

# Comparative Study on Homocysteine Levels between Preeclampsia Patients and Healthy Pregnant Volunteers

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## Abstract

**Background:** Preeclampsia is a pregnancy-specific disorder which complicates about 3–10% of all nulliparous gestation. Hyperhomocysteinemia has been associated with pregnancy-induced hypertension, abruption, vasculopathy, recurrent pregnancy loss, still birth, deep vein thrombosis, and neural tube defects of the newborn.

**Materials and Methods:** This was a case–control study. After obtaining proper informed consent, patients diagnosed with preeclampsia and healthy pregnant volunteers were enrolled for the study. Homocysteine levels were estimated in both healthy volunteers and preeclampsia patients and comparative assessment was carried out.

**Results:** Mean serum homocysteine in preeclamptic women is 16.9, and in normotensive women, it is 9.6, *t*-test for equality of mean is 14, *P* = 0.000, which is statistically very significant. Hence, serum homocysteine is a significant predictor of preeclampsia.

**Conclusion:** From the observations in our study, we can conclude that preeclampsia is associated with hyperhomocysteinemia. In preeclampsia, homocysteine levels are directly related to the severity of preeclampsia. A study involving a larger population is necessary to validate our findings.

**Key words:** Healthy pregnant volunteers, Hyperhomocysteinemia, Preeclampsia

## INTRODUCTION

Preeclampsia is a pregnancy-specific disorder which complicates about 3–10% of all nulliparous gestation.<sup>[1]</sup>

Homocysteine is a non-protein sulfur containing amino acid. It is similar to cysteine and is derived as a result of conversion of methionine. Increased homocysteine levels in the blood causes endothelial cell dysfunction, activation of hemostasis, and oxidative stress. Hyperhomocysteinemia has been associated with pregnancy-induced hypertension, abruption, vasculopathy, recurrent pregnancy loss, still birth, deep vein thrombosis, and neural tube defects of the newborn.

Hyperhomocysteinemia leads to endothelial dysfunction through various mechanisms. In addition to that, homocysteine also affects the fibrinolytic pathway which is contributing to the pathophysiology of preeclampsia. In normal pregnancy, homocysteine levels are decreased compared to the non-pregnant level,<sup>[2]</sup> either due to hemodilution of pregnancy or the relative deficiency due to increase in requirement by the mother and the fetus. It has been proposed that preeclampsia is associated with vascular damages similar to those associated with the hyperhomocysteinemia.

The normal serum homocysteine level in non-pregnant adult female ranges between 5 and 15  $\mu\text{mol/L}$ . Homocysteine exists in two forms. About 75–80% exists as protein bound form and 15–25% exists as acid-soluble free form.<sup>[3]</sup> Numerous studies have found an association between homocysteine and various pregnancy-related disorders. Klai *et al.*<sup>[4]</sup> assessed the genetic makeup of patients with proven placental vasculopathies and found an association with MTHFRA1298C polymorphism which leads to hyperhomocysteinemia. Elevated homocysteine levels are

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associated with the development of vasculopathy of the placenta. Many hypotheses have been proposed for the pathogenesis of homocysteine-induced vasculopathy and endothelial dysfunction.

### Aims and Objectives

The aim of the study was to estimate the homocysteine levels in normal pregnant women and preeclamptic women and to compare the values, and to find the association of the homocysteine levels in preeclampsia and normal pregnancy.

## MATERIALS AND METHODS

This was a case–control study carried out in the Department of Obstetrics and Gynaecology, Government Kilpauk Medical College and Hospital, Chennai, Tamil Nadu, India. A total of 60 age-matched pregnant women were enrolled for the study. Out of the 60 women, 30 normal healthy pregnant women formed the control group while another 30 preeclamptic patients formed the case group. All the patients underwent detailed history taking and clinical examination. Blood pressure was recorded (two measurements 6 h apart in the semi-recumbent position). For the measurement of serum homocysteine, 5 mL of blood was drawn from the antecubital vein after overnight fasting and the specimen was transported immediately to laboratory and centrifugation was done at 3000 rpm for 5–7 min and the clear serum is transferred to a plastic vial and stored in refrigerator until analysis. Serum homocysteine was measured by fluorescence polarization immunoassay run on Abbott AxSYM machine using Abbott's kit.

