

**A Hospital-Based Study Assessing Association of Serum Homocysteine with Pregnancy- Induced Hypertension (PIH)**Sadhna Kumari<sup>1</sup>, Swati<sup>2</sup>, Geeta Sinha<sup>3</sup><sup>1</sup>Senior Resident, Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India<sup>2</sup>Senior Resident, Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India<sup>3</sup>Professor and Head of department, Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India

Received: 09-03-2024 / Revised: 15-04-2024 / Accepted: 19-05-2024

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Conflict of interest: Nil

**Abstract****Aim:** The aim of the present study was to assess the association of serum homocysteine with pregnancy- induced hypertension (PIH).**Methods:** The present study was conducted in the Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India. The study group included 100 pregnant subjects, including 50 subjects with hypertensive disorders of pregnancy presenting in outdoor or emergency as cases and 50 normotensive subjects enrolled for normal antenatal care as controls.**Results:** In our study, among the 50 hypertensive subjects (cases), 36 (72%) had a normal serum homocysteine (< 15 µmol/L), while 14 subjects (28%) had hyperhomocysteinemia (> 15 µmol/L). On comparing this with 30 normotensive subjects (controls), 48 subjects (96%) had serum homocysteine within the normal range, while only 2 subjects had hyperhomocysteinemia. This comparison was found to be statistically significant. We found that the mean value of serum homocysteine was 14.65 + 9.247 µmol/L among the 30 cases (hypertensive subjects), whereas the mean serum homocysteine was 8.63 + 3.71 µmol/L in controls (normotensive subjects). This difference was statistically significant. All the normotensive subjects had a mean serum homocysteine of 8.41 + 3.57 µmol/L. The mean serum homocysteine of Gestational hypertension was 8.18 + 3.79 µmol/L, whereas who had mild preeclampsia had a mean serum homocysteine of 8.85 + 5.57 µmol/L. On analysis, these data were not found to be statistically significant.**Conclusion:** Since hypertensive disorders of pregnancy are one of the leading causes of maternal and neonatal morbidity and mortality, it is important to identify and reduce the modifiable risk factors associated with them; one of them being hyperhomocysteinemia, which has been shown to have implications in adverse maternal and neonatal outcomes.**Keywords:** Homocysteine, Preeclampsia, Pregnancy-induced hypertension, HELLP syndromeThis is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Hypertension is the most common medical problem encountered during pregnancy.

Preeclampsia, a pregnancy-specific syndrome, is a major cause of maternal and perinatal morbidity and mortality with a worldwide incidence of 5 to 8% of all pregnancies. [1] Gestational hypertension is a new hypertension developing after 20 weeks without significant proteinuria (&gt;300mg protein in a 24-hour urine collection or &gt;30mg/mol in a spot urinary protein:creatinine sample). Preeclampsia is a new hypertension developing after 20 weeks with significant proteinuria.

Toxic factors released by the placenta cause endothelial cell dysfunction by directly affecting endothelial cells or by stimulating maternal oxidative stress and inflammatory cytokines. Oxidative stress is the imbalance of antioxidants (e.g., high density lipoprotein (HDL) and transferrin) and prooxidants. Important prooxidants are homocysteine and low density lipoprotein (LDL). Oxidative stress leads to the formation of oxygen-free radicals and lipid peroxides, which are highly reactive and are directly toxic to the endothelial cells. With this endothelial damage, there is decreased production of vasodilators (prostacyclin) and inactivation of circulating

vasodilators (nitric oxide), ultimately leading to vasospasm. The 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. [2]

Homocysteine is a sulfur-containing essential amino acid primarily derived from demethylation of dietary methionine required for the growth of cells and tissues in the human body. [3] Homocysteine concentrations are tightly regulated by two main enzymatic pathways. Homocysteine can be remethylated to methionine by a pathway requiring folic acid as a methyl donor. In addition to adequate folic acid, the pathway requires vitamin B12 as an important cofactor. Alternatively, homocysteine can be removed by transsulfuration, a pathway dependent on the cofactor vitamin B6. [4] High concentrations of plasma total homocysteine are associated with serious pregnancy complications, including PIH, preeclampsia [5] and placental abruption. [6] Higher maternal total homocysteine concentration is associated with a small increased risk for small for gestational age offsprings. [7] The aim of the present study was to assess the association of serum homocysteine with pregnancy-induced hypertension (PIH).

### Materials and Methods

The present study was conducted in the Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar, India from April 2022 to March 2023. The study group included 100 pregnant subjects, including 50 subjects with hypertensive disorders of pregnancy presenting in outdoor or emergency as cases and 50 normotensive subjects enrolled for normal antenatal care as controls.

