Original Research Article

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Study of Serum Homocysteine Levels in Preeclampsia and Relation to Its Severity and Obstetric Outcome

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Abstract

Hypertensive disorder in pregnancy is a common disease. The incidence of pregnancy induced hypertension (PIH) in India range from 5 -15%. Though the exact cause of PE is still undecided, endothelial dysfunction with associated intense vasospasm has been implicated in its causation. Recently homocysteine, a metabolite of essential aminoacid methionine, has been postulated to produce oxidative stress and endothelial cell dysfunction. The present study is aimed at the estimation of homocysteine concentration in both pre-eclamptic and normotensive pregnant women, thereby deducing its relation in causation of pre-eclampsia. The present study was carried out in 90 pregnant women of whom 45 were Preeclampsia (cases) and 45 were normotensive pregnant women(controls) admitted to R.L.Jalappa Medical College, Kolar, Maternal serum homocysteine levels were measured by ELISA method. *Results*: In the present study of 45 preeclamptic women and 45normotensive pregnant women in whom the serum homocysteine levels were compared. Majority of the subjects were in the age group of 21 -25years in both the groups. All the ninety subjects were primigravida. We have found that there is a statistically significant correlation between serum homocysteine levels and severity of PE i.e. the mean serum Hcy levels in controls (7.9±1.3 mol/l), mild preeclampsia (14.5±3.2 mol/l) and severe preeclampsia (19.6±3.9 mol/l). Serum homocysteine levels increased with increasing severity of PE with p - value being highly significant ($p<0.001$). Significant positive correlation was found between serum homocysteine levels and SBP and DBP i.e. with increase in SBP and DBP there was significant increase in serum homocysteine in preeclampsia. In our study, hyperhomocysteinemia was associated with poor pregnancy outcome in preeclampsia; IUGR (48.9%), Preterm (28.9%) and SGA (15.6%). *Interpretation and Conclusion*: Homocysteine concentration decreases during normal pregnancy, but this does not occur in preeclampsia. In preeclampsia there is increase in levels of homocysteine compared to normotensive women. In PET, homocysteine levels further increase with increasing severity of preeclampsia. Hyperhomocysteinemia is associated with poor pregnancy outcome.

Keywords: Homocysteine; Normotensive; Preeclampsia.

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Introduction

Preeclampsia is an obstetric condition characterized by hypertension and proteinuria. This obstetric complication causes preterm delivery, intrauterine growth restriction, maternal and fetal morbidity and mortality [1,2]. In 1998, National Center for Health Statistics showed hypertension was the most common medical risk factor in pregnancy. The worldwide incidence of pre-eclampsia is 5-7% of all pregnancies [3]. The incidence is still higher in India of around 8-10% [4]. As per the World Health Report the

maternal mortality during pregnancy and puerperium is around 12%. In developing countries, hypertension accounts for 17% of direct obstetric deaths [5]. Mortality rate of preeclampsia in the developing and developed countries varies, it has been recorded that approximately eight hundred women die from pregnancy and child birth related complications around the world every day [6].

Preeclampsia is multifactorial. Till date its etiology is indefinite. Studies conducted on animal models to know the pathophysiology of preeclampsia reported that abnormal trophoblast invasion, oxidative stress, inappropriate maternal vascular damage and anomalous maternal-fetal immune interactions play an important role [7].

Though the exact cause of pre-eclampsia is still undecided, endothelial dysfunction with associated intense vasospasm has been implicated in its causation. Recently homocysteine, a sulfur containing essential aminoacid has been implicated as a missing link in causation of preeclampsia. Current hypothesis states that increased levels of homocysteine promote oxidative stress which might damage the vascular endothelium of the developing placenta, thereby increasing contractile response and production of pro-coagulants and vasoconstriction [8]. Further, homocysteine levels is known to increase with increasing severity of preeclampsia.

Present study is aimed at to shed light on Homocysteine, which can be a missing link in the pathogenesis of preeclampsia and also to deduce its effect in relation to severity of pre-eclampsia.

Aims and Objectives

1. To show a relationship between serum homocysteine levels in preeclampsia.
2. Find if any correlation between homocysteine levels and severity of preeclampsia
3. To associate levels of homocysteine in preeclampsia and obstetric outcome.

Materials and Methods

Source of Data

In the present study, a total number of 90 Pregnant women were included out of which 45 were Preeclampsia (cases) and 45 were normotensive pregnant women (control) who attended Department of Obstetrics and Gynecology in R L Jalappa Hospital and Research Centre, attached to Sri Devaraj Urs Academy Of Higher Education, Tamaka, Kolar between March 2015 to July 2016.

Study Design

Case control study

Sample Size

90- 45 control group

- 45 study group

Collection of Data

Data was collected by patient evaluation, which was done by detailed history taking and clinical examination through structured proforma speciall y designed for this study.

All 90 pregnant women were primi gravidae and divided into 2 groups.

45 – pregnant women with pre-eclampsia (study group).

45 – normotensive pregnant women (control group)

Inclusion Criteria

1. Preeclampsia defined as blood pressure constantly greater than 140/90 mmHg with proteinuria with no urinary tract infection and with no previous history of hypertension.
2. Primigravida with singleton pregnancy and gestational age of 28 -40 weeks.

Control Group

The control group includes normotensive primigravida with gestational age beyond 28weeks.

Study Group

All primigravida beyond 28 weeks of gestation with preeclampsia diagnosed as per National High Blood Pressure Education Programme working group (NHBPEP) Classification were included in the study group.

Exclusion Criteria

Pregnant women with

- Diabetes mellitus
- Chronic hypertension
- Renal or liver disease
- H/o thromboembolism
- Neural tube defects
- Repeated miscarriage

- Abruptio placenta
- Preterm labor and delivery
- H/o smoking
- H/o previous medical illness.
- Anemia
- Multigravida
- Gestational hypertension
- Women who were on folic acid and Vit B12 supplements.

