Section: Obstertics and Gynaecology

Original Research Article

STUDY ON SERUM HOMOCYSTEINE LEVELS IN NORMOTENSIVE AND PREECLAMPSIA MOTHERS AND ITS ASSOCIATION WITH SEVERITY OF THE DISEASE

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ABSTRACT

Background: Hypertensive disorders of pregnancy, particularly preeclampsia, are major causes of maternal and perinatal morbidity. Homocysteine has been proposed as a biomarker of endothelial dysfunction. This study evaluated serum homocysteine levels in normotensive and preeclamptic patients and assessed their correlation with disease severity, complications, and predictive cutoff values. **Materials and Methods:** This prospective case-control study was conducted over six months in a tertiary care hospital with 60 pregnant patients divided equally into case and control groups. Blood pressure was measured twice, six hours apart, and detailed clinical evaluation and laboratory investigations were performed, including haemogram, renal and liver function tests, urinalysis, serum uric acid, obstetric ultrasonography, fundoscopy, and 24-hour urine protein. Fasting venous blood samples were analysed for serum homocysteine levels using chemiluminescence immunoassay. Placental histopathology was examined after the delivery. **Results:** Most patients were aged 26–30 years (56.7% vs. 63.3%), with comparable mean age (26.7±3.098 vs. 26.27±2.532; p=0.555), while BMI>25 was higher in cases (50% vs. 36.7%; p>0.05). Normal homocysteine levels were observed only in the controls (100%), whereas the cases showed moderate (40.0%) and severe (60.0%) elevations; the mean levels were 16.81±2.32 vs. 6.87±0.83 (p<0.001). Albuminuria was present only in the cases (p<0.001). Cases had higher urea (37.20±23.37 vs 21.80±2.98), creatinine (1.53±1.88 vs 0.60±0.16), bilirubin (1.24±1.07 vs 0.65±0.16), uric acid (6.82±0.78 vs 5.20±0.46), and urine protein (393.37±106.75 vs 186.43±15.60). Complications were associated with severe homocysteine levels (p<0.001), with intrauterine growth restriction being the most frequent. **Conclusion:** Elevated homocysteine levels are strongly associated with preeclampsia severity, biochemical derangement, and complications, supporting its role as a prognostic biomarker for identifying high-risk patients and guiding early monitoring strategies.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) which includes gestational hypertension, preeclampsia and chronic hypertension are the leading causes of maternal and perinatal mortality worldwide of which preeclampsia is the most severe form complicating 2-8% of the pregnancy.[1] The incidence of the condition increased from 16.30 million to 18.08 million cases (10.92% increase) from 1990 to 2019 globally, though the rate of age standardisation decreased.[2] HDP affects 5 to 10% of pregnancies worldwide, with variation in socioeconomic parameters, especially in low resource setting like rural India.3 Death rates were decreased by 30.05% from 1990 to 2019, but the prevalence was highest in countries with low sociodemographics.[2]

Long-term risks of the HDP include cardiovascular (CV) disease, diabetes, stroke, heart failure, neurological disorder and women require structured postpartum follow-up and targeted preventive measures.[4,5] In children or paediatrics, HDP may lead to placental abruption, intrauterine growth restriction (IUGR), preterm birth and long-term elevated CV and neurodevelopmental risks, which require ongoing monitoring.[3,4] Preeclampsia results from abnormal placentation, which triggers endothelial dysfunction, oxidative stress and

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impaired vasodilation. The pathophysiology of preeclampsia is a two-step process involving impaired or abnormal placentation due to inadequate invasion of trophoblasts, resulting in poor remodelling of the spiral artery and placental hypoxia, and this trigger releases the antiangiogenic factors (sFlt-1 and sEng), causing endothelial dysfunction and systemic inflammation.[6]

Homocysteine, which is a sulfur-containing amino acid produced from the metabolism of methionine, an essential amino acid obtained from the daily diet, circulates in the blood as free and protein-bound forms. The elevation of this amino acid may result from the methylenetetrahydrofolate reductase (MTHFR) gene mutation in women with reduced folate intake, which leads to hyperhomocysteinemia.[7] Apart from genetic defects, there are various factors causing this elevation of homocysteine, including the lack of folic acid, vitamin B6 and B12 deficiency, hypothyroidism, drugs, ageing, and renal dysfunction, while women with normal pregnancies reported lower levels of homocysteine compared to non-pregnant women. Increased amino acid levels in the peripheral blood may lead to vascular illness, coronary artery dysfunction, atherosclerotic changes, and embolic diseases.[6,7]

