

CORRELATION BETWEEN HYPERHOMOCYSTEINEMIA AND PREECLAMPSIA

Dr. Prerna Sharma*, **Dr. Suman Lata Mendiratta****, **Dr. Rajiv Ranjan*****, **Dr. Meenakshi Mittal******
Dr. Smriti Anand*****

*Sr. Resident, ** Sr. Gynaecologist, *** CMO I/C Biochemistry, ****CMO, *****Sr. Resident
Department of Obstetrics and Gynaecology
Hindurao Hospital, New Delhi

Corresponding Author: Dr Suman Lata Mendiratta
Address: A-3/224 JANAK PURI NEW DELHI-110058 INDIA
Tel- 9871858597 OFFICE- 23831937

ABSTRACT

INTRODUCTION -Preeclampsia represents one of the most frequent complications of pregnancy. Homocysteine is an essential amino acid required for the growth of cells and tissues in the human body. Maternal hyperhomocysteinemia is associated with a number of placenta-mediated diseases such as preeclampsia. The aim of this study was to evaluate the plasma level of homocysteine and its association with severity of preeclampsia.

METHODS- A total of 180 women were recruited in our study, which were divided into control and study groups. control group consist of 60 normotensive nonpregnant women and study group consists of two groups, group 1 having 60 normotensive pregnant women and group 2 which were further divided into two subgroups, group 2a having 40 Preeclamptic Pregnant Women with B.P. \geq 140/90mmHg to $<$ 160/100mmHg and group 2b having 20 Preclamptic Pregnant women with B.P. \geq 160/100mmHg out of which 5 had convulsion (Eclampsia). Serum homocysteine levels estimation was done in study and control group by homocysteine enzyme cycling method on fully automated Erba XL-300, Biochemistry analyser.

RESULTS- In our study, maternal serum levels of total homocysteine were significantly higher in preeclamptic group than in normal pregnant women. Women with severe preeclampsia had higher serum levels of total homocysteine than mild preeclamptic patients. Levels of total homocysteine correlated positively with systolic blood pressure values in preeclamptic women.

CONCLUSION-Preeclampsia / Eclampsia is a common medical disorder of human pregnancy complicating about 5-7% of all pregnancies. Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular disease.

keywords- Pregnancy, preeclampsia, homocysteine, hypertension, folic acid

INTRODUCTION

Hypertensive disorders affect 12-22 % of pregnancies; 70 % of these pregnancies are hypertensive secondary to preeclampsia or the preeclampsia-eclampsia syndrome¹. The Incidence of preeclampsia is commonly cited to be about 5-8%, although rather wide variations are reported¹

Homocysteine is primarily derived from the demethylation of methionine, which is an essential amino acid required for the growth of cell and tissues in the human body. Methionine is consumed in the diet, as 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.

Levels of maternal serum homocysteine normally decrease with gestation, whether due to a physiological response to the pregnancy, increase in estrogen, hemodilution from increased plasma volume, or increased demand for methionine by both the mother and fetus. Maternal hyperhomocysteinemia has been associated with a number of pregnancy associated diseases such as preeclampsia, placental abruptions, recurrent pregnancy loss and neural tube defects and IUGR. Homocysteine-mediated vascular changes are similar to those associated with preeclampsia, therefore a hypothesis has been proposed that hyperhomocysteinemia may be associated with this condition. Several studies have indicated that homocysteine concentrations are increased in women with preeclampsia. The study of Hogg et al¹ also showed elevated homocysteine levels in women with PIH and PET at 37 weeks gestation. Therefore, this study is planned to investigate levels of homocysteine in women with preeclampsia and normotensive women, and to assess whether there is an association between hyperhomocysteinemia and preeclampsia.

METHOD

The present study was conducted in Hindu Rao Hospital, New Delhi from **Oct 2009 to Oct 2010**. A total of 180 women were recruited from gynaecology out-patient department and indoor patients from maternity ward, which were divided into two groups.

I) CONTROL GROUP – 60 Normotensive Nonpregnant Women

II) STUDY GROUP – A total number of 120 pregnant women with gestational age ranging from 28-40 weeks were included in the study group. These women were further divided into two subgroups:

GROUP 1 – 60 Normotensive Pregnant Women

GROUP2 – 60 Preeclamptic pregnant Women which were further divided into two subgroups:

a) 40 Preeclamptic Pregnant Women with B.P. \geq 140/90mmHg to $<$ 160/100mmHg.

b) 20 Preeclamptic Pregnant Women with B.P. \geq 160/100mmHg out of which 5 had convulsion (Eclampsia).