### Inclusion Criteria

Hypertensive pregnant females with a gestation period more than or equal to 20 weeks were included.

### Exclusion Criteria

- Chronic hyper tension, renal or liver disease, h/o thromboembolism, h/o smoking, h/o intake of anticoagulant therapy, h/o medical illness causing a

prethrombotic state, multiple pregnancies, molar pregnancy, and h/o epilepsy in the prepregnancy state.

### Control Group

Normotensive patients with a gestational age more than or equal to 20 weeks.

### Study Group

Patients with hypertensive disorders of pregnancy with and without treatment presenting beyond 20 weeks of gestation with blood pressure more than or equal to 140/90 mm Hg.

All patients meeting the inclusion criteria were enrolled, and after taking their written informed consent, a detailed history was taken including complaints during the present pregnancy, past history, menstrual history, and obstetric history. Detailed general physical examination and obstetric examination were done.

Five milliliters of the venous sample were collected in a red-topped vacutainer and processed for serum homocysteine. A fasting sample of serum homocysteine was taken. The sample so collected was placed immediately on ice and the serum separated within 1 hour of collection. The test was based on an immunoassay technique.

The normal range of serum homocysteine was taken as 5–15  $\mu\text{mol/L}$ .

Patients of both the groups were followed up, and their data were collected, collated, and analyzed thoroughly. The maternal condition was assessed clinically and by ultrasound and Doppler velocimetry. Peripheral blood film, liver function tests, and complete blood counts were analyzed to confirm the diagnosis of HELLP syndrome along with the alarming symptoms in the subjects.

The decision for termination was made on the basis of gestational age and maternal and fetal status.

The data so collected were statistically analyzed.

### Statistical Analysis

The recorded data were analyzed using SPSS version 20. Statistical tests applied were Pearson's Chi-square test, Student's t-test, and one-way analysis of variance (ANOVA).

### Results

**Table 1: Incidence of hyperhomocysteinemia in cases and controls**

Serum homocysteine	Cases (n = 50)	Control (n = 50)	p value
<15 $\mu\text{mol/L}$	36 (72%)	48 (96%)	0.018
>15 $\mu\text{mol/L}$	14 (28%)	2 (4%)	
Total	50 (100%)	50 (100%)	

In our study, among the 50 hypertensive subjects (cases), 36 (72%) had a normal serum homocysteine (< 15  $\mu\text{mol/L}$ ), while 14 subjects (28%) had hyperhomocysteinemia (> 15  $\mu\text{mol/L}$ ). On comparing this with 30 normotensive subjects

(controls), 48 subjects (96%) had serum homocysteine within the normal range, while only 2 subjects had hyperhomocysteinemia. This comparison was found to be statistically significant.

**Table 2: Comparison of mean serum homocysteine between cases and controls**

Variables	Group	N	Mean	Standard deviation	p value
Serum homocysteine	Cases	50	14.65	9.247	0.012
	Controls	50	8.63	3.71	

We found that the mean value of serum homocysteine was  $14.65 + 9.247 \mu\text{mol/L}$  among the 30 cases (hypertensive subjects), whereas the mean serum homocysteine was  $8.63 + 3.71 \mu\text{mol/L}$  in controls (normotensive subjects). This difference was statistically significant.

**Table 3: Comparison of mean serum homocysteine in normotensive subjects and subjects of non severe forms of PIH**

Variables	Mean homocysteine	Standard deviation	p value
Normotensive	8.41	3.57	0.7
Gestational hypertension	8.18	3.79	
Mild preeclampsia	8.85	5.57	

All the normotensive subjects had a mean serum homocysteine of  $8.41 + 3.57 \mu\text{mol/L}$ . The mean serum homocysteine of Gestational hypertension was  $8.18 + 3.79 \mu\text{mol/L}$ , whereas who had mild

preeclampsia had a mean serum homocysteine of  $8.85 + 5.57 \mu\text{mol/L}$ . On analysis, these data were not found to be statistically significant.

**Table 4: Correlation of mean serum homocysteine with grades of PIH**

Grade of PIH	Mean homocysteine	Standard deviation	p value
Gestational hypertension	8.18	3.79	0.022
Mild preclampsia	8.85	5.57	
Severe preeclampsia	9.93	5.10	
HELLP syndrome	19.63	26.29	
Eclampsia	16.06	4.68	

Among the hypertensive subjects, mean serum homocysteine of gestational hypertension was  $8.18 + 3.79 \mu\text{mol/L}$ , mean serum homocysteine of mild preeclampsia was  $8.85 + 5.57 \mu\text{mol/L}$ , a mean serum homocysteine of severe preeclampsia was  $9.93 + 5.10 \mu\text{mol/L}$ , mean serum homocysteine of HELLP syndrome was  $19.63 + 26.29 \mu\text{mol/L}$ , and mean serum homocysteine of eclampsia was  $16.06 + 4.68 \mu\text{mol/L}$ . This correlation was found to be statistically significant.