The subjects in the two groups were age and gestational age matched, were included in the study after obtaining the ethical committee approval of the institute and patient information consent. A standard proforma was used to collect the data.

Subjects in control and study group underwent detailed clinical examination and following investigations.

- Urine for albumin, sugar and microscopy.
- Complete hemogram
- Blood grouping and Rh typing
- HIV and HBsAg
- RBS, blood urea, serum creatinine, serum uric acid 43
- Liver function tests (if required)

Special Investigation

- Serum homocysteine levels.

Specimen Collection

Five ml of fasting blood samples are collected in plain vacutainer from control and preeclamptic subjects. Samples are centrifuged at 3000 x g to separate serum and stored at -20^{0}C in ultra-freezer until analysis. Homocysteine is measured by ELISA method.

Estimation of Serum Homocysteine Level

The method used for assay of serum homocysteine level was Enzyme Linked ImmunoSorbent Assay (ELISA) with the aid of Micro ELISA plate reader.

Assay Method

The kit uses a double- antibody sandwich enzyme-linked immunosorbent one-step process assay (ELISA) to assay the level of homocysteine (Hcy) in samples.

Results

The present study is carried out from March 2015 to July 2016 to estimate serum homocysteine levels in pre-eclampsia and its relation to severity and perinatal outcome. The total of 90 cases were studied and results obtained are presented as here under:

Table 1 shows there is no significant differences in age, gestational age between control and study groups. The mean age in control group was 24.8 years and in study group was 23.9 years. Women in study group had higher mean systolic and diastolic blood pressure ($p < 0.001$).

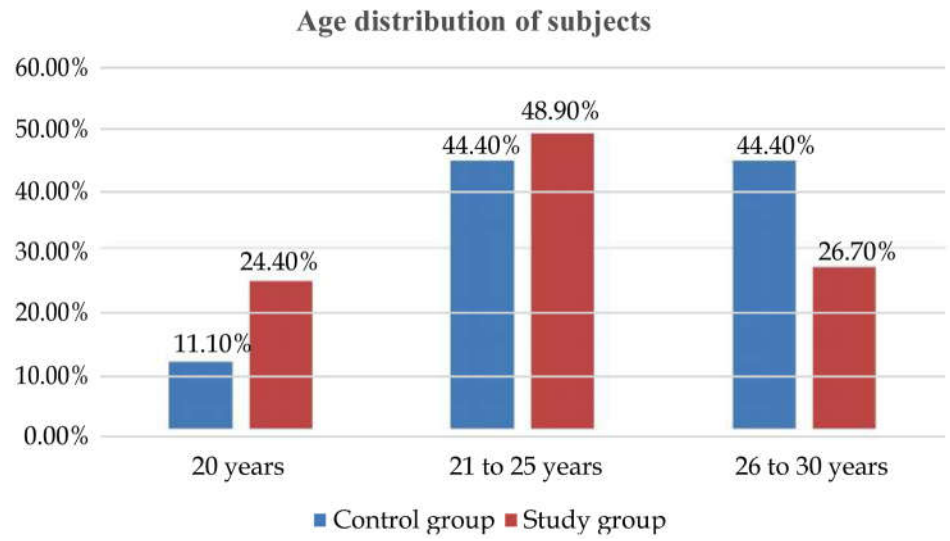
Majority of subjects in both the groups were in the age group 21 to 25 years. In control group, 44.4% of the subjects and 48.9% subjects of study group belong to 21-25 years age group. There was no significant difference in age distribution between two groups (Table 2 & Graph 1).

Table 1: Characteristics of control and study groups

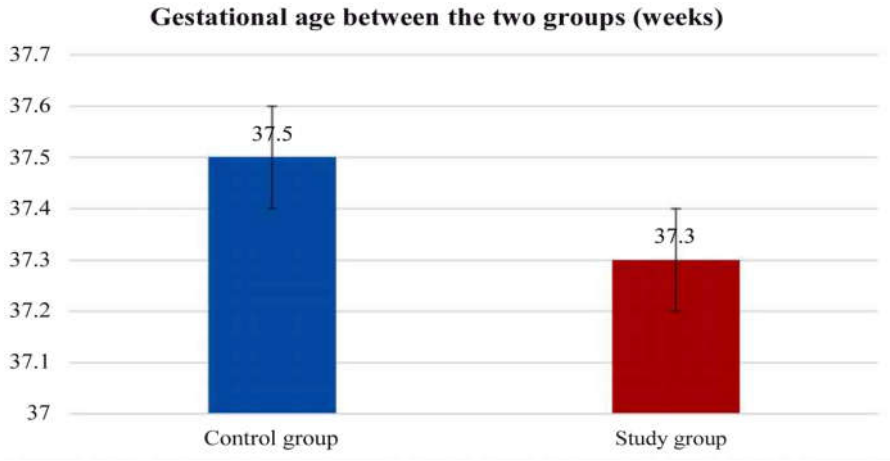
Parameter	Control group (n=45)	Study group (n=45)	p value
Age (years)	24.8± 3.2	23.9 ± 3.3	0.114
Gestational age (weeks)	37.5±1.4	37.3± 1.2	0.523
Systolic Blood pressure(mmHg)	113.1±7.8	150.5± 11	< 0.001*
Diastolic Blood pressure (mmHg)	74.4 ± 4.6	103±11.3	< 0.001*

Table 2: Age distribution of subjects between two groups

	Groups			
	Control Group		Study Group	
	No. of Subjects (n)	Percentage (%)	No. of subjects(n)	Percentage (%)
Age (years)				
20	5	11.1%	11	24.4%
21 to 25	20	44.4%	22	48.9%
26 to 30	20	44.4%	12	26.7%