Homocysteine is a promising biochemical marker for predicting and assessing preeclampsia severity. Gaiday et al. reported elevated homocysteine levels in patients with preeclampsia (16.07 µmol/L at 10-14 weeks, compared to those in normotensive pregnancies (7.19 µmol/L) ($p < 0.0001$), with a first-trimester cutoff of >9.55 µmol/L, an AUC of 0.859, 91.67% sensitivity, and 72.24% specificity.[8] Chen et al. showed high diagnostic performance with an AUC of 0.978, 93.4% sensitivity, and 95.0% specificity at a 9.230 µmol/L threshold, confirming it as a significant predictor with other markers.[9] The clinical utility of serum homocysteine levels for preeclampsia prediction is uncertain due to inconsistent findings. There is no universal threshold available for normal versus pathological pregnancy. Given the role of endothelial dysfunction in preeclampsia, homocysteine may indicate damage. If elevated levels correlate with severe disease, they could enable early risk identification.

Aim

To compare serum homocysteine levels in preeclamptic and normotensive pregnant women and to evaluate their association with disease severity and fetomaternal complications using a predefined reference value.

MATERIALS AND METHODS

This prospective case-control, open-label study was conducted in 60 pregnant women attending the Antenatal OPD, Labour Ward, and Antenatal Ward, Department of Obstetrics and Gynaecology, Government Rajaji Hospital, Madurai Medical College, Madurai, over 6 months. Ethical approval was obtained from the institutional ethics committee, and written informed consent was obtained from the participants before the study initiation.

Inclusion Criteria

This study included pregnant women with blood pressure >140/90 mmHg in previously normotensive women on two occasions, 6 h apart, with a gestational age of 28-40 weeks confirmed by the last menstrual period or ultrasonography in the first or early second trimester, and healthy normotensive pregnant women at 28-40 weeks.

Exclusion Criteria

Pregnant women with chronic hypertension, gestational diabetes, type 1 or 2 diabetes, connective tissue disorders, multiple pregnancies, liver diseases, severe anaemia, smoking, obesity, and antiphospholipid antibody syndrome.

Materials

Materials used included a sphygmomanometer, laboratory equipment for blood and urine investigations, a centrifuge, plastic storage vials, and chemiluminescence immunoassay reagents for serum homocysteine levels.

Methods

Sixty pregnant women were divided into case (n=30) and control (n=30) groups. Cases were recruited consecutively from women undergoing preeclampsia workup, and an equal number of gestational age–matched healthy normotensive pregnant women were included as controls. Blood pressure was recorded semi-recumbently with two measurements 6 h apart. All patients underwent detailed history taking and clinical examination. Patients underwent investigations, including urine routine examination, renal and liver function tests, serum uric acid, and 24-hour urinary protein estimation. Urine culture was performed when necessary.

Peripheral smear examination was performed for all patients to exclude megaloblastic anaemia, dimorphic anaemia, and HELLP syndrome. Serum folate and vitamin B12 could not be estimated due to resource constraints; hence, peripheral smear findings were used as indirect indicators. Serum homocysteine levels were estimated after excluding vitamin deficiency. For measurement, 5 mL of blood was drawn from the antecubital vein after overnight fasting, transported to the laboratory, centrifuged at 3000 rpm for 5-7 min, and the clear serum was stored under refrigeration until analysis. Serum homocysteine was measured by chemiluminescence immunoassay. After delivery, the placenta was sent for histopathological examination to assess villous ischaemia, syncytial knots, trophoblastic basement membrane thickening, villous hypovascularity, and retroplacental clots.

Statistical analysis

Data were presented as mean, standard deviation, frequency, and percentage. Variables were compared using the unpaired t-test for continuous data and Fisher's exact test for categorical data analysis. Significance was defined as $P<0.05$, and analysis was

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performed using IBM-SPSS version 21 (IBM-SPSS Science Inc., Chicago, IL, USA).

RESULTS

Most patients were aged 26-30 years (56.7% and 63.3%), followed by 21-25 years (20% and 26.7%). The mean age was comparable between the groups (26.7 ± 3.098 vs. 26.27 ± 2.532; p>0.05). 50% of the case group had BMI <25 kg/m² versus 63.3% in the control group, while BMI ≥25 kg/m² was found in 50.0% of cases and 36.7% of controls (p>0.05) (Table 1). The average gestational age of cases was 36.1 weeks, and that of controls was 35.7 weeks (p>0.05). [Table 1]

