollment in the study shortly after diagnosis was confirmed. The quantitative estimation of serum homocysteine and serum folate levels in normal pregnant women and preeclamptic women was measured by enzyme linked immunosorbant assay. Blood for homocysteine was collected in plain vials with 3 ml sample volume. Serum was stored at 2-8 degree Celsius until the assay was performed within 72 hours after collection . The levels of serum homocysteine and serum folate between normal antenatal women and preeclamptic women at term was compared and plotted on graphs. Mild and Severe preeclampsia were classified as per ACOG 2013 guidelines. The statistical analysis was done using SPSS version 21.0 and tests applied were Unpaired t-test/Mann-Whitney test, Chi-square test /Fisher's exact test and Pearson correlation coefficient/ Spearsman rank correlation coefficient. P value <0.05 was considered statistically significant.

RESULT

The maternal demographics age, parity, BMI and gestational ages were similar between the cases and the controls. The mean serum homocysteine level was 9.45±2.68µmol/l in cases and 4.99 ± 0.96µmol/l in controls (table 1, figure 1). A significant difference emerged between the two groups ($p < 0.0001$). The mean serum homocysteine level in mild preeclampsia was 8.13±1.2µmol/l, while in severe preeclampsia was found to be 13.62±1.5µmol/l and was statistically significant ,$p<0.0001$ (table 2, figure 3).

The mean serum folate was 9.28 ± 1.96ng/ml in cases and 15.48 ± 2.47ng/ml in controls; a significant difference was evident between the two groups ($p <0.0001$) (table 1, figure 2).

An inverse correlation was seen between serum homocysteine and serum folate but it was not statistically significant (p=0.5242) (table 3).

Table 1. Serum homocysteine and folate levels in preeclamptic patients and controls:

Biochemical Parameters	Preeclampsia (n=51)	Control group (n=51)	p-value
Homocysteine (µmol/L)	9.45±2.68	4.99±0.96	<0.0001
Folate (ng/mL)	9.28±1.96	15.48±2.47	<0.0001

Table 2. Serum homocysteine in mild and severe preeclampsia

	Mild preeclampsia(n=38)	Severe preeclampsia (n=12)	P value
S.homocysteine (µmol/l)	8.13±1.2	13.62±1.5	<.0001

Table 3. Correlation of total homocysteine and folic acid in preeclamptic patients

		S.homocysteine(µmol/l)
S.folate(ng/ml)	Correlation coefficient,r	-0.092
	P value	0.5242
	n(total no. of preeclamptic pts.)	50

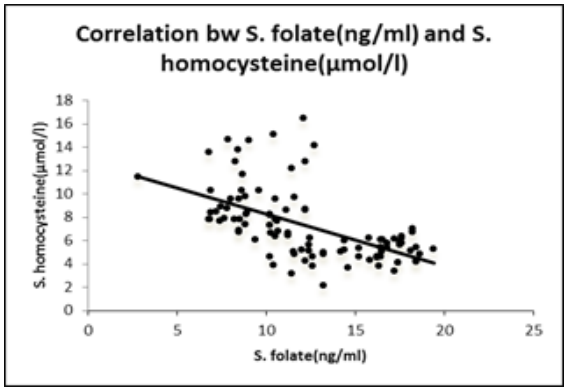


FIGURE 1 : DISTRIBUTION OF SERUM HOMOCYSTEINE BETWEEN CASES AND CONTROL:

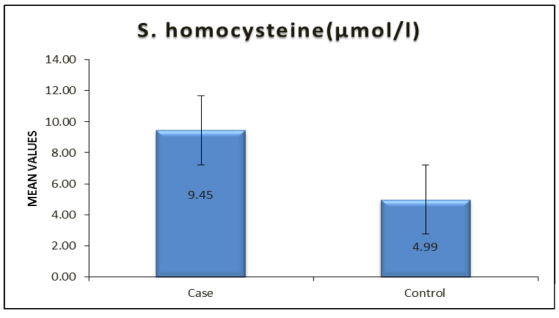


FIGURE 2: DISTRIBUTION OF SERUM FOLATE BETWEEN CASES AND CONTROL:

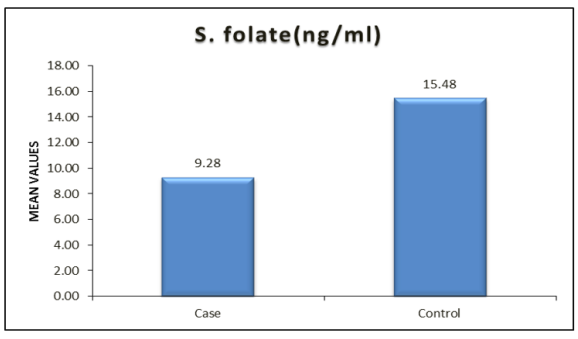
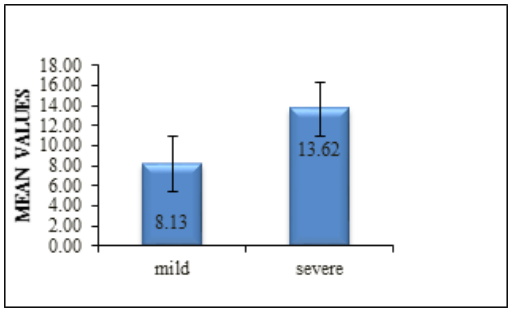


FIGURE 3: DISTRIBUTION OF SERUM HOMOCYSTEINE BETWEEN MILD AND SEVERE PREECLAMPSIA:



DISCUSSION

The results of this study show that serum levels of homocysteine and folic acid are altered in preeclamptic patients as compared to normal antenatal women . Significantly elevated levels of homocysteine and decreased serum folate levels were found in women with preeclampsia. High concentrations of homocysteine are a proven risk factor for vascular disease . High levels of homocysteine can damage endothelial cells and cause endothelial dysfunction by formation of free radicals which is characteristic of preeclampsia. Many similar case control studies have shown high concentrations of maternal serum homocysteine in preeclampsia and the result from our present study support these outcomes. [8-11]On the contrary Hietala R et al (2001)[12] and Zeeman GG et al (2003) [13]did not agree with our observations . Women with severe preeclampsia had higher serum levels of total homocysteine than those in mild preeclamptic women..[11,14]This shows that the severity of preeclampsia is directly correlated with degree of hyperhomocysteinemia . Homocysteine metabolizes in two pathways. One is remethylation to methionine . It needs folate as a substrate and vitamin B12 as a coenzyme. The absence or lack of any of these will lead to homocysteine accumulation . In our study serum folate levels were significantly lower in preeclamptic women as compared to controls which was similar to study conducted by Nahid Shahbazian et al[11] . There are contradictory studies also which show no significant difference in serum folate levels in preeclamptic patients and the normal antenatal patients.[8,15] Thus , reduced folate levels might be associated with the development of preeclampsia. In the present study, association and risk of preeclampsia with hyperhomocysteinemia at term period of gestation was found to be as OR=54.662, 95%CI = 4.897 – 610.109, P= 0.0012. This indicates that elevated serum homocysteine levels at term period of gestation were significantly associated with risk of preeclampsia and for each 1 unit rise in serum homocysteine , there was a 54.662 fold increased risk of preeclampsia at term period of gestation.Therefore , in the present study, elevated serum homocysteine levels were found to be a significant risk factor for development of preeclampsia at term period of gestation . In the present study ,association and risk of preeclampsia with reduced serum folate levels at term period of gestation was found to be as OR= 0.252, 95% CI= 0.127 – 0.498 , P=0.0001.This indicates that reduced serum folate levels at term period of gestation were significantly associated with risk of preeclampsia and for one unit decrease in serum folate level , there was 74.8% increased risk of developing preeclampsia at term period of gestation . Therefore decreased serum folate levels were found to be a significant risk factor for development of preeclampsia at term period of gestation. Thus, in this study, an inverse correlation was found between serum homocysteine and serum folate but was statistically in significant. This was similar to study conducted by Shahid A Mujawar et al[16]. However the study conducted by Nahid Shahbazian et al found a significant difference between the two groups. In several studies, the inverse correlation between levels of serum folate and homocysteine has been demonstrated .[16-19] Thus, this implies low levels of serum folate levels might be associated with hyperhomocystenemia in preeclampsia.

Conclusion

From the present study , it can be concluded that elevated levels of

serum homocysteine and decreased levels of serum folate are associated with significantly higher risk of developing preeclampsia during pregnancy . Also, the degree of elevation of serum homocysteine was significantly associated with the severity of preeclampsia. Furthermore, an inverse correlation was found between levels of serum folate and serum homocysteine. Hence it may be recommended that prospective studies measuring serum homocysteine levels throughout pregnancy and postpartum period are needed to further understand the importance of maternal hyperhomocysteinemia in determining the risk of preeclampsia .Further studies are needed to confirm if the folic acid supplementation in women deficient with this vitamin could decrease the level of hyperhomocysteinemia , thereby reducing the risk of preeclampsia and its severity.

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