Graph 1: Age distribution of subjects between two groups



Graph 2: Bar diagram showing Period of Gestation between two groups

Table 3: Gestational age between two groups

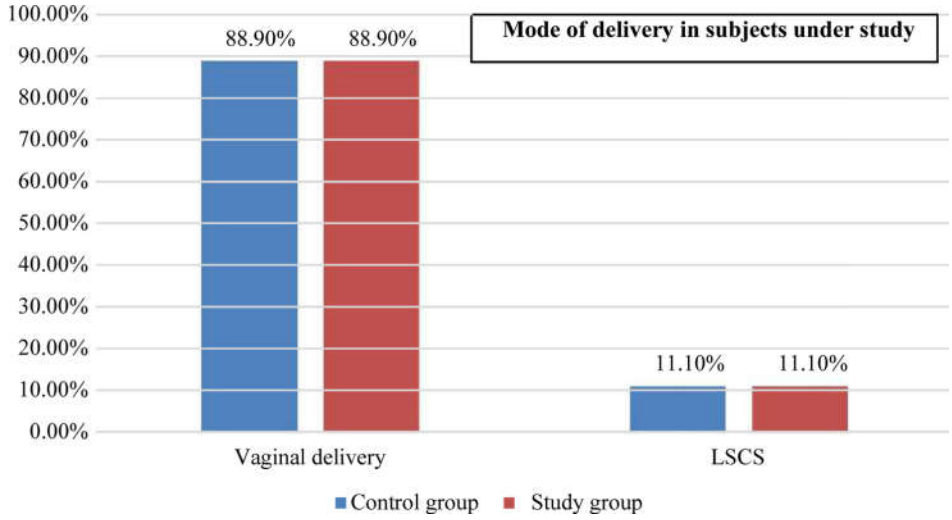
	Gestational Age (Weeks) Mean ±SD	P value
Groups		
Control group	37.5 ± 1.4	0.523
Study group	37.3 ±1.2	

Mean period of gestation among controls was 37.5±1.4 weeks and in cases was 37.3±1.2 weeks. There was no significant difference in period of gestation between two groups. (Table 3 & Graph 2).

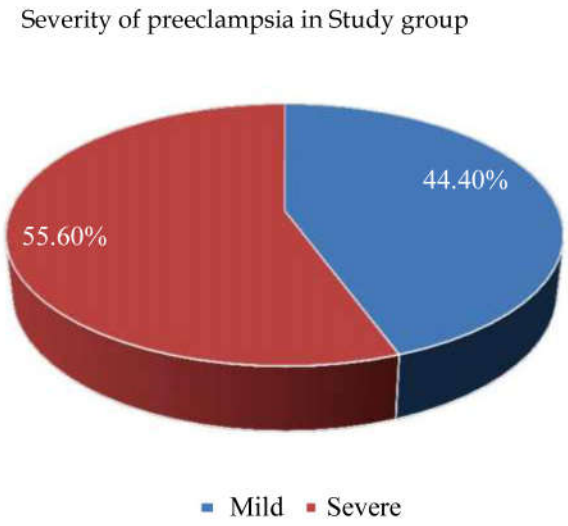
In both cases and controls 88.9% delivered at term vaginally and 11.1% were delivered by LSCS. This was no difference in mode of delivery between two groups. (Table 4 & Graph 3).

Table 4: Mode of Delivery between two groups

	Group(n=90)			
	Control Group(n=45)		Study Group (n=45)	
	N	%	N	%
Mode of Delivery				
Vaginal delivery	40	88.9%	40	88.9%
LSCS	5	11.1%	5	11.1%



Graph 3: Bar diagram showing Mode of Delivery between two groups



Graph 4: Pie diagram showing Severity comparison between two groups

Table 5: Distribution of study group based on Severity of preeclampsia

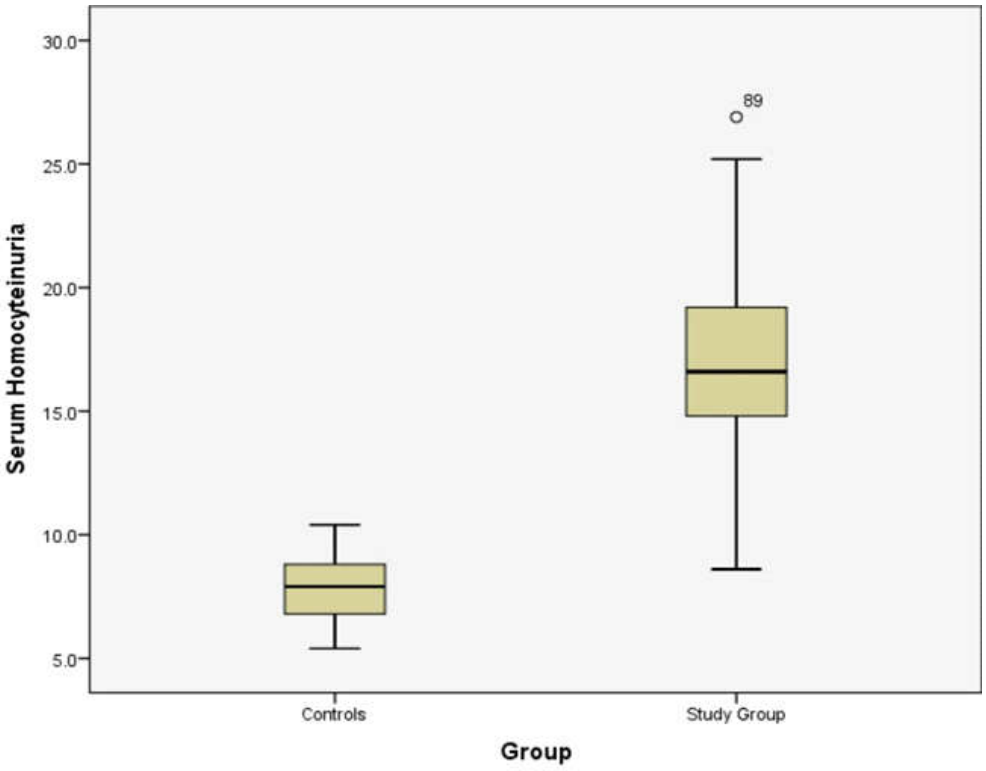
	Study group (n=45)	
	No. of subjects (n)	**Percentage (%)**
Preeclampsia severity		
Mild	20	44.4%
Severe	25	55.6%

Total number of subjects in study group were 45.Among them, 44.4% had mild preeclampsia and 55.6% had severe preeclampsia. (Table 5 & Graph 4).

