

Homocysteine as Predictive Marker for Pregnancy-Induced Hypertension—A Comparative Study of Homocysteine Levels in Normal Versus Patients of PIH and Its Complications

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Abstract

Objective To find the correlation between serum homocysteine levels, relevant laboratory investigations and complications associated with PIH.

Methods This was a prospective study conducted over 2 years. Two hundred and fourteen cases were studied. They

were divided into mild preeclampsia (64), severe preeclampsia (50), eclampsia (32) and control groups (68). Parameters evaluated for statistical analysis were blood pressure, platelet counts, SGOT, SGPT and serum homocysteine levels.

Results A definite statistical correlation was found between the homocysteine levels and severity of hypertension (8 mmol/l, $p = .759$). A higher level of homocysteine was also associated with many maternal complications like abruption, retinopathy, MODS, maternal mortality and eclampsia. Sixty-nine out of 87 patients with elevated homocysteine levels were complicated with some or the other condition, making a high percentage of 79.31 %. Patients with normal level of homocysteine delivered healthy babies (88.1 %). There were 6 maternal mortalities and 20 stillbirths in the hyperhomocysteinemia group.

Conclusion Homocysteine levels have a direct statistical correlation with the severity of hypertension and complication with preeclampsia and eclampsia. It can be

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considered as a reliable predictive marker for PIH and its wide syndrome.

Keywords Pregnancy induced hypertension · Homocysteine · Predictive marker · Maternal mortality and morbidity

Abbreviations

HCY	Homocysteine
ARF	Acute renal failure
CVA	Cerebrovascular accident
MODS	Multiorgan dysfunction syndrome
DIC	Disseminated intravascular coagulation
MAP	Mean arterial pressure
IUD	Intrauterine death
DP	Diastolic pressure
SP	Systolic pressure
PC	Platelet count

Introduction

Preeclampsia is a pregnancy-specific syndrome recognized from antiquity as a leading cause of maternal and perinatal mortality. This age long disease of hypertension in pregnancy has been still a mystery in terms of etiopathogenesis. It also forms the biggest cause of mortality still in our country. The disease has been influencing the lives of the women and the obstetrician associated. This makes it one of the most researched topics in the medicine field.

The aim of our study is to understand the etiopathogenesis, identifying risk factors and prognostic factors and management of long-term sequelae of eclampsia, and to study the association between severity of disease process and serum homocysteine levels.

Endothelial dysfunction, inflammation and angiogenesis are the most explainable theories about etiology and pathogenesis. Hyperhomocysteinemia is a risk factor for endothelial dysfunction and vascular disease. Previously, it has been reported to be associated with placenta-mediated diseases such as preeclampsia.

Aims and Objectives

1. To identify risk complications of preeclampsia and eclampsia and its relation with homocysteine levels.
2. To study the relevant laboratory investigations in cases of preeclampsia.

Materials and Methods

The present study was conducted in Department of Obstetrics and Gynecology, MGM Medical College and Associated M. Y. Hospital, Indore, MP, India. It is a prospective study, and study period was of 2 years.

Selection of Cases

The cases were selected from patients who were admitted in labor room as emergency cases, irrespective of age and parity. A written informed consent was taken from the patients. On a specially designed proforma for the study, the patients particulars like detail obstetric history, examination and laboratory findings were recorded. Patients were matched according to gestational age and body mass index. Informed consent was taken from each pregnant women enrolled in study. Two hundred and fourteen cases were studied, and thorough examination was carried out including follow-up visits up to 3 months.

Patients were divided into mild preeclampsia, severe preeclampsia, eclampsia and control groups, containing 64, 50, 32 and 68 patients, respectively.

Control groups consisted of uncomplicated normotensive.

Inclusion Criteria

- Singleton pregnancies,
- None of the subjects were in active labor,
- No signs of infection,
- All subjects received folic acid supplementation until 12 weeks of gestation.

Exclusion Criteria

- Essential hypertension suggested by history or documentation of hypertension in pre pregnant state or hypertension before 20 weeks of gestation. Cardiovascular or renal disease,
- Liver disease,
- Multiple pregnancy,
- Diabetes mellitus,
- Inflammatory or infective disorders,
- Coincidental seizures in pregnancy,
- History or documentation of epilepsy in prepregnant state,
- Space occupying lesion in brain like tuberculoma or brain tumor,
- Trauma to brain,
- Hyperpyrexia,
- On treatment with antifolate drugs such as methotrexate.

The following parameters were evaluated for statistical analysis:

1. *Blood pressure recording*: $MAP \simeq DP + \frac{1}{3}(SP - DP)$.
2. *Hematologic parameter*: The platelet counts were studied for statistical comparison.
3. *Liver function test*: Liver function test were done in all patients. SGOT and SGPT levels were studied.
4. *Serum homocysteine*

Measurement of Homocysteine Levels

Plasma homocysteine levels were measured by immune chemiluminescence by using commercial kit.

