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Association of serum homocysteine with vitamin B12 and folate levels in women with pre-eclampsia in a tertiary health care center in Nepal

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Abstract

Background Pre-eclampsia is a syndrome that chiefly includes the development of new-onset hypertension and proteinuria after 20 weeks of pregnancy. Pre-eclampsia is one of the major causes of mortality and morbidity in Nepal. Hyperhomocysteinemia may be a cause of the endothelial dysfunction provoked by oxidative stress in pre-eclampsia. This study was designed to evaluate the association of homocysteine with Vitamin B12 and folate in patients with pre-eclampsia.

Method An observational cross sectional study was performed in the Gynecology and Obstetrics Department of TUTH involving seventy two subjects with pre-eclampsia. Blood pressure, urinary protein levels, serum homocysteine, Vitamin B12 and folate levels were compared in both mild and severe forms of pre-eclampsia. Concentration of Vitamin B12 and folate were measured using Vitros ECI and homocysteine was measured using CLIA. SPSS 23.0 was used to analyze the data. Tests were performed with Mann Whitney Test and Spearman's rank correlation test. A p-value < 0.05 was considered statistically significant.

Results This study showed no significant difference in age and weeks of gestation in both mild and severe forms of pre-eclampsia. Mean concentration of homocysteine was higher (13.1 ± 6.4 micromol/L) in severe Pre-eclampsia as compared to mild cases (7.6 ± 2.8 micromol/L). Mean concentration of folate was lower in severe cases (35.4 ± 24.1 micromol/L) when compared with mild cases of pre-eclampsia (57 ± 23.4 micromol/L).

Conclusion Homocysteine levels were increased in severe Pre-eclampsia when compared with mild pre-eclampsia and this finding can be used to predict and prevent complications in patients with pre-eclampsia.

Keywords Pre-eclampsia, Hypertension, Homocysteine, Pregnancy

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Introduction

Pre-eclampsia is considered as the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive patient [1–3]. Pre-eclampsia affects approximately 2–8% of pregnancies worldwide [4]. The World Health Organization (WHO) estimated that the incidence rate of preeclampsia in developing countries is 7-times higher (2.8%) than in developed countries (0.45%) [5]. In Nepal, the incidence of preeclampsia or eclampsia was 20 cases to 1,000 hospital deliveries [6].

Both maternal and fetal/placental variables are probably involved in the pathophysiology of pre-eclampsia. This systemic condition is closely linked to pathological placental blood flow, endothelial activation, oxidative stress and generalized inflammation. The most prominent feature of this disease is endothelial dysfunction, which is caused by the release of soluble Fms-like tyrosine kinase 1(sFlt1), soluble endoglin and low levels of proangiogenic factors like placental growth factor (PlGF), vascular endothelial growth factor (VEGF) from the ischemic placenta into maternal plasma [7]. Poor uterine and placental perfusion as a result of improper implantation and placentation causes oxidative stress, hypoxia, and the production of several anti-angiogenic factors, all of which contribute to generalised endothelial dysfunction [8].

Micronutrients like folate and Vitamin B12, which are components of the one carbon cycle are important elements of pregnancy outcome. It has been recommended that the pathophysiology of pre-eclampsia may be influenced by an imbalance in the levels of folate and other B vitamins [9, 10]. It is well known that low levels of folate and B12 can lead to increased levels of homocysteine, which further result in increased oxidative stress [11]. Tetrahydrofolate, the active form of folate, can only be produced through the conversion of folate with the help of Vitamin B12. An impaired folate and vitamin B12 status is known to alter homocysteine levels [12]. Folate deficiency could be one of such factors that affects the vasculogenesis of the yolk sac, embryonic tissues and placenta. Trophoblast apoptosis is a possible mechanism because of hyperhomocysteinemia during early pregnancy prior to the development of pre-eclampsia [13].