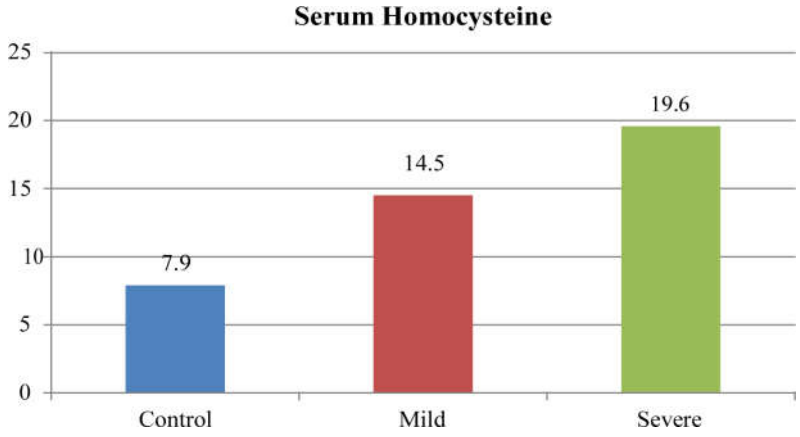
Mean Homocysteine levels in controls was 7.9± 1.3µmol/l and among cases was 17.3 ± 4.4µmol/l.. This difference in mean homocysteine levels was statistically significant. Higher homocysteine levels was observed in cases than controls (Table 6 & Gaph 5).

Table 6: Comparison of Serum Homocysteine levels between two groups

	Serum Homocysteine(µmol/l) Mean ± SD	**P value**
Groups		
Control group	7.9 ± 1.3	<0.01*
Study group	17.3 ± 4.4	



Graph 5: Box plot showing Serum Homocysteine levels comparison between two groups



Graph 6: Bar diagram showing Mean serum Homocysteine levels in control group, mild and severe preeclampsia groups

Table 7: Comparison Mean serum Homocysteine levels between controls, mild and severe preeclampsia

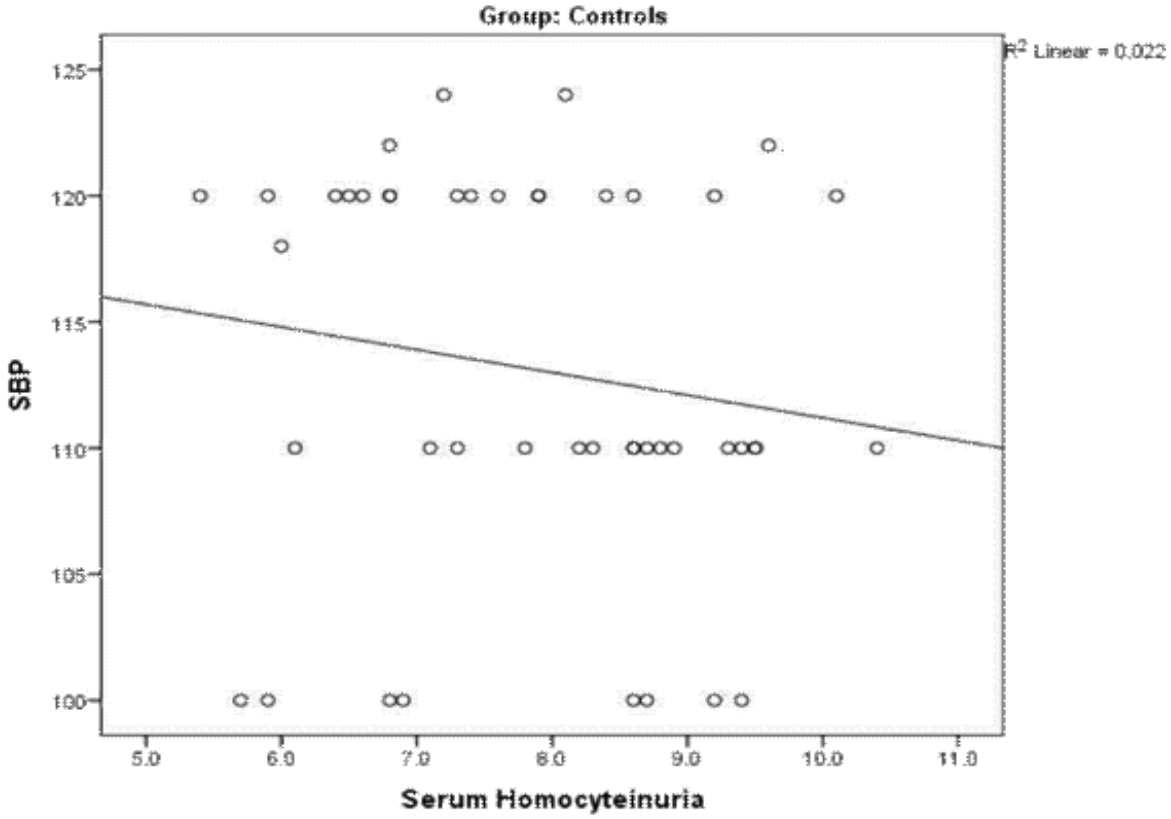
Group	Serum Homocysteine levels (µmol/l) Mean ± SD
Control	7.9±1.3
Mild preeclampsia	14.5±3.2
Severe preeclampsia	19.6±3.9
p value	< 0.001

Mean Homocysteine among controls was 7.9± 1.3µmol/l, among subjects with mild preeclampsia 14.5 ± 3.2µmol/l and among subjects with severe preeclampsia 19.6 ± 3.9µmol/l This difference in mean serum Homocysteine levels was statistically significant.(Table 7 & Graph 6).