### Inclusion Criteria

#### Cases

Cases include

1. Pregnant women with BP  $\geq$  140/90 mmHg (previously normotensive women) on at least two occasions 6 h apart
2. Gestational age 28–40 weeks (sure of gestational age by last menstrual period or ultrasonography in the 1<sup>st</sup> or early 2<sup>nd</sup> trimester).

#### Controls

Healthy pregnant normotensive women of gestational age of 28–40 weeks formed the control group.

### Exclusion Criteria

Subjects with the following diseases or disorders were excluded from the study: Chronic hypertension, gestational diabetes mellitus type 1 and 2 diabetes mellitus, connective tissue disorders, multiple pregnancy, liver diseases, severe anemia, smoking, obesity, and pregnancy with antiphospholipid syndrome.

## OBSERVATION AND RESULTS

As shown in Table 1, mean gestational age for preeclamptic women is 36.03 years and that of normotensive women is 35.70 years, *t*-test for equality of mean is  $P = 0.372$ . Gestational age difference between cases and controls is not statistically significant. Hence, they are matched by age [Figure 1].

As shown in Table 2, mean serum homocysteine in preeclamptic women is 16.9, and in normotensive women, it is 9.6, *t*-test for equality of mean 14,  $P = 0.000$ , which is statistically very significant. Hence, serum homocysteine is a significant predictor of preeclampsia [Figure 2].

As shown in Table 3, the area under the ROC is 0.998333  $P < 0.0001$ . Hence, serum homocysteine is a statistically significant variable to predict preeclampsia.

### Statistical Significance

$P < 0.0001$  was considered statistically significant. Hence, serum homocysteine is a statistically significant variable to predict preeclampsia with  $P < 0.0001$  [Figure 3].

As shown in Table 4, the Youden index *J* is 1.000 which suggests that homocysteine is a perfect test to predict preeclampsia in pregnant women.

## DISCUSSION

In our study, 60 pregnant women were included after fulfilling the inclusion and exclusion criteria. Thirty of the women had preeclampsia and 30 of them had normal pregnancy. The average gestational age of preeclamptic women was 36.03 weeks and normal pregnant was 35.70 weeks. There was no statistical difference in the gestational age in both the groups.

In our study, the mean homocysteine level among normal pregnant mothers was 9.624  $\mu\text{mol/L}$ . This is similar to the study conducted by Hoque *et al.*<sup>[5]</sup> which had homocysteine levels of 8.46  $\mu\text{mol/L}$  in. In the study conducted by Stolkova *et al.*,<sup>[6]</sup> the mean homocysteine level was 9.24  $\mu\text{mol/L}$  almost similar to our study.

In our study, the homocysteine level among the preeclamptic women was 16.92  $\mu\text{mol/L}$ . This is close to the study of Hasanzadeh *et al.*<sup>[7]</sup> where the homocysteine level was  $13.8 \pm 7$ . In another study by Ingec *et al.*,<sup>[8]</sup> the homocysteine level among preeclamptic women was  $16.7 \pm 10.1 \mu\text{mol/L}$  which is almost similar to our study. In our study, there was a statistically significant difference between the homocysteine level among normal pregnant women and women with preeclampsia ( $P < 0.001$ ). Hence, our study proves that serum homocysteine