Statistical Analysis

Statistical analysis is done with SPSS-17 program. Variable are described first and compared with four groups using ANOVA and Chi-square test. *P* value less .01 was considered significant.

The ethical committee approval was taken for the study.

Results

PIH and its complications are a major cause of death in the developing nation like India where the maternal mortality is still at year 2013, 190 per lakh live births [1]. Identification and prompt treatment are keys to managing such patients and wishing a lower maternal mortality rate in the country. Here we hence study the levels of homocysteine and other laboratory parameters to try and reach to an accurate predictive marker for this dreaded disease.

The results of the study were as follows: low platelet counts (<1 lakh) and elevated SGOT and SGPT (>72) were not found in the normotensive controls (*n* = 68), while 6 normotensive patients were found to have an elevated level of homocysteine (>8 mmol/l).

There was marked elevation of SGOT and SGPT homocysteine and low platelets in the patients with hypertension. In the mild preeclampsia group (*n* = 64), low platelets were found in 9 patients and SGOT and SGPT was elevated in 63 and 62 patients, respectively. Homocysteine level (>8 mmol/l) was elevated in 8 patients (Table 1).

In the severe preeclampsia group (*n* = 50), though the number of patients with elevated SGOT (43) and SGPT (44) was less, low platelets were found in as high as 36 patients (72 %). Homocysteine levels were elevated in 43 patients (86 %).

In the eclampsia group (*n* = 32), low platelets were found in 24 patients. Homocysteine was elevated in almost all patients (30).

Table 1 Laboratory parameters in PIH

	Platelet (<1 lakh)	SGOT (>72 IU/l)	SGPT (>72 IU/l)	HCY (>8)
Normal (<i>n</i> = 68)	0	0	0	6
Mild preeclampsia (<i>n</i> = 64)	9	63	62	8
Severe preeclampsia (<i>n</i> = 50)	36	43	44	43
Eclampsia (<i>n</i> = 32)	24	25	26	30

Table 2 Homocysteine levels and its correlation with hypertension

	Group 1 (HCY < 8 mmol/l) (<i>n</i> = 127)		Group 2 (HCY > 8 mmol/l) (<i>n</i> = 87)	
Hypertension				
Normal (<i>n</i> = 68)	62	91.17 %	6	8.82 %
Mild preeclampsia (<i>n</i> = 64)	56	87.5 %	8	12.5 %
Severe preeclampsia (<i>n</i> = 50)	7	14 %	43	86 %
Eclampsia (<i>n</i> = 32)	2	6.25 %	30	93.75 %
Complications				
Abruption	2	8.66 % (11/127)	7	79.31 % (69/87)
Retinopathy	9		36	
ARF	0		5	
CVA	0		2	
MODS	0		7	
DIC	0		1	
Shock	0		5	
Mortality	0		6	
Perinatal outcome				
Healthy	112	88.1 %	29	33.33 %
Sick	13	10.23 %	38	43.67 %
IUD	2		20	22.98 %

Table 2 shows a clear correlation between homocysteine levels and hypertension. Out of 87 patients with hyperhomocysteinemia (>8 mmol/l), 81 patients had hypertension of various level and associated complications. Complications such as abruption, retinopathy, ARF, CVA, MODS, DIC, shock were present in the hyperhomocysteinemia group (69/87, 79.31 %). There were five patients with shock. Two of them had severe preeclampsia, and three had eclampsia. Three patients went into hemorrhagic shock due to postpartum hemorrhage. All of them could be saved by timely management and adequate blood and components transfusion. One patient went into ARF and dialysis saved her too. One patient had pulmonary embolism. There were 6 maternal mortalities in the study, all of which had an

Table 3 Period of gestation of patients

	>40 weeks	37–40 weeks	<37 weeks
Normal (<i>n</i> = 68)	8	57	3
Mild preeclampsia (<i>n</i> = 64)	10	51	3
Severe preeclampsia (<i>n</i> = 50)	5	43	2
Eclampsia (<i>n</i> = 32)	1	25	6

elevated homocysteine level. A postmortem was not conducted on any of the patients to confirm the cause of death. By clinical presentation and laboratory parameters, the most probable cause of death was assigned to them. Five patients of eclampsia died. Three patients went into ARF with MODS. One patient went into DIC with abruption and PPH. One patient had CVA with MODS.

One patient had severe preeclampsia that expired due to sudden postpartum collapse. She had pulmonary embolism amniotic fluid embolism.

The perinatal outcome of the hyperhomocysteinemia group was also not good. This group had babies that were sick at birth (38, 43.67 %). By sick babies we mean babies requiring admission to nursery. There were 20 stillbirths in the group 2 as compared to the group 1 where there were only 2 stillbirths. All findings were statistically correlated. Strong statistical correlation was found between the laboratory parameters (platelet—*p* value = $-.569$) (SGOT—*p* value = $.704$) (SGPT—*p* value = $.686$) and serum homocysteine levels (*p* value = $.759$).