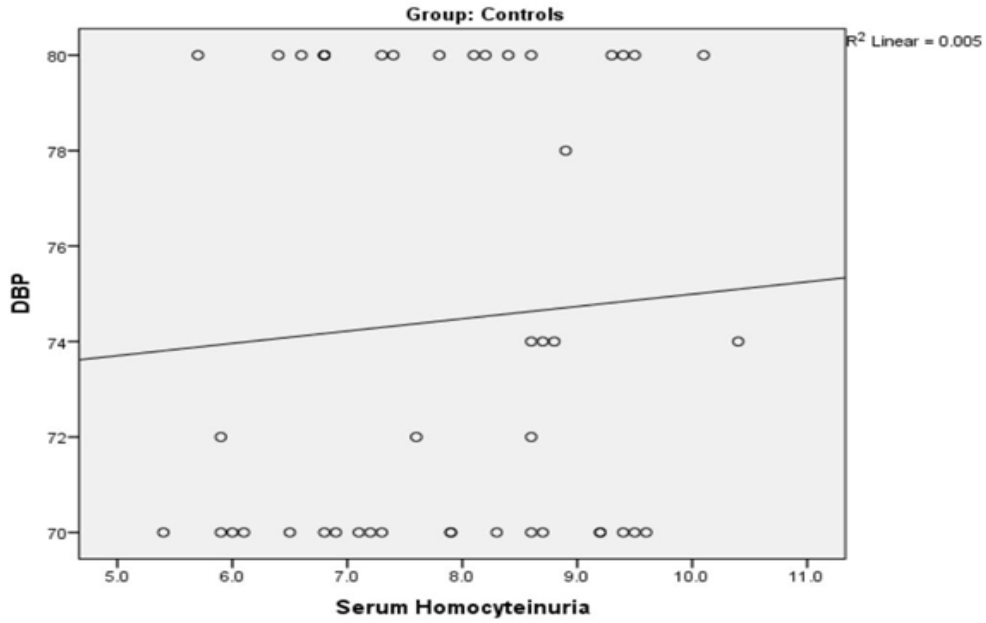
There was negative correlation between Homocysteine and SBP among controls, and slight positive correlation was observed between homocysteine and DBP. However there was no significant correlation between them in control group. (Table 8 & Graph 7 and 8).

Table 8: Correlation between Serum Homocysteine levels and Period of gestation, SBP and DBP in controls

Control Group	Serum Homocysteine	Period of Gestation	SBP	DBP
Serum Homocysteine				
Pearson Correlation	1	-0.272	-0.149	0.072
P value		0.071	0.328	0.638
N	45	45	45	45



Graph 7: Scatter plot showing correlation between serum homocysteine and SBP in controls



Graph 8: Scatter plot showing correlation between serum homocysteine and DBP in controls

Table 9: Correlation between Serum Homocysteine levels and Period of gestation, SBP and DBP in Study group

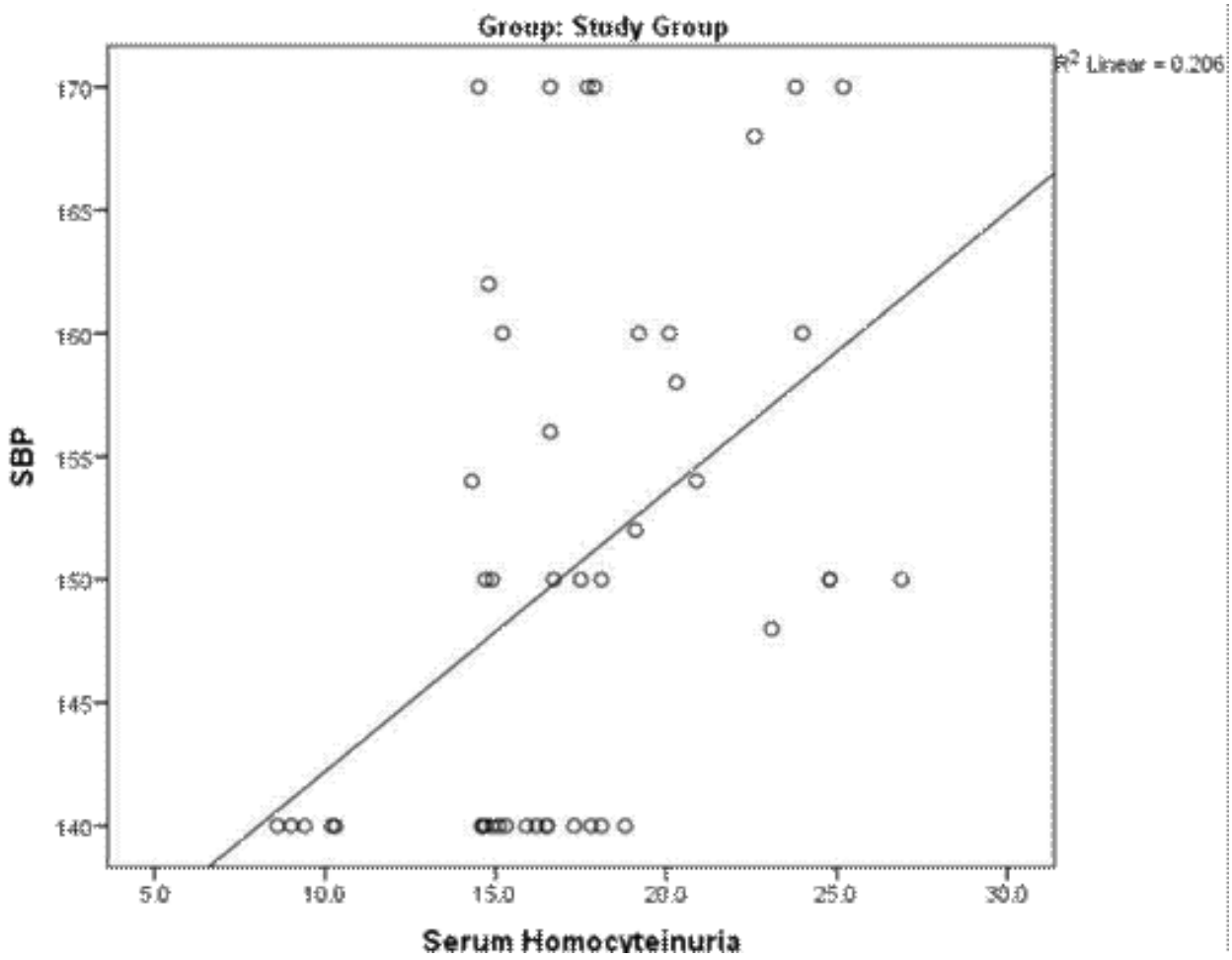
Study Group	Serum Homocysteine	Period of Gestation	SBP	DBP
Serum Homocysteine				
Pearson Correlation	1	0.023	0.454**	0.544**
P value		0.878	0.002*	<0.001*
N	45	45	45	45

