International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2021; 5(6): 290-293
Received: 01-09-2021
Accepted: 03-10-2021

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Homocysteine association in preeclampsia and normotensive patients in a semi urban setting in Tamilnadu

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DOI: https://doi.org/10.33545/gynae.2021.v5.i6e.1093

Abstract
Introduction: Hypertensive disorders of pregnancy complicate 5-10 percent of all pregnancies [1]. It occurs mainly because of vasospasm and vascular endothelial malfunction that occurs after 20 weeks of gestation. Preeclampsia is a condition characterised by hypertension with proteinuria or hypertension with multiorgan involvement. It is one of the causes of maternal mortality and morbidity and also affects fetal outcomes. In this study we are going to know the association of increased homocysteine levels with severity of pre eclampsia and its fetal outcomes.
Materials and Method: We conducted a case control study in a semi urban setting in tamilnadu to find the association of serum homocysteine levels in preeclampsia and normotensive pregnancy and its correlation with severity of preeclampsia. 100 women with singleton pregnancy and gestational age of 28-40 weeks were selected into study and control group consecutively as and when they presented. After a detailed clinical history and examination and routine blood investigations were taken along with 5ml blood for serum homocysteine levels.
Observation and Results: Serum homocysteine levels were measured in both cases and control groups and was found to significantly raised among patients with preeclampsia. Serum homocysteine levels were raised depending upon the severity of preeclampsia. There was statistically significant difference found between mild and severe preeclampsia cases in homocysteine values who delivered IUGR babies. (p value <0.05).
Discussion: Serum homocysteine levels were raised in 96% of the cases diagnosed with preeclampsia. Comparison of homocysteine based on perinatal outcomes in different groups showed that there was statistical significance in raise of serum homocysteine levels in women who delivered IUGR babies.
Conclusion : Our study concluded that serum homocysteine levels were significantly raised in cases with preeclampsia and the levels of homocysteine directly correlated with severity of preeclampsia. The study also concluded that serum homocysteine levels were raised in cases who presented with various maternal complications and those who had IUGR babies.

Keywords: homocysteine, preeclampsia, proteinuria, IUGR (Intrauterine growth restriction)

Introduction
Hypertensive disorders of pregnancy complicate 5-10 percent of all pregnancies [1]. It forms one of the most deadly triad along with haemorrhage and infection. It occurs mainly because of vasospasm and vascular endothelial malfunction that occurs after 20 weeks of gestation. Pre eclampsia is a condition characterised by hypertension with proteinuria or hypertension with multiorgan involvement like hemolysis, abnormal liver function, pulmonary edema, neurologic involvement and thrombocytopenia. It is one of the causes of maternal mortality and morbidity and also affects fetal outcomes. The exact cause of preeclampsia is still unknown. It is assumed to have occurred due to abnormal placentation. Mostly unpropitious outcomes of the disease is because of not identifying the high risk cases and not managing them adequately during the antenatal period. Early detection can prevent a lot of complications like fetal growth restriction, perinatal mortality and placental abruption.
Among various biohumoral parameters for preeclampsia, homocysteine is been considered a possible remarkable cause of vascular damage [2-6]. Serum concentrations of homocysteine decrease during pregnancy. This occurs because of its association with the physiologic fall in albumin during pregnancy, as well as with folic acid supplementation [7].

Homocysteine is a non proteinogenic amino acid which mainly consists of sulphur, it is derived from methionine that is involved in methylation and sulphuration pathways such as lipid peroxidation and oxidative stress. It has structural similarity with cysteine. Blood concentration of homocysteine is mainly influenced by two factors that is folic acid and Vitamin B12. Increased levels of homocysteine is associated with vascular diseases. Maternal hyperhomocysteinemia is associated with placental vascular abnormalities which leads to pre eclampsia, abruption and recurrent pregnancy loss. Hyperhomocysteinemia can also lead to dysfunction of the endothelium through various other mechanisms. Homocysteine will also affect the fibrinolytic pathway which in turn leads to preeclampsia.