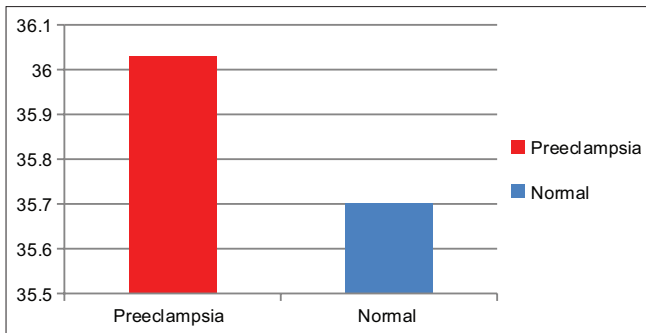


Figure 1: Age matching

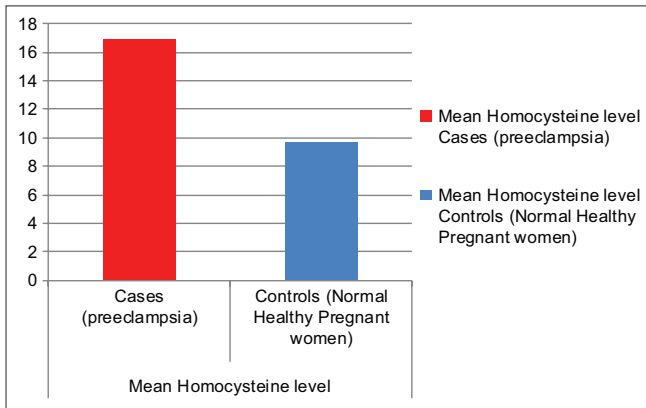


Figure 2: Mean homocysteine level

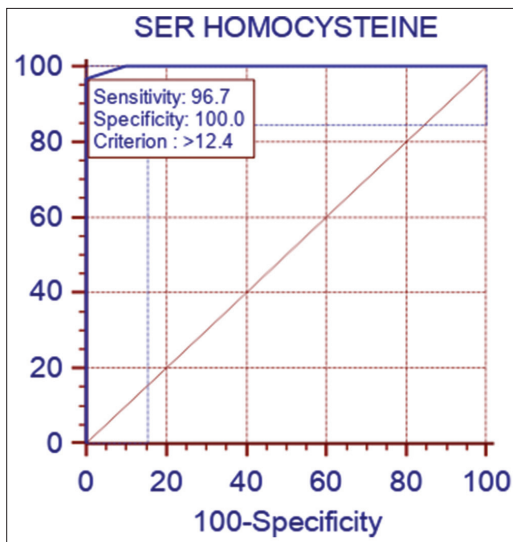


Figure 3: Receiver operating characteristic curve for serum homocysteine in relation to preeclampsia

is raised in preeclampsia and there is an association between preeclampsia and hyperhomocysteinemia. Several studies have proven this concept that preeclampsia is associated with hyperhomocysteinemia.<sup>[5-13]</sup> The large Hordaland Homocysteine Study – a population-based study<sup>[14]</sup> done over a period of 7 years in a population of about 7053, concluded that hyperhomocysteinemia is a risk factor for preeclampsia.

Table 1: Age matching

Study group	n	Age	Standard deviation	Std. error mean	P-value
Cases (preeclampsia)	30	36.03	1.326	0.242	0.372
Controls (normal pregnant women)	30	35.70	1.535	0.280	

Table 2: Comparison of mean homocysteine levels ( $\mu\text{mol/L}$ )

Study group	n	Mean homocysteine level	Standard deviation	Std. error mean	P-value
Cases (preeclampsia)	30	16.923	2.3218	0.4239	0.000
Controls (normal pregnant women)	30	9.647	1.4088	0.2572	

Table 3: Area under the receiver operating characteristic (ROC) curve

Statistical Parameter	Value
Area under the ROC curve (AUC)	0.998333
Standard error <sup>a</sup>	0.00254
95% confidence interval <sup>b</sup>	0.937079–1.000000
Z statistic	196.319
Significance level P (area=0.5)	<0.0001

Table 4: Youden index

Statistical Parameter	Value
Youden index J	1.0000
Associated criterion	>12.2

In the study conducted by Stolkova *et al.*,<sup>[6]</sup> maternal homocysteine level correlated with the severity of preeclampsia. Our study shows that maternal homocysteine level is directly associated with the severity of preeclampsia.

Baksu *et al.*<sup>[12]</sup> in his study showed that levels differed significantly among the severe and non-severe group. However, another study by Hasanzadeh *et al.*<sup>[9]</sup> failed to show an association between the severity of preeclampsia maternal homocysteine level although this study confirmed hyperhomocysteinemia in preeclampsia.<sup>[9]</sup> These findings reveal that hyperhomocysteinemia has a potential role in the pathogenesis of preeclampsia.

## CONCLUSION

Hyperhomocysteinemia is seen in preeclampsia and it plays a major role in the pathogenesis of preeclampsia. In preeclampsia, homocysteine levels are directly related to the severity of preeclampsia.

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