There was significant positive correlation between Homocysteine and SBP and DBP among cases. i.e. with increase in SBP and DBP there was significant increase in Serum homocysteine levels in study group. (Table 9 & Graph 9 and10).

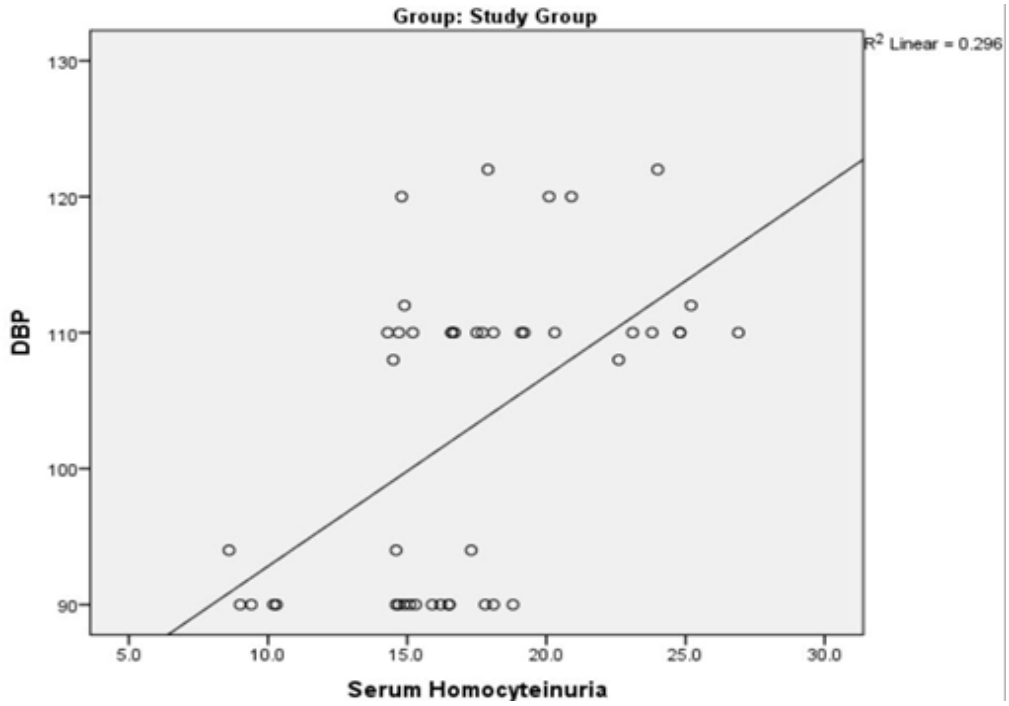
Mean serum Homocysteine levels were high with increase in albumin levels in the urine. There was significant difference observed in mean Homocysteine levels in comparison with urine albumin levels (Table 10).

Table 10: Comparison of Proteinuria with Mean Homocysteine levels

Estimation Proteinuria on Dipstick	Serum Homocysteine(µmol/l) Mean ± SD
Proteinuria	
1+	14.3 ± 3.5
2+	19.8 ± 4.2
3+	18.1 ± 3.2
4+	20.7 ± 4.5
Traces	14.5 ± 3.1
P value	0.001*



Graph 9: Scatter plot showing correlation between serum homocysteine and SBP in Study group



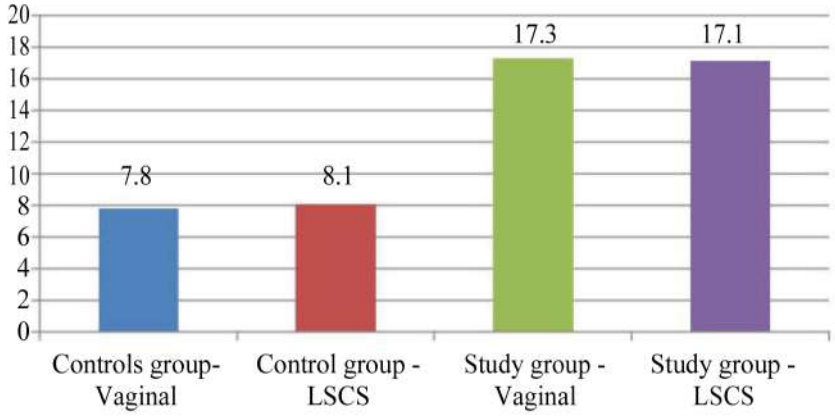
Graph 10: Scatter plot showing correlation between serum homocysteine and DBP in Study group