Homocysteine is considered to be a valuable marker of vitamin B12, B6 and folic acid deficiency and precedes deficiency of circulating vitamins. Homocysteine measurements can be done as a measure to screen for deficiency of vitamins in both high risk and general population. When homocysteine levels are detected to be high in early pregnancy it is considered as an important predictor of both maternal and fetal risks of pre eclampsia in later pregnancy. Hence homocysteine remains as a marker to predict the severity of preeclampsia and can help in early detection and treatment of women with hypertensive disorders in pregnancy. Though similar studies are done in various parts of the world, it is less familiar in southern regions of India. This is a case control study in semi urban area in order to know the association of increased homocysteine levels with severity of preeclampsia and its fetal outcomes.

Aim

To study association serum homocysteine levels with preeclampsia and normotensive pregnancy

Objectives

To compare serum homocysteine levels between normotensive pregnant women and women with preeclampsia (both mild preeclampsia and severe preeclampsia).

To find out correlation between homocysteine concentration and severity of preeclampsia.

Study Design: Case control study

Study Setting: Department of Obstetrics and Gynaecology, Rajah Muthiah Medical College and Hospital, Chidambaram

Study Period: October 2019 to October 2021 (2 years)

Sample Size: 100

Inclusion Criteria

Women with singleton pregnancy and gestational age of 28-40 weeks

Control group: 50 normotensive pregnant women

Study group: 50 preeclamptic pregnant women (both mild and severe preeclampsia)

Members of the study group were selected consecutively as and when they presented

Exclusion Criteria

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, Anaemia, Patient refusal

Materials and Methods

During the period of October 2019 to October 2021, patients coming to Obstetrics and Gynaecology Department in Rajah Muthiah Medical College and Hospital, Chidambaram, Tamilnadu with above criteria are grouped. A detailed history including patient's age race, parity, socioeconomic status menstrual, medical history, obstetric, past, dietary and treatment history noted. General examination, systems and obstetric examinations done.

Routine investigations like complete blood count, blood grouping, urine albumin and sugar, HIV, HbsAg, Blood Sugar, VDRL and Ultra Sound are done and also special investigations of blood urea, serum creatinine, bleeding time, clotting time, liver enzymes, serum uric acid were done. Serum homocysteine levels were done in all patients. 5ml of venous blood drawn from antecubital vein and sent in labelled bottles to lab immediately and centrifuged within 3000 rpm for 5 mins. Serum separated is analysed by chemilumniscent microparticle immuno assay and values were recorded.

Observation and Results

Table 1: Distribution of age and parity in both cases and control groups

		Cases (n=50)		Controls (n=50)	
		No. of patients	**% of patients**	**No. of patients**	**% of patients**
Age (in years)	</= 20 years	9	18	7	14
	21 – 30 years	37	74	29	58
	>30 years	4	8	14	28
Parity	Primi	32	64	34	68
	Multi	18	36	16	32

Table 2: Association of homocysteine levels in normotensive women and those with mild and severe preeclampsia

	No. of patients (n=100)	**Mean serum homocysteine levels (in µmol/L)**	**SD**	**F value**	**P Value**
Control	50	6.72	1.41		
Mild Preeclampsia	14	13.76	3.16		
Severe Preeclampsia	36	17.88	1.94	359.13	0.000*

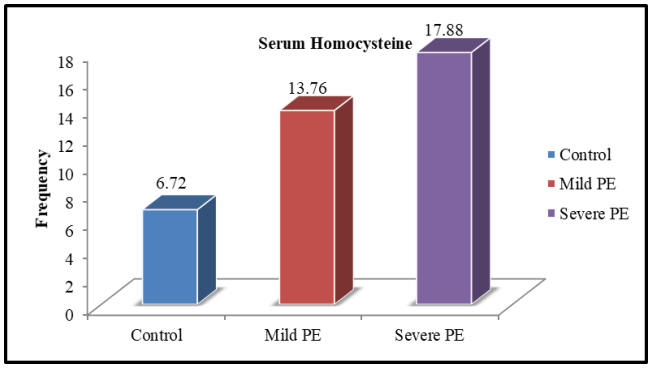

Fig 1: Homocysteine levels in normotensive patients and those with mild and severe preeclampsia