Table 1: Comparison of age distribution and body mass index between groups

Parameters		Case (n=30)	Control (n=30)	p value
Age (years)	< 20	2(6.7%)	1(3.3%)	0.555
	21–25	6(20%)	8(26.7%)	
	26–30	17(56.7%)	19(63.3%)	
	> 30	5(16.7%)	2(6.7%)	
	Mean ± SD	26.7 ± 3.098	26.27±2.532	>0.05
BMI (kg/m2)	< 25	15(50%)	19(63.3%)	>0.05
	≥ 25	15(50%)	11(36.7%)	

Normal homocysteine values (<8) were observed in all control patients (100.0%), and none in the case group. Moderate levels (8-16) were observed in 40.0% of the case group, and severe levels (>16) in 60.0%. The mean level was significantly higher in the case group (16.81 ± 2.32 vs. 6.87 ± 0.83) (p < 0.001). The case group had 4+ albuminuria most often (53.3%), followed by 2+ (30.0%), 3+ (13.3%), and 1+ (3.3%), while the control group had no albuminuria (p < 0.001).[Table 2]

Table 2: Comparison of homocysteine levels and urine albumin between groups

Parameters		Case (n=30)	Control (n=30)	p value
Homocysteine Level	Normal (<8)	0	30 (100%)	-
	Moderate (8–16)	12(40%)	0	
	Severe (>16)	18(60%)	0	
	Mean ± SD	16.81 ± 2.32	6.87 ± 0.83	<0.001
Urine Albumin	1+	1(3.3%)	0	<0.001
	2+	9(30%)	0	
	3+	4(13.3%)	0	
	4+	16(53.3%)	0	

Serum urea levels were higher in the case group (37.20 ± 23.37 vs. 21.80 ± 2.98, p < 0.001). Serum creatinine was significantly higher in the case group (1.53 ± 1.88 vs. 0.60 ± 0.16, p = 0.009). Serum bilirubin was elevated in the case group (1.24 ± 1.07 vs. 0.65 ± 0.16, p = 0.004). Serum uric acid was significantly higher in the case group (6.82 ± 0.78 vs. 5.20 ± 0.46, p < 0.001). The 24-hour urine protein was greater in the case group (393.37 ± 106.75, 186.43 ± 15.60, p < 0.001). [Table 3]

Table 3: Comparison of biochemical parameters between groups

Parameters	Case (n=30)	Control (n=30)	p value
Urea	37.20±23.37	21.80±2.98	< 0.001
Creatinine	1.53±1.88	0.60±0.16	0.009
Sr Bilirubin	1.24±1.07	0.65±0.16	0.004
Uric acid	6.82±0.78	5.20±0.46	< 0.001
24-hour urine protein	393.37±106.75	186.43±15.60	< 0.001

A total of 69 complications were reported, with several patients having multiple complications. The majority occurred in women with severe homocysteine elevation (>16 µmol/L) (n = 61), compared to those with moderate elevation (<16 µmol/L) (n = 8). In the severe group, IUGR (72.2%) was the most frequent, followed by disseminated intravascular coagulation (DIC) and placental abruption (61.1% each), and atonic postpartum haemorrhage (PPH, 55.6%). No cases of pulmonary oedema, acute kidney injury (AKI), atonic PPH, or intrauterine death (IUD) were observed in the moderate group (p < 0.001). [Table 4]

Table 4: Comparison of complications according to homocysteine level

Parameters		Homocysteine level		p value
		> 16 (Severe Elevation)	< 16 (Moderate Elevation)	
Complications	Pulmonary Edema	6(33.3%)	0(0.0%)	< 0.001
	AKI	4(22.2%)	0(0.0%)	
	DIC	11(61.1%)	1(8.3%)	
	HELLP	3(16.7%)	1(8.3%)	
	Abruption	11(61.1%)	1(8.3%)	

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	Atonic PPH	10(55.6%)	0(0.0%)	
	IUGR	13(72.2%)	5(41.7%)	
	IUD	3(16.7%)	0(0.0%)	

DISCUSSION

Preeclampsia is a major contributor to maternal and perinatal morbidity, with endothelial dysfunction and placental insufficiency playing main roles in its pathogenesis. This study evaluated serum homocysteine levels in preeclamptic and normotensive pregnant women and examined their association with biochemical derangements, degree of proteinuria, and the spectrum of maternal and fetal complications. Elevated homocysteine levels were observed only in the preeclampsia group and were significantly associated with worsening renal and hepatic parameters, higher 24-hour urinary protein, and increased frequency of complications.