Table 11: Comparison of Mean Homocysteine levels with mode of delivery

				Serum Homocysteine(µmol/l) Mean ±SD	P value
Group	Control	Mode of Delivery	Vaginal	7.8 ± 1.3	0.655
			LSCS	8.1 ± 1.3	
	Study	Mode of Delivery	Vaginal	17.3 ± 4.6	0.919
			LSCS	17.1 ± 2.4	

In this study, among controls mean homocysteine levels in vaginal delivery subjects was 7.8± .3µmol/l and in LSCS subjects was 8.1±1.3µmol/l. There was no significant difference in mean Homocysteine levels between modes of delivery in controls. In this study, among cases mean Homocysteine levels in vaginal delivery subjects was 17.3±4.6µmol/l and in LSCS subjects was 17.1±2.4µmol/l. There was no significant difference in mean Homocysteine levels between modes of delivery in cases. (Table 11 & Graph 11).

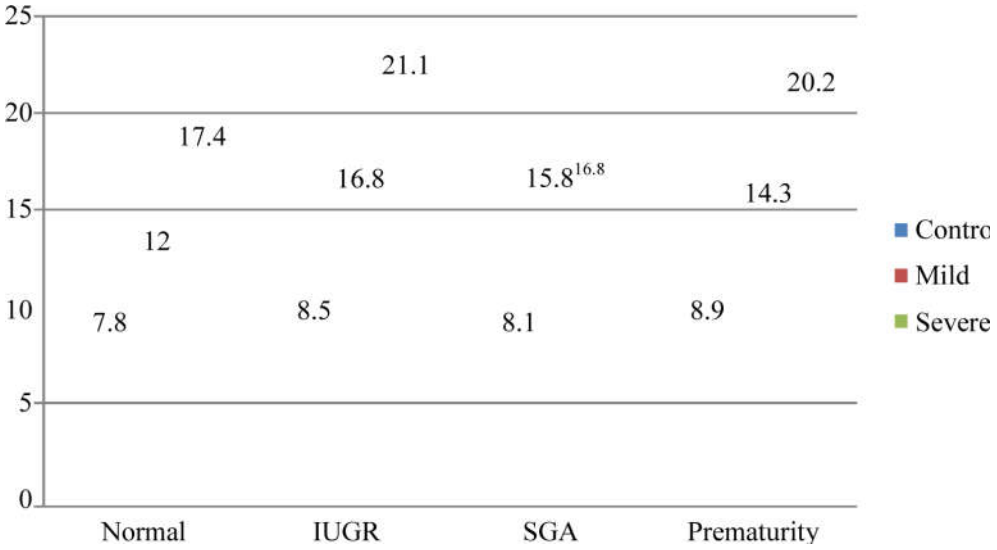
In the study mean Homocysteine levels were highest in IUGR subjects among controls and subjects with mild and severe preeclampsia. This difference was statistically significant. (Table 12 and Graph 12).



Graph 11: Bar diagram showing Comparison of Mean Homocysteine levels with mode of delivery between two groups

Table 12: Comparison of Mean Serum Homocysteine levels and Perinatal

	Severity					
	Control		Cases			
	No	Mean Serum Homocysteine	Mild No	Mean Serum Homocysteine	Severe No	Mean Serum Homocysteine
Perinatal Outcomes						
Normal	38 (84.4%)	7.8	9 (45%)	12.0	7 (28%)	17.4
IUGR	2 (4.4%)	8.5	7 (35%)	16.8	15 (60%)	21.1
SGA	5 (11.1%)	8.1	4 (20%)	15.8	3 (12%)	16.8
Prematurity	8 (17.8%)	8.9	6 (30%)	14.3	7 (28%)	20.2
P value		<0.001*		<0.001*		<0.001*



Graph 12: Comparison of Mean Serum Homocysteine levels and Perinatal

Discussion

Pre-eclampsia is a leading cause of maternal and fetal morbidity. Although, the exact cause of pre-eclampsia is still unknown, it is known that in pre-eclampsia the basic pathology is endothelial dysfunction and intense vasospasm. Recently homocysteine, a metabolite of essential aminoacid methionine, has been postulated to produce oxidative stress and endothelial cell dysfunction.

Elevated plasma homocysteine concentration is an independent risk factor for peripheral vascular diseases and for coronary artery diseases.

Serum homocysteine may prove to be the missing link in the etiology of pre-eclampsia.

The most relevant findings in the present study were (i) elevation of maternal serum homocysteine levels in preeclampsia compared to normal pregnant women, (ii) a significant increase in the maternal serum homocysteine levels in both mild and severe preeclampsia groups than in control group, (iii) a significant positive correlation between serum homocysteine levels and systolic and diastolic blood pressure and proteinuria (iv) a significant correlation between serum homocysteine levels and perinatal outcome.

In the present study, the mean serum homocysteine levels in the control is 7.9±1.3µmol/l. Our study is supported by various other studies viz., Singh Urmila et al. [9]., showed that the value in the normotensive pregnant women is 11.5±4 µmol/l, Karg et al. (9.39±1.3µmol/l), Rajkovic et al. [10] (9.93 ± 1.3 µmol/l), Hoque et al. [11] (6.86±2.47µmol/l), Georgios Makedos et al. [12] (6.40 µmol/l).