Most of the patients presented at term in all groups, as shown in Table 3. Twenty-four patients came at or beyond 40 weeks of gestation. Fourteen patients were preterm presenting before 37 weeks of gestation. Rest of all patients presented at term (>37–40 weeks). We tried to take patients with same gestational age. Not any patient was <35 weeks of gestation or more than 41 weeks of gestation.

Discussion

Preeclampsia is a pregnancy-specific syndrome recognized from antiquity as a leading cause of maternal mortality. Hyperhomocysteinemia is a risk factor for endothelial dysfunction and vascular disease just as is preeclampsia. Over the past two decades, endothelial cell activation has become the center piece in the contemporary understanding of the pathogenesis of preeclampsia. Intact endothelium has anticoagulant properties, and it blunts the response of vascular smooth muscle to agonists by releasing nitric oxide. Damaged or activated endothelial cells secrete substances that promote coagulation and increase the

sensitivity to vasopressors. The vascular changes induced by homocysteine are similar to those associated with preeclampsia and include atherosclerosis and endothelial dysfunction resulting in blunted vasorelaxation mechanism [2, 3]. Hyperhomocysteinemia appears to cause endothelial dysfunction through direct toxic and oxidative stress mechanism. The association of hyperhomocysteinemia and preeclampsia has been suggested by Dekker et al. [4] in 1995 who demonstrated that homocysteine was seven times more common in women with history of severe preeclampsia [5]. Since then there have been multiple studies concluding the strong association of hyperhomocysteinemia and preeclampsia. There is an extreme need of a reliable predictive marker to prevent the complications of preeclampsia and timely management. Homocysteine shows a good potential in becoming that most required predictive marker.

Dr. Kilmer McCully in 1960 described the importance of homocysteine to human health. Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality. In preeclampsia, there is elevated homocysteine-related injuries and abnormal vascular endothelium, which contribute to the pathogenesis of the preeclampsia. In addition, vascular endothelium in pregnant women may be more sensitive to homocysteine injury. There was a definite correlation between the severity of hypertension and levels of homocysteine. There was a direct correlation with a statistical significance in our study. Of the 32 patients, 30 patients of eclampsia had an elevated level of homocysteine which is as high as 93.75 %. Of the 87 patients with elevated homocysteine levels, 81 patients had hypertension of varied severity. Similar finding is suggested in the study conducted at Nagpur (India) which showed a correlation in 86.67 % [6]. Elevated homocysteine levels were also found in a study conducted by Laskowska et al. [7] at Poland. In a study conducted at Ankara, Turkey, the mean of homocysteine values was significantly higher in preeclamptic women ($9.0 \pm 3.4 \mu\text{mol/l}$) than healthy controls ($5.3 \pm 1.3 \mu\text{mol/l}$). Homocysteine levels were found to be increased as the severity of preeclampsia increased, with highest level in eclamptic patients ($14.0 \pm 1.8 \mu\text{mol/l}$, $p < .001$) [8].

A higher level of homocysteine is also associated with many maternal complications like abruption, retinopathy, MODS and even higher mortality rates. In our study, we found that 69 patients out of 87 patients with elevated homocysteine levels were complicated with some or other condition, making a high percentage of 79.31 %. There were six mortalities in this group, while no mortality was found in the group with normal levels of homocysteine. More of the complications were due to the direct implication of homocysteine on the endothelial damage. Hyperhomocysteinemia is associated with vascular

diseases such as hypertension, cerebrovascular accidents, peripheral vascular diseases, as well as early pregnancy loss and placental abruption [9–13]. Abruption was found in 2 patients in the study conducted by Sunita et al. [6].

Patients with a normal level of homocysteine delivered healthy babies (88.1 %) as compared to the patients with hyperhomocysteinemia. Twenty babies were still born out of 87 patients with high levels of homocysteine. This forms a high proportion of 22.98 %. There were two stillbirths (6.66 %) in the study of Sunita et al. [6]. A significant finding in Poland study was higher levels of maternal serum homocysteine in the group of normotensive pregnant patients with isolated fetal intrauterine growth restriction [7]. Similar results with higher total homocysteine levels in women delivering IUGR infants were presented by Lindblad et al. [14]. Different results in pregnancy complicated by IUGR were presented by Hogg et al. [15]. They did not find any correlation between the levels of homocysteine and incidence of IUGR.

Direct correlation was also found in the other laboratory parameters with the severity of hypertension like SGOT and SGPT and platelet counts.

Summary

Homocysteine levels are directly correlated with hypertension in pregnancy. The levels also correlate with the severity of hypertension and complication with preeclampsia and eclampsia. It is an easy and less time-consuming test that can be reliably be considered as the predictive marker for pregnancy-induced hypertension. More studies on larger scales are required for the recommendation of this test as the predictive marker.

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Compliance with Ethical Standards

Conflicts of interest There are no conflicts of interest among the authors. Dr Laxmi Maru, Dr Monica Verma and Dr Neha Jinsiwale have no conflict of interest.

Ethical Statements Ethical clearance was obtained from the ethical committee. This study was self-funded, and no grants were received in the form of sponsorship from any company/NGO.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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