## Discussion

High homocysteine levels have also been associated with placental vasculopathies and complications related to the placenta, such as fetal growth restriction, abruption, hypertensive disorders of pregnancy, and recurrent abortions. There is a lack of knowledge on how hyperhomocysteinemia increases the likelihood of complications during pregnancy and other negative effects. According to a theory, high homocysteine levels lead to endothelial dysfunction, making women with the condition more likely to have it in the placental vasculature. [8] During gestation, the woman's body prepares itself for the hemostatic challenge of delivery by creating a physiologically hypercoagulable state. However, this entails a higher risk of venous thrombosis and problems caused by the placenta, which poses significant difficulties for the mother and fetus. A significant problem for women's health is the prevention of these placenta-mediated problems, which altogether complicate up to 15% of pregnancies. [9]

In our study, among the 50 hypertensive subjects (cases), 36 (72%) had a normal serum homocysteine ( $< 15 \mu\text{mol/L}$ ), while 14 subjects (28%) had hyperhomocysteinemia ( $> 15 \mu\text{mol/L}$ ). On comparing this with 30 normotensive subjects (controls), 48 subjects (96%) had serum homocysteine within the normal range, while only 2 subjects had hyperhomocysteinemia. This comparison was found to be statistically significant. We found that the mean value of serum homocysteine was  $14.65 + 9.247 \mu\text{mol/L}$  among the 30 cases (hypertensive subjects), whereas the mean serum homocysteine was  $8.63 + 3.71 \mu\text{mol/L}$  in controls (normotensive subjects). This difference was statistically significant. The results were similar to another study conducted by Makedos et al [10], who found in their study that the mean level of serum homocysteine was  $11.11 \mu\text{mol/L}$  in preeclamptic women, while it was lower in normotensive subjects, i.e.,  $6.40 \mu\text{mol/L}$ . Powers et al [11] in the year 2001 conducted a study and also found a similar and significant difference in the serum level of homocysteine in preeclamptic subjects and normotensive subjects. Zeeman et al [12] in the year 2003 studied that the serum homocysteine concentration in patients with preeclampsia was higher in comparison to those with uncomplicated pregnancies.

All the normotensive subjects had a mean serum homocysteine of  $8.41 + 3.57 \mu\text{mol/L}$ . The mean serum homocysteine of Gestational hypertension was  $8.18 + 3.79 \mu\text{mol/L}$ , whereas who had mild preeclampsia had a mean serum homocysteine of

8.85 + 5.57  $\mu\text{mol/L}$ . On analysis, these data were not found to be statistically significant. Our study was similar to another study conducted by Haranzadeh et al [13] in 2008, in which they concluded that there is no significant difference in the mean serum homocysteine level between normotensive pregnant women (8.8 +  $\mu\text{mol/L}$  vs 10.4 + 2.3  $\mu\text{mol/L}$ ) and women with mild preeclampsia. Among the hypertensive subjects, mean serum homocysteine of gestational hypertension was 8.18 + 3.79  $\mu\text{mol/L}$ , mean serum homocysteine of mild preeclampsia was 8.85 + 5.57  $\mu\text{mol/L}$ , a mean serum homocysteine of severe preeclampsia was 9.93 + 5.10  $\mu\text{mol/L}$ , mean serum homocysteine of HELLP syndrome was 19.63 + 26.29  $\mu\text{mol/L}$ , and mean serum homocysteine of eclampsia was 16.06 + 4.68  $\mu\text{mol/L}$ . This correlation was found to be statistically significant. Ingec et al [14], in the year 2005, also demonstrated a positive relationship between increased serum homocysteine and the severity of preeclampsia. Singh et al [15] in 2008 supported the fact, through their study, that the severity of preeclampsia was directly related to homocysteine concentration. Guven et al [16] conducted a study in the year 2009 and found that the mean serum homocysteine levels in subjects with mild PIH were 8.2  $\mu\text{mol/L}$ , while in subjects with severe PIH, the mean value was 8.9  $\mu\text{mol/L}$ .

### Conclusion

Since hypertensive disorders of pregnancy are one of the leading causes of maternal and neonatal morbidity and mortality, it is important to identify and reduce the modifiable risk factors associated with them; one of them being hyperhomocysteinemia, which has been shown to have implications in adverse maternal and neonatal outcomes.

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