Levels of homocysteine are generally lowered during pregnancy either due to physiological response to pregnancy like hemodilution, increased glomerular filtration rate, hormonal changes or increased demand for methionine by both mother and the fetus. In our study, 45 subjects were diagnosed PE and the mean serum homocysteine level was 17.3 ±

4.4 µmol/l in them which was statistically highly significant (p<0.01) compared to control group. This observation conforms to other similar studies done by Rajkovic et al., Khosrowbeygi et al. [13], Hoque et al, Karunashree et al. [14].

This shows that the decrease in homocysteine levels which occurs in normal pregnancy do not occur in pre-eclampsia. So it is possible that the increase in homocysteine concentration in pre-eclampsia is related to the defect in the mechanism that usually decreases homocysteine during normal pregnancy.

In our study group (diagnosed PE cases), 20 cases were mild PE, 25 cases were severe PE. The mean serum homocysteine levels in mild PE case s was 14.5±3.2µmol/l, which when compared to normotensive pregnant wo men is elevated and is highly statistically significant (p<0.001).These results were consistent with results of Cotter et al and Khosrowbeygi et al; however this findings differ from Metin Ingec et al. [15] showed that serum homocysteine levels were not significantly different between mild preeclampsia (7.7±2.4µmol/l) and controls (6.7±1.6µmol/l) and other study conducted by Hasanzadeh et al. [16] detected no significant difference of homocysteine levels among mild preeclampsia and control groups (10.4±2.3µmol/l and 8.8±2.8µmol/l respectively).

In the present study, the mean serum homocysteine levels in severe PE cases is 19.6± 3.9µmol/l, which is highly statistically significant (p<0.001) than those women without preeclampsia. Similar studies done by Ingec et al., Cotter et al. and Khosrowbeygi et al found same results.

In present study, the mean serum homocysteine levels were significantly higher in severe PE cases (19.6±3.9 µmol/l) than in mild PE cases (14.5± 3.2µmol/l) and p< 0.001 which is highly statistically significant. This suggests that homocysteine levels are directly correlated with the severity of pre -eclampsia.

Our study is supported by Singh Urmila et al., who found that the mean value in pre-eclamptic pregnant women was 13.6±3.5 µmol/l in mild PE and 16.69±4.18 µmol/l in severe PE group. In other studies conducted by Rajovic et al., mean serum homocysteine levels in pre-eclamptic pregnant women was 13.9±4.8 µmol/l, Asmitha Kulkarni et al. [17] found it in the range 14.8±7.3 µmol/l. However, Salikan F et al found that there is no significant difference statistically in homocysteine levels between mild and severe preeclampsia groups (p>0.05).

Our study showed significant positive correlation between Homocysteine and SBP and DBP among cases. i.e. with increase in SBP and DBP there was significant increase in Serum homocysteine in cases. This positive correlation was also seen in a study conducted by Ferdusai et al. [18]. Positive correlation was noticed between serum homocysteine levels and urinary total protein (p value is 0.001). These findings were consistent with findings of Ingec et al. and Ferdusai et al.

In our study, maternal serum homocysteine levels did not show any correlation with mode of delivery (LSCS and vaginal delivery). A study by Jian Van, in which majority of the subjects were delivered by LSCS not related to homocysteine level. But Karunashree et al. demonstrated that majority of the subjects who underwent LSCS had hyperhomocy-steinemia.

In present study, we found that hyperhomocy-steinemia has increased incidence of preeclampsia with poor pregnancy outcome. Our study showed pregnancy outcome like IUGR (48.9%), Preterm (28.9%) and SGA (15.6%). Studies done by Rajkovic and Stein Emil et al. [19] found elevated homocysteine levels associated with preterm delivery. Leida et al. found correlation between homocysteine and IUGR. Homocysteine has atherogenic property and proved to be independent risk factor for atherosclerosis and atherothrombosis. The reason for this poor pregnancy outcome is due to hyperhomocysteinemia causing thrombosis in the placental blood vessels leading to ischemia and infarction of placenta resulting in fetoplacental insufficiency.

It is possible that in pre-eclampsia, the elevated homocysteine level injures the vascular endothelium which contribute to the pathogenesis of PE. In addition vascular endothelium in pregnant women may be more sensitive to injury. Therefore, elevation in homocysteine levels may lead to endothelial injury with subsequent activation of various factors that eventually results in pre-eclampsia.

Conclusion

In present study, maternal serum Hcy levels were significantly increased in preeclampsia compared to normotensive subjects. Serum Hcy was significantly rised in severe pre-eclampsia than in mild preeclampsia. This shows association between serum Hcy and severity of preeclampsia. Our findings suggested that hyperhomocysteinemia is related to poor pregnancy outcome like IUGR, prematurity and SGA.

The exact mechanism how hyperhomocysteinemia promotes endothelial dysfunction is still unclear,

but involves both cytotoxic and oxidative stress mechanism to promote endothelial dysfunction in preeclampsia. Therefore, further cohort or case control studies with large sample should be carried out to evaluate the association of serum Hcy with preeclampsia. Elevated levels of homocysteine can be due to genetic or nutritional deficit or a combination of both. Nutritional defects involve inadequate intake of folic acid, vitamin B12 and vitamin B6.All these vitamins are involved in metabolism of homocysteine. Hyperhomocysteinemia is a marker of low B - vitamin status or decreased methylation capacity of cells.

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

Elevated levels of homocysteine can be reduced by administering vitamins which help by increasing the metabolism of homocysteine. The internationally accepted treatment for hyperhomocy-steinemia is using a combination of 3 vitamins viz., folic acid 400µg, vitamin B12 500 µg and pyridoxine 10 mg initiating from conception.

Continuing these agents in the therapeutic dose in second and third trimester would help to reduce increased levels of homocysteine and might help substantially to reduce the adverse pregnancy outcome.

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