Raised levels of homocysteine have been linked with atherosclerosis and cardiovascular disorders attributing to endothelial dysfunction [14]. Maternal plasma homocysteine concentration has been proposed to be associated with pregnancy complications including pre-eclampsia, placental abruption, intrauterine growth restriction (IUGR), and pregnancy loss [15]. Hyperhomocysteinemia has been hypothesized to be associated with preeclampsia because of its role in endothelial dysfunction [16]. Although some of the previous reports suggested several possible mechanisms for the occurrence of hyperhomocysteinemia in pre-eclampsia, the exact

mechanisms are not known. The purpose of present study is to find the association of homocysteine, folate and B12 levels in women diagnosed with preeclampsia.

Materials and methods

This study was carried out at Institute of Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu. Institutional Review Board at the Tribhuvan University, Institute of Medicine, Maharajgunj, Nepal approved the study (Approval number: 368 [6–11]E²/075 /76). All the participants completed a medical history form and provided informed consent. Seventy two Pre-eclamptic patients in the age group 19–44 years were studied for estimation of serum homocysteine, folic acid and vitamin B12 over a period of February 2019 to November 2019.

Pre-eclampsia is considered as the onset of a new episode of hypertension during pregnancy (with persistent systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg) with the occurrence of substantial proteinuria (> 0.3 g/24 h). The clinical findings of Preeclampsia are assorted by the presence of systemic endothelial dysfunction and microangiopathy, affecting the liver (hemolysis, elevated liver function tests and low platelet count, namely HELLP syndrome) and the kidney (proteinuria) [8].

Patients with symptoms and signs suggestive of eclampsia supported by laboratory investigations and with normal renal and liver function tests were included in the study. However, patients were excluded from the study in case of multiple gestation, placental insufficiency, seizure disorder, history of chronic hypertension, causes of Proteinuria other than Pre-eclampsia, history of cardiovascular disease and in-vitro fertility related pregnancies.

In all patients, blood samples were obtained by taking aseptic precautions and then placed in serum separator tubes. Blood samples were centrifuged at 4,000 rpm for 5 min at room temperature and the separated serum was stored at -40 °C until the assays were performed.

The concentration of serum Vitamin B12 and folate levels were assayed by immunochemiluminescence technique by using VITROS 3600 (Ortho Clinical Diagnostics). Measuring range for Vitamin B12 is 50–2000 pg/ml and measuring range for folate is 0.6–20 ng/ml. The serum homocysteine level was measured by competitive binding immunoassay technique by using ADVIA Centaur CP (Siemens Healthcare Diagnostics). Measuring range for homocysteine is 1–50 micromol/L.

Data analyses included standard descriptive statistics using SPSS version 23 (IBM Corporation, Armonk, NY, USA), with variables expressed as mean ± standard deviation or medians as appropriate. Tests were performed with Mann Whitney Test and Spearman's rank

Table 1 Descriptive characteristics for various parameters in the study levels

Parameters	Mean	Median (IQR)	95% CI
Age (years)	28.2 ± 5.1	27.5 (7)	(25,29)
Gestational age (WOG)	35.5 ± 3.7	36.0 (6)	(35, 38)
DBP(mm Hg)	100.9 ± 8.7	100.0 (20)	(100, 100)
SBP(mm Hg)	148.6 ± 9.9	150.0 (20)	(140, 150)
Body Mass Index (kg/m ²)	30.5 ± 4.1	30.10 (6.6)	(28.6, 32.03)
Homocysteine(micromol/L)	9.57 ± 5 0.10	8.2 (5.2)	(7.3, 9.8)
Vitamin B12(pg/ml)	213.2 ± 62.0	201.0 (85.8)	(191, 223)
Folate(ng/ml)	49.53 ± 25.7	53.5(40.5)	(36, 63)

Table 2 Descriptive characteristics for various parameters in patients with pre-eclampsia

Parameters	Mild	Severe
Age (years)	28.1 ± 4.5	28.2 ± 6.2
Gestational age (WOG)	36.3 ± 3	34.0 ± 4.4
Body Mass Index (kg/m ²)	30.6 ± 3.8	30.2 ± 4.9
Homocysteine (micromol/L)	7.6 ± 2.8	13.1 ± 6.4
Vitamin B12 (pg/ml)	220 ± 61.7	200.5 ± 61.7
Folate (ng/ml)	57 ± 23.4	35.4 ± 24.1

Table 3 Mann Whitney Test results for categories of pre-eclampsia

Variable	Group	Mean Rank	Z	Sig (2-tailed)
Homocysteine	Mild	29.0	-4.15	0.000*
	Severe	50.5		
Vitamin B12	Mild	39.4	-1.62	0.104
	Severe	31.0		
Folate	Mild	42.5	-3.36	0.001*
	Severe	25.1		

*Significant at the 0.01 level

correlation test. A P-value of <0.05 was considered statistically significant.

