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Association of serum homocysteine with socio-demographic factors in normotensive women and women with preeclampsia

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Abstract

Introduction: Elevated levels of homocysteine are associated with a number of placenta-mediated diseases such as preeclampsia and several pregnancy complications. In general, homocysteine concentration increases with age and decreases as pregnancy advances. Keeping this in mind the present study was done to find any association of homocysteine with socio-demographic factors of normotensive pregnant women and women with preeclampsia.

Material and Methods: 54 normotensive women, 54 women with mild and 54 women with severe preeclampsia were enrolled in the study after written informed consent. S homocysteine levels were measured and results were analysed to find association of homocysteine with socio-demographic factors.

Results: The mean serum homocysteine levels were 11.3 ± 4.4 μmol/L, 12.3 ± 4.2 μmol/L and 15.9 ± 6.3 μmol/L in normotensive group, mild preeclampsia group and severe preeclampsia group respectively and the levels were significantly higher in severe preeclampsia group ($P < 0.001$). The positive correlation was found between the mean maternal age, systolic, diastolic blood pressure and mean serum homocysteine levels. Negative correlation was observed between mean serum homocysteine levels and gravidity($r=-0.1$). S. homocysteine increases as BMI increases this is more marked in severe preeclampsia group. The severe preeclampsia group had higher mean serum homocysteine levels (17.6 ± 5.6 μmol/L) in women with gestational age above 36 wks ($P = 0.001$).

Conclusion: Serum homocysteine levels also have positive correlation with systolic and diastolic blood pressure. Maternal demographic status except age and BMI had no significant association with serum homocysteine.

Keywords: homocysteine, socio-demographic factors, preeclampsia, BMI

Introduction

Homocysteine, a sulphur containing amino acid, 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. According to Ghike S et al (2011) the concentration of plasma homocysteine is regulated by several factors which include

genetically determined metabolic enzyme alterations and environmental factors.

Walker et al. (1999) stated that levels of maternal serum homocysteine normally decrease with gestation, either 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. According to de la Calle M (2003) hyperhomocysteinaemia is associated with obstetric complications such as placental abruption, preeclampsia, neural tube defect, stillbirth and recurrent miscarriage. Chambers Je et al1997stated that the mechanisms involved remain unknown but there is experimental evidence to indicate that hyperhomocysteinemia causes endothelial dysunction.

In vitro studies (Welch GN, 1997) suggest that this dysfunction is mediated through the generation of potent reactive oxyen species, in particular hydrogen peroxide. Rodgers GM1990 observed that in vivo, homocysteinaemia alters the effect of many clotting proteins on the endothelial cell surface, leadng to a prothrombotic environment. Thus, it is conceivable that hyperhomocysteinaemia could affect placental function or maternal uteroplacental perfusion via any of these mechanisms.In general, homocysteine concentration increases with age and decreases as pregnancy advances. Keeping this in mind the present study was done to find any association of homocysteine with socio-demographic factors of normotensive pregnant women and women with preeclampsia.

Material and methods

The present study was a hospital-based analytical study done at Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur from April 2012 to March 2013 involving pregnant woman with gestational age of 28 weeks or more presenting with mild pre-eclampsia, severe pre-eclampsia and women with uncomplicated normotensive pregnancies.

Expecting the mean homocysteine levels in all 3 groups (Normal normotensive pregnant women v/s mild preeclampsia v/s severe preeclampsia) as 17.03 ± 5.69, 11.58 ± 4.01 and 14.5 ± 4.16. To determine this difference at 95% confidence interval and power of 80%, sample size was calculated as 54 in each group. Group A comprised of 54 normotensive pregnant women, Group B 54 pregnant women with mild preeclampsia and Group C 54 pregnant women with severe preeclampsia. All women were enrolled in the study after taking written informed consent. A detailed history and examination was carried out for each included woman.

We collected the blood sample using standard sampling tube, then centrifuged, at 3439 g for 10 min and serum was separated out. Fully automated Erba 360 auto-analyzer is used to estimate the serum homocysteine concentration. Results were evaluated statistically.