In study Group all patient had singleton pregnancy 28-40 weeks gestation. Those with abruptio placentae , multiple gestation, repeated miscarriage, preterm labor and delivery were excluded from the study. Patients with history of smoking, other medical illnesses were excluded from study. In both groups, a detailed history was taken and history of iron, folic acid , vitamins and any other drug intake was also taken. Complete general physical and antenatal examination was done, All routine Investigations with haemoglobin and general blood picture were done to rule out anaemia and folic acid deficiency along with specific investigation of preclampsia. Serum homocystine levels estimation was done in study and control group by homocystine enzyme cycling method on fully automated Erba XL-300, Biochemistry analyser .These investigations were repeated after 3 months in case of control group (Normotensive nonpregnant women) and after 3 month of delivery in case of study group IIa & IIb (Normotensive and preeclamptic pregnant women) respectively.

RESULTS

- In all the groups, majority of women had their **age** between 20 to 25 years of age.
- In **CONTROL GROUP** (Normotensive Nonpregnant Women). Mean systolic blood pressure was 117.68 ± 4.897 mmHg at time of admission/ first visit and after 3 month mean blood pressure was 119.87 ± 10.094 mmHg. The mean diastolic blood pressure was 74 ± 8.867 mmHg at the time of admission and after 3 month mean blood pressure was 76.85 ± 7.966 mmHg.
- In **STUDY GROUP 1** (Normotensive pregnant Women), mean systolic blood pressure was 114.3 ± 8.313 mmHg at time of admission and after 3 months of delivery mean blood pressure was 113.73 ± 7.619 mmHg. The mean diastolic blood pressure was 75.233 ± 6.686 mmHg at the time of admission and after 3 month of delivery mean blood pressure was 75.717 ± 5.076 mmHg.
- In **STUDY GROUP 2a** (Preeclamptic Pregnant Women with B.P. \geq 140/90mmHg to $<$ 160/100mmHg) the mean systolic blood pressure was 143.25 ± 3.766 mmHg at the time of admission. After 3 month of delivery pressure was 92.25 ± 3.238 mmHg at the time of admission. After 3 month of delivery blood pressure was 8.46 ± 6.390 mmHg.
- In **STUDY GROUP 2b** (Preeclamptic Pregnant Women with blood pressure \geq 160/100mmHg) the mean systolic blood pressure was 164.55 ± 5.191 mmHg at the time of admission. After 3 month of delivery blood pressure was 142.2 ± 10.191 mmHg. The mean diastolic blood pressure was 108.45 ± 4.005 mmHg at the time of admission. After 3 month of delivery blood pressure was 89.8 ± 4.422 mmHg.