Results

The mean age of patients diagnosed with Pre-eclampsia was 28.2 ± 5.1 years. The mean gestational age of the patients diagnosed with Pre-eclampsia was 35.5 ± 3.7 WOG (weeks of gestation). (Table 1) Forty (55%) women with Pre-eclampsia were Primigravid and thirty two (45%) women were multigravida.

Cases of Pre-eclampsia were divided into mild and severe cases as defined by the American College of Obstetricians and Gynecologists 2012–2013 [17]. Forty-seven (65%) cases with preeclampsia were mild and Twenty five (35%) cases with pre-eclampsia were severe.

Mean levels of serum homocysteine in mild and severe cases of Pre-eclampsia were 7.6 ± 2.8 micromol/L and 13.1 ± 6.4 micromol/L respectively. Mean serum Vitamin B12 levels of women with mild and severe Pre-eclampsia were 220 ± 61.7pg/ml and 200 ± 61.7 pg/ml respectively. Mean serum folate levels of women with mild and severe

Table 4 Correlation of means of homocysteine, vitamin B12 and folate

Spearman's Rho	Homocysteine	B12	Folate
Homocysteine Correlation coefficient	-	0.365	0.647
Sig. (2 tailed)	-	0.002*	0.001*

*Significant at the 0.05 level

pre-eclampsia were 57 ± 23.4 ng/ml and 35 ± 24.1 ng/ml respectively. (Table 2)

The Mann Whitney results indicated that homocysteine levels in severe pre-eclampsia was significantly higher than in mild pre-eclampsia. (Z value: -4.15, p=0.001) and folate levels were low in severe Pre-eclampsia than in mild pre-eclampsia. (Z value: -3.36, p=0.001) (Table 3).

A spearman's correlation was done to find out the correlation between homocysteine, folate and B12 according to severity of Pre-eclampsia. There was significant correlation found between homocysteine and folate levels (p value 0.001) and homocysteine and B12 levels (p value 0.002). (Table 4)

Discussion

The present study tested the levels of maternal plasma folate, vitamin B12 and homocysteine in women with pre-eclampsia. Our outcomes demonstrated a few remarkable observations in Pre-eclampsia which are as follows: (1) Serum levels of homocysteine were raised in subjects with severe pre-eclampsia contrasted to mild pre-eclampsia. (2) Serum levels of folate were decreased in severe pre-eclampsia contrasted to mild pre-eclampsia. (3) Homocysteine and vitamin B12 and homocysteine and folate showed a strong link (p value<0.01), whereas folate and vitamin B12 showed no significant association.

In this study, the mean homocysteine was found to be 9.57 micromol/L. Similar study done by Rajkovic et al. reported a mean homocysteine level of 12.7 micromol/L as compared to 9.93 micromol/L in normal pregnant women, suggesting association between homocysteine levels and pre-eclampsia [18]. The data of the present study is consistent with the previous studies of Bergen et al [19] and Braekke et al [20] who also made discoveries of raised levels of homocysteine in Pre-eclampsia. In normal pregnancy, the plasma concentration of

homocysteine tends to decrease. This may be because of increased plasma volume and resulting hemodilution, increased glomerular filtration rate, pregnancy related hormonal changes and increased uptake of homocysteine by the fetus [21–23]. It is believed that increased homocysteine in pre-eclampsia damages the vascular endothelium. Furthermore, the endothelium in pregnant women may be more predisposed to harm, even a little rise in homocysteine levels has the potential to damage the endothelium and activate a number of mechanisms that cause Pre-eclampsia.