Results

Majority of cases in Group-A (normotensive) 53.70% and in Group-B (mild preeclampsia) 38.89% had serum homocysteine levels in the range of 5-9.9 μmol/L, while in the Group-C (severe preeclampsia) 40.74% had serum homocysteine levels in the range of 15-19.9 μmol/L. None of the women in Group-A and Group-B had serum homocysteine levels more than 20 μmol/L while 24.1% women in Group-C had serum homocysteine levels more than 20 μmol/L. (Table 1) Mean serumhomocysteine levels was 11.3 ± 4.4, 12.3 ± 4.2 and 15.9 ± 6.3 in Group A, Group B and Group C respectively. The Tukey post hoc tests indicated that mean serum homocysteine levels were significantly higher in Group-C (severe preeclampsia) than those in Group-A (normotensive) and Group-B (mild preeclampsia) (P<.001), but

Table 1: Distribution of Cases According to Serum Homocysteine Levels

Serum Homocysteine Levels (μmol/L)	Group-A		Group-B		Group-C	
	No.	%	No.	%	No.	%
0 - 4.9	0	0.00	1	1.85	0	0.00
5 - 9.9	29	53.70	21	38.89	15	27.78
10 - 14.9	11	20.37	17	31.38	4	7.41
15 - 19.9	14	25.93	15	27.78	22	40.74
20 - 24.9	0	0.00	0	0.00	8	14.81
>25	0	0.00	0	0.00	5	9.26
Total	**54**	**100.00**	**54**	**100.00**	**54**	**100.00**

the levels of mean serum homocysteine were not significantly different between Group-B and Group-A.

Association of mean serum homocysteine levels with various demographic factors is shown in table 1. The Tukey post hoc tests indicated that mean serum homocysteine levels were significantly higher in Group-C compared to Group-A in the age group 18 to 24 years (P = 0.01), while in the age group 25 to 29 years mean serum homocysteine levels in Group-C were significantly higher than Group-A and Group-B (P<0.001).There was no significant difference in mean serum homocysteine levels in the age group of 30-34 years among all the three groups. The r was 0.06 for Group-A, 0.12 for Group-B and 0.17 for Group-C. This showed that as correlation coefficient of mean serum homocysteine levels with mean age increases with severity increased (positive). The overall r was 0.09 showed positive correlation between the mean age and mean serum homocysteine levels. The differences in the mean serum homocysteine levels in between groups were statistically significant in middle and lower socio-economic status (P<0.05, Sig). It was significantly higher in Group-C than Group-A. There was no significant difference between Group-B and Group-A.In women belonged to upper socio-economic status no significant difference was found in mean serum homocysteine levels among all the three groups. There was no statistically significant difference in mean serum homocysteine levels in rural areas among all the three groups. In urban areas mean serum homocysteine levels were significantly higher in Group-C than Group-B and Group-A (p<0.001), while no significant differences were found between Group-A and Group-B. The differences in mean serum homocysteine levels when compared between literate and illiterate women, were not statistically significant. Among literate women the mean serum homocysteine levels were significantly higher in Group-C than Group-A and Group-B (P<0.001), while the levels were not statistically different between Group-B and Group-A. There was no significant difference in mean serum homocysteine levels among illiterate women in all the three groups.

Table 2 shows association of mean serum homocysteine levels with mean systolic and diastolic blood pressure. The positive correlation was observed between the systolic blood pressure. The r2 = 0.14, it means 14 % of the total variation in SBP was explained by the linear relation with serum homocystiene levels. (Fig 1) The