- Majority of women did not have albuminuria in **control group** and **study group 1**. In **study group 2a**, majority of women were found to have urine albumin in range of 1+ and 2+ at the time of admission. Urine albumin drops down maximally to trace and 1+ range after 3 month of delivery. In **study group 2b**, urine albumin found to be in range of grade 2+ to 3+ at the time of admission. After 3 month of delivery in most women albumin in urine was found from grade 1+ to traces. In **study group 2b (Eclampsia)** at the time of admission majority of women had urine albumin in the range of of 3+ and 4+ .After 3 month of delivery urine albumin decreased to 1+ and 3+.
- Majority of women in all groups found to have **haemoglobin** between 9-11 gm% except for **study group 2a** (Preeclamptic pregnant women with B.P.≥ 140/90mmHg), in which maximum number of women had haemoglobin more than 11gm%. None of the women had haemoglobin less than 7mg%.
- There was improvement in women with microcytic hypochromic anaemia and macrocytic anaemia to Normochromic Normocytic picture after 3 month of iron-folic – vitamin B₁₂ therapy except for eclampsia group where number number of women in each category remained same.
- In **control group** (Normotensive Nonpregnant Women) mean serum homocysteine levels at the time of admission was 16.57043±6.8812 μmol/l and after 3 month was 14.3377±6.4118 μmol/l.
- In **Study Group 1** (Normotensive Pregnant Women) mean serum homocysteine levels at the time of admission was 14.38033±6.0899 μmol/l while after 3 month of delivery was 13.7555±5.0469 μmol/l. (P value: 0.5534, insignificant decrease in homocysteine levels).
- In **Study group 2a** (Preeclamptic Pregnant Women with B.P.≥140/90mmHg to <160/100mmHg), the mean serum homocysteine level at the time of admission was 19.268±6.1818 μmol/l and after 3 month of delivery was 17.2045±5.705μmol/l (P-value: 0.1294, insignificant decrease in homocysteine levels).
- In **Study group 2b** (Preeclamptic pregnant women with B.P.≥160/100mmHg without convulsions) the mean serum homocysteine level at the time of admission was 22.726±5.9875 μmol/l and after 3 month of delivery was 20.398±5.588 μmol/l. The mean serum homocysteine level at the time of admission in preeclamptic women with convulsions was 24.438± 3.735 μmol/l and after 3 month of delivery was 23.164±4.567 μmol/l.
- **Study Group 1** (Normotensive pregnant Women): 53.33% underwent spontaneous labour while 40% were induced, 23.33% of women underwent caesarean section while pre-term vaginal delivery was not seen in any women and only 1 instrumental delivery (vacuum) was seen in this group.
- **Study Group 2a** (Preeclamptic Pregnant Women with B.P.≥ 140/90 mmHg to <160//100mmHg): 25% spontaneously went into labour while 70% needed to be induced 17.5% of women landed in caesarean section while pre-term vaginal delivery occurred in 30% of women and no instrumental delivery was conducted in this group.

- **Study Group 2b** (Preeclamptic Pregnant Women with B.P. \geq 16.0/100mmHg): 25% spontaneously went into labour while 70% needed to be induced. 5% of women landed in caesarean section while pre-term vaginal delivery seen in 55% of women and 5% instrumental delivery (vacuum) was seen in this group.
 - **Distribution of birth weight** in different group:
 - Mean birth weight in **Study Group 1** (Normotensive Pregnant Women) was 2.7675 ± 0.3056 Kg.
 - Mean birth weight in **Study Group 2a** (Preeclamptic Pregnant Women with B.P. \geq 140/90mmHg to $<$ 160/100mmHg) was 2.691 ± 0.457 Kg.
 - Mean birth weight in **Study Group 2b** (Eclampsia) was 2.038 ± 0.482 .
 - Mean apgar score of **study group 1** was 7.45 ± 1.064 (1 minute), 8.6 ± 0.738 (5 minute) while apgar score of **study group 2a** was 7.375 ± 0.837 (1 minute) and 8.7 ± 0.563 (5 minute). In **study group 2a** mean apgar score was 6.7 ± 1.260 (1 minute) and 7.75 ± 1.164 (5 minute). In case of eclampsia mean apgar score was 6.2 ± 1.095 (1 minute) and 7.2 ± 1.095 (5 minute).
 - It was seen in our study that birth weight and apgar score are inversely related with the severity of blood pressure.
- On all group majority of the women were between 20-25 years the women in all groups were of comparable age may only of the (48.33%) patient in study group I and study group II b (55%) unbooked where as just 27.5% women in study group IIa were booked cases.

Discussion:-

Preeclampsia is a leading cause of maternal and fetal morbidity and mortality. Although the exact, cause of preeclampsia is still unknown, it may be possible that the basic pathology behind preeclampsia is endothelial dysfunction and intense vasospasm. Elevated plasma homocysteine concentration is an independent risk factor for peripheral vascular diseases and for coronary artery disease. (Singh U 2009)².

To study the co-relation between plasma homocysteine and preeclampsia total of 180 women were recruited in the study. In our study, control group comprised of normal healthy Normotensive nonpregnant women, similar to that of Walker et al³ in their study.

As shown in Table no.2 below mean blood pressures in our study are comparable to Tug N et al in 2003⁴, Gurbuz A et al in 2004⁵ and Kale A et al in 2006⁶

There was no difference in Hb level (P-value was insignificant) in Normotensive pregnant women preeclamptic women and eclamptic women^{4, 5, 6, 7}.

The number of women with microcytic hypochromic and macrocytic were nearly same in all groups except for study group 2b. Our results were consistent with the study of **powers et al (2001)**⁸, **Makedos G (2006)**⁹, **Brackke K et al 2007**¹⁰.