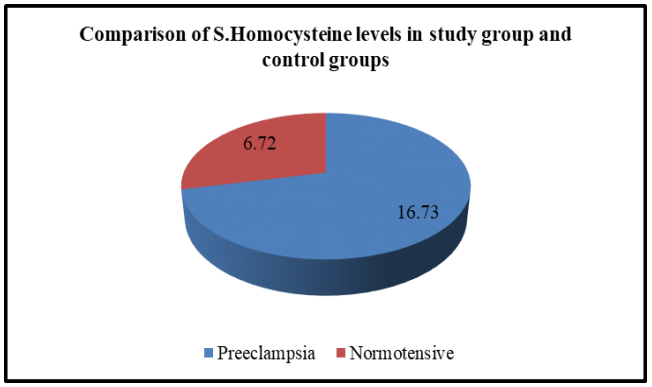

Fig 2: Comparison of serum homocysteine levels in normotensive patients and those with preeclampsia

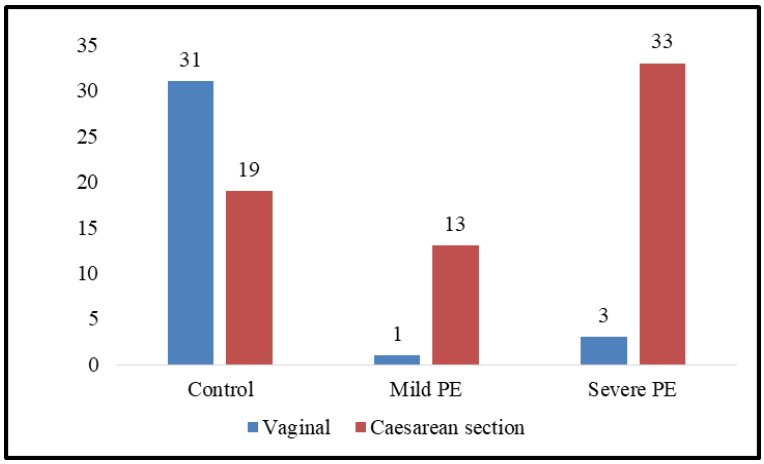

Fig 3: Mode of deliveries in normotensive women and those with mild and severe preeclampsia

Table 3: Comparison of perinatal outcomes with serum homocysteine levels in normotensive and those mild and severe preeclampsia

	Control		Mild Preeclampsia		Severe Preeclampsia			
Perinatal outcome	**No. of patients**	**Mean Serum Homocyteine (µmol/l)**	**N**	**Mean Serum homocysteine (µmol/l)**	**N**	**Mean Serum homocyste ine (µmol/l)**	**F/ t value**	**P Value**
Normal	50	6.72±1.41	11	13.03 ±3.06	15	16.87 ±2.26	185.24	0.000**
SGA	0	0	2	17.11±2.53	8	18.42 ±1.25	1.267	0.293 NS
IUGR	-	-	1	15.06±0	11	18.69 ±1.50	12.121	0.043 *

The mean age of the participants in the control group was 24 years and that in cases was 26 years. Primigravida among the preeclamptic group was 64% and 36% were multigravida. Table 1 shows that women with preeclampsia were often younger and primigravidas.

Table 2 shows that serum homocysteine levels were raised in cases with preeclampsia than the normotensive women there was a statistically significant difference found among groups with F=359.13, p<0.001. In this study serum homocysteine levels were directly proportional to severity of the disease.92% of women with preeclampsia delivered by caesarean section due to various obstetric indications statistically significant difference found p<0.001 and the same in shown in figure 3.