In our study, most patients belonged to the 26-30-year age category, with those younger than 20 years being the least represented, and the age distribution was comparable between groups. Women with a BMI ≥ 25 were common in cases without any significant difference. Qureshi et al. analysed 132 pregnant women and found that higher BMI (≥25 kg/m²) was significantly associated with preeclampsia, with a 2.66-fold increased risk (p = 0.021). The mean age of the cases and controls was 26.76 ± 5.82 years and 25.39 ± 4.69 years.[10] The comparable age distribution between cases and controls indicates that age was not a confounding factor across the studies. Unlike the previous study, there was no association between BMI and the cases in our study, which may be due to the smaller sample size in our study, reducing the statistical power to detect modest associations. Variations in study design, inclusion criteria, and the proportion of overweight and obese patients could have contributed to the lack of a significant association in our findings.

In our study, homocysteine levels showed differences between groups, with elevated levels only in cases, while controls had normal values. Urine albumin excretion differed significantly, with albuminuria present only in the cases. Qureshi et al. found mean homocysteine levels of 16.05±2.25 µmol/L in preeclamptic women versus 9.44±2.83 µmol/L in controls (p<0.001), with an odds ratio of 4.72.[10] Latha et al. reported elevated homocysteine levels in 96% of preeclampsia cases, with levels correlating with disease severity and differences between mild and severe cases (P <0.05).[11] Ananthathirtha et al. (2019) found a mean serum homocysteine level of 13.87±4.01 µmol/L in cases compared to controls (p<0.001).[12] Thes findings suggest the possible role of homocysteine as a biochemical marker for identifying women at higher risk and for assessing disease severity.

In our study, the biochemical parameters, including serum urea, creatinine, bilirubin, uric acid, and 24-hour urine protein, were significantly higher in the case group than in the control group. Tesfa et al. report significantly higher concentrations of serum uric acid and blood urea values in pre-eclampsia compared with normotensive pregnant women, concluding that serum uric acid, blood urea and creatinine levels could be carefully utilised as a diagnostic marker for PE.[13] Latha et al. found that serum homocysteine levels were significantly increased in women with preeclampsia.[11] The significantly elevated biochemical parameters in preeclamptic women indicate underlying renal impairment, endothelial dysfunction, hepatic involvement, and altered metabolic status. Therefore, routine monitoring of these parameters can help in surveillance and support timely obstetric decision-making to improve maternal and foetal outcomes.

In our study, severe homocysteine level elevation was significantly associated with IUGR, followed by coagulation abnormalities, placental abruption, atonic PPH, pulmonary oedema, renal injury, HELLP syndrome, and IUD. Latha et al.'s study of 100 women found 96% of preeclamptic cases had elevated homocysteine, with complications including acute kidney injury, placental abruption, and pulmonary oedema. Homocysteine levels correlated with disease severity and IUGR (F=359.13, p<0.001).[11]

Yelikar et al. found median homocysteine levels of 16.25 µmol/L in preeclampsia and 31.34 µmol/L in eclampsia (p<0.001).[14] Maru et al. showed that 79.31% of patients with elevated homocysteine levels experienced complications in their study.[15] Chaudhry et al.'s study (7,587 participants) found homocysteine associated with small-for-gestational-age infants (OR 1.76, 95% CI 1.25-2.46).[16] This indicates that higher homocysteine levels are associated with high disease severity and poorer fetomaternal outcomes.

Limitations

The sample size was relatively small, which may have limited the statistical power to detect modest associations. The study was conducted at a single tertiary care centre, which may restrict the generalisability of the results to the broader population. As a case–control study with measurements taken in the third trimester after the diagnosis of preeclampsia, it could not assess the temporal or causal relationship between elevated homocysteine levels and the development of the disease. Serum folate and vitamin B12 levels were not directly measured due to resource constraints, which might cause residual confounding. Advanced statistical analyses, such as correlation coefficients, regression models, or receiver operating characteristic curve analysis, were not performed to determine independent associations or to establish an optimal diagnostic or prognostic cut-off value. Long-term maternal and neonatal outcomes were not

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followed up, so the prognostic implications of elevated homocysteine could not be fully assessed.

CONCLUSION

Preeclampsia is associated with hyperhomocysteinemia, and homocysteine levels are directly proportional to disease severity. Serum homocysteine levels above 16 mol/L can predict poor maternal and foetal complications until larger studies determine the exact value. High maternal homocysteine levels are linked to morbidities such as placental abruption, DIVC, Atonic PPH, HELLP, and foetal complications such as IUGR, low birth weight, stillbirth, and preterm labour. Future research should focus on large, multicentric prospective cohort studies to analyse the association between serum homocysteine levels and the development as well as the severity of preeclampsia across diverse populations.

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