In the present study, the mean homocysteine level in the control group was $16.843 \pm 6.547 \mu\text{mol/l}$ (Table1). The review article of **Ueland et al (1993)**¹¹ showed that the value between 5 and 15 $\mu\text{mol/l}$ in fasting subjects are normal.

In our study it was found that with increase in blood pressure in pregnant women there was increase in albuminuria and accordingly there was increase in levels of homocysteine. Similar results were reported by **Tug N et al in 2003**⁴ **Gurbuz A et al in 2004**⁵, **Ingec M et al in 2005**⁷ and **Kale A et al in 2006**⁶. It was seen in our study that with supplementation of Iron, Folic acid and Vitamin B₁₂, there were no changes in the levels of homocysteine. The reason for this may be because homocysteine levels are increased either due to nutritional or genetic factor and in our patients it may be that homocysteine levels are raised due to genetic defect and the other reason might be that, since we have given folic acid and vitamin B₁₂ for the shorter duration of time (3 month) and for the homocysteine levels to be corrected the duration of Folic acid and vitamin B₁₂ need to be given for a longer duration of time. **Rajkovic A et al in 1997**¹² also observed similar finding.

In our study it was found that majority of women in control and study group 1, there was no albuminuria. In study group 2a majority of women had urine albumin as 1+ and 2+, on the other hand study group 2b had urine albumin as 2+, 3+, and 4+. In eclamptic women (study group 2b) urine albumin as 3+ and 4+. Thus it was seen that with increase in blood pressure there was increase in albuminuria. Similar observation was found by **Tug N et al in 2003**⁴, **Ingec M et al in 2005**⁷, **Kale et al in 2006**⁶.

APGAR SCORE

In present study we observed that mean apgar score decreases with increase in severity of blood pressure. Similar results were observed by **Kale A et al**⁶.

BIRTH WEIGHT

It was found that in Study group1 (Normotensive Pregnant women) birth weight was more (mean; 2.767 ± 0.305 kg) than Study group 2a, 2b and eclampsia. Least birth weight was found in eclampsia group (2.038 ± 0.482 kg).

Our results are consistent with **Makedos G et al** in 2006⁹ who found that mean birth weight (1.719 ± 0.230 kg) was less and complication were more in preeclampsia as compared to controls (2.1 ± 0.235 kg) Similar observations were found by **Ingec M et al** in 2005⁷ who found maximum birth weight (3.013 ± 0.530) in Normotensive women and least birth weight in women with eclampsia (2.275 ± 0.735 kg).

Conclusion

Preeclampsia / Eclampsia is a common medical disorder of human pregnancy complicating about 5-7% of all pregnancies. Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular disease.

Our study showed that homocysteine concentration decreases during normal pregnancy, this does not occur in preeclampsia. There was an increase in levels of homocysteine in preeclampsia and this increase was more profound with increasing severity of preeclampsia (Table: 1). In our study we found that increase in serum homocysteine was positively correlated with clinical severity of disease.

It was observed in our study that birth weight and apgar score were inversely related to the severity of blood pressure. We have observed in our study that, since homocysteine value remains consistently elevated even after 3 month of delivery in preeclampsia, there should be regular follow up of these patients as high homocysteine concentrations causes vascular endothelial dysfunction and these patients are prone to coronary heart disease and its sequelae.

The present study concludes that measurement of serum homocysteine should be done in pregnancy with risk factors for hypertension / PET / eclampsia as a routine work up. Proper monitoring for development of sign and symptoms of preeclampsia can be done in women with hyperhomocysteinaemia. Early diagnosis, management and timely intervention can prevent deadly fetal and maternal complications arising due to vascular disease and hypertension and thereby, can improve pregnancy outcome.