Table 3 shows the comparison of serum homocysteine based on perinatal outcomes in different groups showed that there was a statistically significant difference found in the mean homosysteine level among different groups studied among cases who delivered normal child. There was no statistically significant difference found between mild and severe preeclampsia cases in homocysteine values who delivered small for gestation age babies. There was statistically significant difference found between mild and severe preeclampsia cases in homocysteine values who delivered IUGR babies.

Discussion

The primary outcome of the study is to establish the association between homocysteine and patients with preeclampsia. The study also aims at finding the relationship between increasing levels of homocysteine based on the severity of preeclampsia. In the present study mean age of the participants was 24 years in the control group and 26 years in the cases group. In the study group 74% of the women fell into age group between 21 to 30 years. The obstetric score of women in both the control and the study group was majority primi cases, 68% and 64% respectively. It means the women with preeclampsia were younger and mostly primigravida and this coincides with the conclusion obtained in a similar study conducted by Sunita Ghike *et al.* [8]

It means average period of gestation in the control group was 38.26 weeks and that in the cases group was 35.52 weeks. The mean blood pressure in the control group was 110/70 mmHg and that in the study group was 150/100 mmHg. In this study various biochemical parameters was compared between mild and severe preeclampsia group but there was no statistical significance between urea, creatinine and serum bilirubin in cases with mild and severe preeclampsia. There was significant raise in levels of serum uric acid and serum homocysteine in patients with severe

preeclampsia than in those with mild preeclampsia. This finding was contrast to the study conducted by Laxmi Maru *et al*. [9] in which there marked elevation of SGOT, SGPT and low platelets in women with severe preeclampsia.

In the study group out of 50 cases 72% of the cases had severe preeclampsia and the 28% were diagnosed with mild preeclampsia. Amongst the 50 cases 48 of them had elevated homocysteine levels depending upon the severity of the diseases. Two cases with mild pre eclampsia had normal homocysteine levels. In this study relationship between systolic blood pressure and diastolic blood pressure to serum homocysteine levels were studied and found to have a positive relationship. In this study 92% of the cases amongst preeclampsia delivered through caesarean section due to various obstetric indications.

During the study various maternal complications was looked for in women with preeclampsia out of fifty preeclamptic women six of them had various complications. One case was diagnosed to have acute kidney injury, three cases of abruption was reported and one case of pulmonary edema. All these six had elevated levels of homocysteine when compared to all other study participants in the study.

Lastly perinatal outcomes were also compared with homocysteine levels in this study. Homocysteine levels were significantly elevated in preeclamptic women with IUGR babies but there was no statistical significance in those who delivered small for gestational age babies. Neelamma Patil *et al*. [10] performed a study which inferred that there was elevated homocysteine levels found in preeclamptic women who presented with unexplained abruption and those with fetal growth restriction and oligohydraminos.

Based on this study in can be understood that elevated homocysteine levels are found in women with preeclampsia and this increases with severity of the disease. So when measures are taken to reduce homocysteine levels like proper folic acid, B6 and B12 supplementation it can improve perinatal outcomes and also reduce maternal complications. There were few limitations of the study, one such limitation is less sample size.

Conclusion

Further studies with larger sample size is needed to prove the association of homocysteine levels with severity of preeclampsia. As there is direct relationship with elevated homocysteine levels to increased chance of maternal complications and adverse perinatal outcome, it can be used as a predictor of preeclampsia. When measures are taken to reduce homocysteine levels it can in turn help in reduce both perinatal and maternal morbidity. Proper supplementation with folic acid, vitamin B6 and vitamin B12 can reduce homocysteine levels and can help to overcome effects of hyperhomocysteinemia. Being a simple laboratory investigation it can help in preventing various complications.

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