Folate, Vitamin B12 and B6 are necessary for DNA synthesis and cell proliferation and are involved in homocysteine metabolism. In the present study, we found that severe pre-eclampsia had lower levels of folate than moderate pre-eclampsia. Some observational studies that show reduced levels of folate in pregnant women with pre-eclampsia confirm our findings [19, 24–27]. In contrast, few studies report higher levels of folate [28–30]. In a systematic review by Mignini et al., folic acid and vitamin B12 concentrations were lower in preeclamptic women when compared with those of normotensive women [31]. The results of this study are in line with a number of studies conducted by Yanez et al. and Mujawar et al., who reported similar relationships between higher homocysteine concentration and lower folate concentrations [24, 32]. Homocysteine is metabolized by pathways: remethylation and transsulfuration. Vitamin B6 is required for the transsulfuration of homocysteine to cysteine while, folic acid has to be present as 5-methyltetrahydrofolate (FMTHF) to be an effective donor for the remethylation of homocysteine to methionine [33]. Homocysteine builds up as a result of impaired homocysteine re-methylation to methionine caused by insufficient vitamin B availability (B₆, B₁₂ and folic acid) [34].

In summary, homocysteine level is still a relatively novel term in obstetrics, especially in a developing country like Nepal. This must be the first study done in Nepalese population that showed increased levels of homocysteine and decreased levels of folate in severe form of pre-eclampsia as compared to mild pre-eclampsia. Although majority of women had decreased Vitamin B12 levels, there was no significant difference when mild and severe forms of preeclampsia were compared. Though higher homocysteine levels have been shown to be associated with pre-eclampsia and may also be considered as a predictive risk factor for preeclampsia and yet, it cannot be used as a screening tool.

Our finding is important for future clinical studies in suspected cases of pre-eclampsia. The limitations of our study is that the samples were exclusively obtained from suspected cases of pre-eclampsia. The inclusion of case-control studies would have strengthened the study to establish association between homocysteine, vitamin B12

and folate levels. Additionally, we recognized that not following up with patients with pre-eclampsia until delivery limits the depth of our statistical analysis regarding homocysteine levels and their fetomaternal outcomes.

Conclusion

From the above discussion, we can assume that biochemical screening such as homocysteine, folic acid and vitamin B12 are of supreme importance in pre-eclampsia. Homocysteine levels were elevated in patients with severe Pre-eclampsia as compared to mild pre-eclampsia. Thus, hyperhomocysteinemia is a treatable risk factor as folic acid and vitamin B12 supplementation can help decrease plasma homocysteine concentration, thereby, reducing the risk of developing pre-eclampsia and its consequences. Conversely, further prospective, large scale, longitudinal studies is essential to define the practicality of homocysteine in evaluating pre-eclampsia.

Acknowledgements

We would like to thank Nepal Health Research Council for the grant which helped us with the research. We would also like to thank Dr Vivek Pant (Consultant Biochemist, Samyak Diagnostics, Nepal) for his insight and constant encouragement. We would like to acknowledge the contribution of participants, residents and nurses of TU Teaching Hospital, Maharajgunj.

Author contributions

Dr Salina Pradhananga wrote the main manuscript. Dr Binod Kumar Yadav, Dr Suvana Maskey and Dr Aseem Bhattarai were involved in reviewing the manuscript. Dr Astha Regmi and Sabina Shakya were involved in data acquisition, data analysis and statistical analysis. All authors reviewed and approved the manuscript.

Funding

This study was funded by Nepal Health Research Council, which is an apical body responsible for providing scientific study and quality health research in the country.

Data availability

All data that are generated during this study are included in this article. The data that support the findings of this study are available on request from the corresponding author, Pradhananga et al., upon reasonable request. The data is not available due to the information that could compromise the privacy of the research participants.

Declarations

Ethics approval and consent to participate

Institutional Review Board at the Tribhuvan University, Institute of Medicine, Maharajgunj, Nepal approved the study (Approval number: 368(6-1)E² /075 /76). All the participants provided informed and written consent. All necessary methods were conducted under the guidelines of the institution and declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 25 September 2023 / Accepted: 29 July 2024

Published online: 09 August 2024

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