Table 2: Association of Mean Serum Homocysteine with demographic factors

Variables	Group A	Group B	Group C	P-Value LS
Age (in yrs)				
18 – 24	11.5 ± 4.6	12.0 ± 3.8	14.9 ± 6.3	0.01, Sig
25 – 29	10.3 ± 3.7	12.8 ± 3.9	18.0 ± 6.4	<0.001, HS
30 – 34	12.9 ± 4.3	12.6 ± 6.2	17.6 ± 5.6	0.3, NS
Socio-economic Status				
Upper	12.7 ± 4.6	13.6 ± 4.4	16.3 ± 5.4	0.32, NS
Middle	10.3 ± 3.9	11.9 ± 4.3	15.0 ± 5.5	0.002, Sig
Lower	12.5 ± 4.8	11.6 ± 3.7	16.5 ± 7.3	0.03, Sig
Residence				
Rural	11.6 ± 4.7	10.85 ± 4.383	15.2 ± 7.2	<0.08, NS
Urban	11.2 ± 4.3	12.76 ± 4.116	16.4 ± 5.5	<0.001, HS
Literacy Status				
Illiterate	11.4 ± 4.7	11.6 ± 4.4	16.2 ± 7.5	0.12, NS
Literate	11.3 ± 4.3	12.4 ± 4.2	15.8 ± 6.0	<0.00, HS

positive correlation was also observed between the diastolic blood pressure and serum homocysteine. Correlation of serum homocysteine levels with diastolic blood pressure was observed significant. The r2= 0.09, it means 9% of the total variation in DBP was explained by the linear relation with serum homocysteine. (Fig 2)

It was observed in Table-3, that the mean serum homocysteine levels increase with increase in BMI of the women with preeclampsia (both mild and severe).The difference in mean serum homocysteine levels in the BMI range of 18-24.9 kg/m^2 and >30 kg/m^2 was statistically not significant among the three groups, while the difference in mean serum homocysteine levels in BMI range of 25-29.9 kg/m^2 were significantly higher in Group-C than Group-A (p=0.01).

The mean serum homocysteine levels were higher in Group-C than Group-A and Group-B irrespective of their gravida status, but it was statistically significant only in G1 and G3 (p=0.01 and 0,001 respectively), while there were no significant differences in mean serum homocysteine levels between Group-A and Group-B. Negative correlation was observed (r=-0.1) in mean serum homocysteine levels with their gravidity. (Table 4)

The post hoc test indicated that mean serum homocysteine levels in the G.A. of 32-36 weeks were significantly higher in Group-C than Group-A and Group-B, while in G.A. of 36-40 weeks Group-C was significantly different from Group B only (P<0.05).There was no statistically significant differences in mean serum homocysteine levels in the G.A. of 28-32 weeks among all the three groups {P>0.05}(Table 5).

Discussion

Importance of homocysteine to human health has been described by Dr Kilmer McCully as early as in 1960. Homocysteine is critically important during pregnancy. Ray JG & Laskin CA (1999) observed that high maternal homocysteine level causes endothelial damage and dysfunction, platelet dysfunction, thrombus formation and smooth muscle proliferation. Probably this cause increase incidence of preeclampsia, miscarriages, placental abruption, intrauterine fetal death and fetal growth restriction.

In our study it was observed that mean serum homocysteine levels were significantly higher in Group-C (severe

Fig 1: Relationship between Serum Homocysteine levels and Systolic Blood Pressure