References

1. Hogg BB, Tamura T, Kelley E, et al. second-trimester plasma homocysteine levels and pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction. *Am J Obstet Gynecol* 2000;183:805-9.
2. Singh U, Gupta HP, Singh Rk, Shukla M, Mehrotra S, Prasad S, Homocysteine : Association with preeclampsia and Normotensive pregnancy. *J Obstet Gynecol India* Vol. 59, No.3: May / June 2009 pg 235-238.
3. Walker J: Pre-eclampsia. *Lancet* 356:1260. 2000.
4. Tug N , Celik H , Cikim G , Ozcelik O, Ayar A (2003) The correlation between plasma homocysteine and malodialdehyde levels in preeclampsia. *Neuroendocrinology Letters* No.6 December Vol.24,2003.
5. Gurbaz A, Karateke A, Mengulluoglu M. Elevated plasma homocysteine levels in preeclampsia and eclampsia. *Int. J. Gynecol. Obstet* (2004) 87, 165-166
6. Kale A, Kale E, Akdeniz N, Erdemoglu M, Yalinkaya A, Yayla M (2006) Investigation of folic acid, vitamin B 12, vitamin B6, and homocysteine levels in preeclamptic pregnancies. *Perinatal Journal* 2006; 14(1): 31-36.
7. Ingen M, Borekei B, Kadanali S. Elevated plasma homocysteine concentration in serve preeclampsia and eclampsia. *The Tohoku Journal of Experimental Medicine: Vol.206(2005), No.3 pp.225-231.*
8. Powers RW, Evans RW, Ness RB, Cromblehome WR, Roberts JM (2001) Homocysteine and cellular fibronectin are increased in preeclampsia, not transient hypertension of pregnancy. *Hypertens pregnancy* 20: 69-77.
9. Makedos G, Papanicolaou A, Hitoglou A, Kalogiannidis I, Makedos A, Vrazioti V, Goutzioulis M. Homocysteine, Folic acid and B12 serum levels in pregnancy complicated with preeclampsia. *Arch Gynecol Obstet* (2007)275: 121-124.
10. Brakke K, Ueland PM, Harsem NK, Karlsen A, Blomhoff R, Staff AC. Homocysteine, Cysteine , and related metabolites in maternal and fetal plasma in preeclampsia. *Pediatr Res* 2007 Jul 6.
11. Ueland PM, Refsum H, Stabler SP et al. Total homocysteine in plasma or serum: method and clinical applications. *Clin Chem* 1993; 39:1764-79.
12. Raijkovic A, Catalano PM, Mailnow MR. Elevated homocyst(e)ine levels with preeclampsia. *Obstet Gynecol* 1997; 90:489-93.

TABLE – 1: DISTRUBUTION OF SERUM HOMOCYSTEINE IN DIFFERENT GROUPS

<u>GROUPS</u>	<u>SERUM HOMOCYSTEINE (μ mol/1)</u>		<u>P-value</u>
	<u>At admission</u>	<u>After 3 month</u>	
<u>CONTROL GROUP</u> (Normotensive Nonpregnant Women)	16.570 \pm 6.881	14.337 \pm 6.411	0.068
	<u>At Admission</u>	<u>After 3 month of Delivery</u>	
<u>STUDY GROUP 1</u> (Normotensive Pregnant Women)	14.380 \pm 6.089	13.755 \pm 5.405	0.553
<u>STUDY GROUP 2a</u> (Preeclamptic Pregnant Women, B.P. \geq 140/90mmHg to < 160/100 mmHg)	19.268 \pm 6.181	17.204 \pm 5.705	0.129
<u>STUDY GROUP 2b</u> (Preeclamptic Pregnant Women, B.P. \geq 160/100mmHg)	22.726 \pm 5.987	20.398 \pm 5.588	0.222
<u>STUDY GROUP 2b</u> (Eclampsia)	24.438 \pm 3.735	23.164 \pm 4.567	0.677

Table no. 2 BLOOD PRESSURE (B.P) IN DIFFERENT GROUPS.

Different Groups	B.P (mmHg)	<u>Our study</u>	<u>Tug N et al in 2003</u>	<u>Gurbuz A et al in 2004</u>	<u>Kale A et al in 2006</u>
Normotensive Pregnant Women (study group 1)	Systolic	114.3+3.1	116+12	102.0+5.0	113.78+11.66
	Diastolic	75.23+6.68	74+6	62.2+5.10	71.48+8.55
<u>Mild Preeclamptic women (study Groups 2a)</u>	Systolic	143.25+3.76		140.0+7.39	
	Diastolic	92.25+3.23		90.+8.53	
<u>Severe Preeclamptic women (study Group 2b)</u>	Systolic	164.55+5.19	164+14	153.26+11.9	158.30+16.57
	Diastolic	108.45+4.01	114+5	99.46+8.04	96.45+11.74