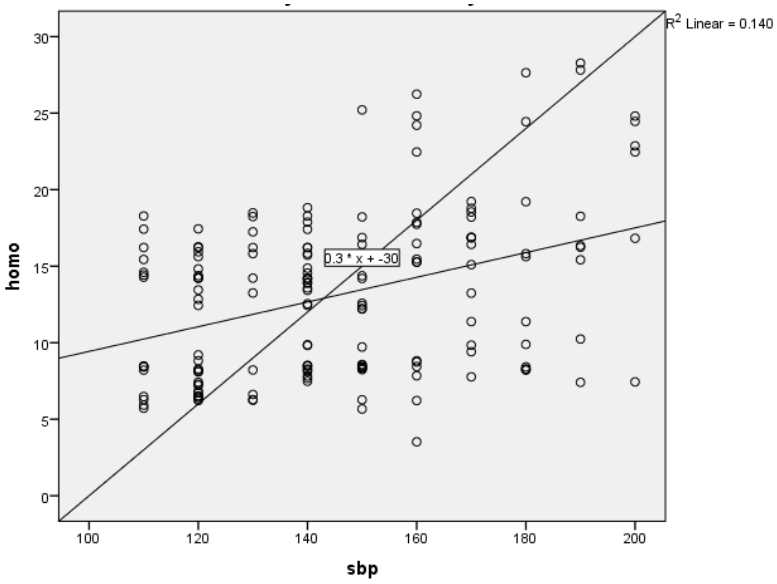

Fig 2: Relationship between Serum Homocysteine levels and Diastolic Blood Pressure

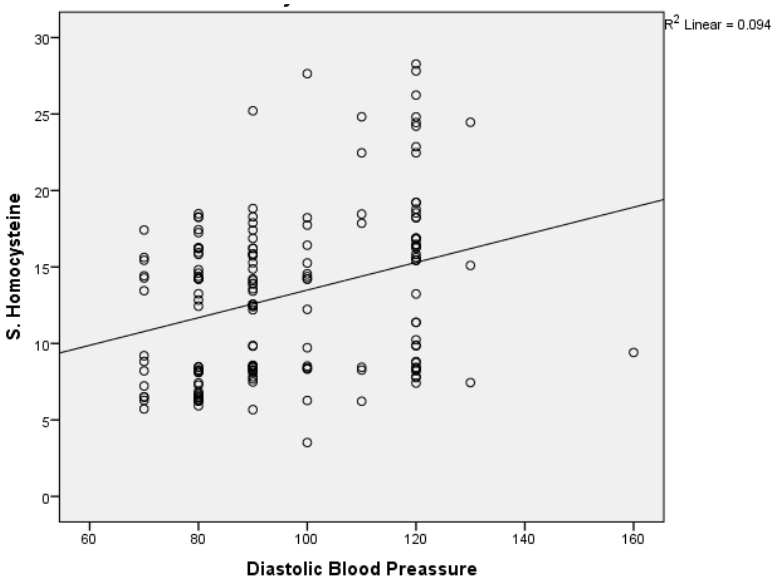

Table 3: Correlation of Systolic Blood Pressure and Diastolic Blood Pressure with Serum Homocyseine

n = 162	Mean ± SD	R	R Square	Equation	P-value LS
Systolic Blood Pressure	146.36 ± 24.966				
Homocysteine	13.17 ± 5.394	.374[a]	.140	y=1.360+0.8	<0.001, HS
Diastolic Blood Pressure	96.48 ± 18.296				
Homocysteine	13.17 ± 5.394	.306[a]	.094	y=4.46+0.09x	<0.001, Sig

Table 4: Association of BMI with Mean Serum Homocysteine

BMI (kg/m^2)	Group-A	Group-B	Group-C	P-ValueLS
18 - 24.9	10.2 ± 4.3	11.6 ± 3.3	12.5 ± 4.7	0.2, NS
25 - 29.9	11.7 ± 4.5	12.8 ± 3.9	15.3 ± 5.5	0.01, Sig
>30	11.2 ± 6.7	15.4 ± 6.7	20.2 ± 7.1	0.16, NS

Table 5 Association of Gravidity with Mean Serum Homocysteine

Gravidity	Group-A	Group-B	Group-C	P-ValueLS
G_1	12.4 ± 4.4	12.34 ± 3.9	15.96 ± 6.6	0.01, Sig
G_2	9.8 ± 4.2	13.53 ± 5.1	14.17 ± 6.6	0.07, NS
G_3	10.5 ± 4.1	10.95 ± 3.7	18.98 ± 6.8	0.001, HS
≥G_4	12.3 ± 5.5	11.65 ± 2.7	12.66 ± 6.0	0.95, NS

Table 6: Association of Gestational Age with Mean Serum Homocysteine

Gestational Age (in wks)	Group-A	Group-B	Group-C	P-ValueLS
28 – 32	12.82 ± 7.3	11.7 ± 4.9	18.04 ± 6.8	0.5, NS
32 – 36	11.58 ± 3.6	11.1 ± 3.5	15.83 ± 6.7	0.01, Sig
36 – 40	12.66 ± 4.0	11.3 ± 4.6	15.45 ± 6.1	0.001, HS

preeclampsia) than those in Group-A (normotensive) and Group-B (mild preeclampsia) (P<.001), but the levels of mean serum homocysteine were not significantly different between Group-B and Group-A. Our observations are in consonance with Robert W. Power et al (1998) and Rajkovic, Aleksandar et al (1999) studies in which mean homocysteine levels were greater in preeclampsia than normotensive controls (P < 0.01). Powers RW 2001, Ingec M et al 2005,Singh U 2008,Yurdanur G Acılmıs2011, Shahid A. Mujawar 2011 and Ezzatalsadat Haji Seid 2012 also observed similar results that homocysteine is raised in women with preeclampsia than in normotensive women.

De Laet C1999, Brasileiro RS 2005 and Martinez Laborda S 2008 observed thathomocysteine level may vary depending on age, sex, insulin resistance, and pubertal status. It has also been shown to positively correlate with age and sex in healthy children. In their study on healthy children, De Laet et al. determined that the homocysteine level of the adolescents, 15-19 years of age, was higher than that of the children, 5-9 years of age. In the same study, a comparison by sex of healthy children, 15-19 years of age, showed that the homocysteine level was statistically significantly higher in the males than in the females. Ayhan ABACI in their study also observed that thehomocysteine level was significantly correlated with age, in both the control and obese groups, and the male subjects had significantly higher homocysteine levels than female subjects in the obese group.Similarly De Laet C et al, Taskin G et al and Angelova EA also observed that homocysteine levels significantly increased with age and higher in men than in women in each age group. In our study mean serum homocysteine levels with mean age increases with severity increased (positive). The overall r was 0.09 showed positive correlation between the

mean age and mean serum homocysteine levels.

In our study a positive correlation was observed between the Systolic as well as diastolic blood pressure and serum homocysteine. Our findings were consistent with findings observed by Ganji V, Kafai MR (2004) and Sengwana D (2013) who found the statistically significant relation between homocyseine and systolic and diastolic blood pressure.

It was observed in our study, that the mean serum homocysteine levels increase with increase in BMI of the women with preeclampsia (both mild and severe). Sanlier N and Yabanci N.in their study observed that as long as body weight and Mean fat mass percentage increase homocysteine level also increases. They concluded that obesity effects blood lipid and homocysteine levels negatively.Similarly Karatela RA (2009) found a raise in BMI was associated with elevated homocysteine levels and reduced vitamins levels among hypertensive patients while Mio Nakazato, et al, Han et al and Mariano Mascarenhas in their studies observed that Serum homocysteine levels are not significantly associated with body mass index,

Negative correlation was observed (r=-0.1) in mean serum homocysteine levels with their gravidity. In our study mean homocysteine level was slightly lower in 32 to 34 weeks than 28 to 32 weeks and again increased in 36 to 40 weeks. Similarly there was no significant variation with the mean period of gestation at which the samples were taken with the serum homocysteine concentrations. This may be due to the factor that the time window in which the samples were taken itself was short, and the study by Murphy et al and Dodds et al on the homocysteine levels longitudinally through pregnancy suggests that the homocysteine levels may be more stabilized from 8 weeks of gestation onward up to the middle of second trimester; there is a reduction in homocysteine levels prior to 8 weeks and a rise in homocysteine levels in the third trimester.

Conclusion

In our study also it has been observed that serum homocysteine levels were significantly elevated in severe preeclampsia and also associated with severity of preeclampsia. Serum homocysteine levels also have positive correlation with systolic and diastolic blood pressure. Maternal demographic status except age and BMI had no significant association with serum homocysteine.

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