Original Research Article
Relationship of Maternal Serum Zinc Level with Preeclampsia

Abstract
Preeclampsia is an important cause of maternal and perinatal morbidities. Zinc is an essential trace element that is presumed to have a role in the regulation of blood pressure through its antioxidant properties and modulation of renal sodium transport. The objective of the study was to determine the relationship between maternal serum zinc level and preeclampsia. This case-control study was conducted among 100 pregnant women at the Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Among the 100 patients, 50 were pregnant women with preeclampsia (cases) and 50 were pregnant women without preeclampsia (controls). The serum zinc level was measured for all of them. The mean serum zinc level of the cases and controls were 59.58±31.79 μg/dl and 89.02±31.14 μg/dl respectively (P=<0.001). The respondents with zinc level <68 μg/dl had 6.05 times more chances to have preeclampsia compared to that of the respondents with zinc level ≥68 μg/dL (p<0.001; OR=6.048; 95% CI=2.540-14.399). There was significant negative correlation of serum zinc level with both systolic blood pressure (r= -0.340, p=0.001) and diastolic blood pressure (r=-0.404, p<0.001). In conclusion, low maternal serum zinc level was found related to preeclampsia.

Keywords: Preeclampsia, Serum zinc level.

Introduction
Preeclampsia (PE) is characterized by new onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the new-onset conditions: proteinuria, other maternal organ dysfunction like renal impairment, hepatic dysfunction, neurological complications or haematological complications (thrombocytopenia, disseminated intravascular coagulation) and/or uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis or stillbirth [1]. An estimated 2-10% of pregnancies are complicated by preeclampsia globally, while its prevalence in developing nations ranges from 1.8% to 16.7% [2]. In Bangladesh, the overall prevalence of preeclampsia is 14.4% [3]. Complications of preeclampsia are maternal such as eclampsia, abruptio placentae, renal failure, cerebral haemorrhage, HELLP syndrome, pulmonary edema and visual loss. Risks to the fetus include fetal growth restriction (FGR), premature birth, low APGAR score, stillbirth, neonatal intensive care unit admission and neonatal death. Since preeclampsia is caused by multiple factors, finding any factor related to this disorder can help in its prevention and can reduce the maternal and perinatal mortality and morbidity. As micronutrients are essential for normal physiological function, growth and development, the possible role of maternal serum zinc status also needs to be evaluated to understand the precise etiopathogenesis of preeclampsia and therefore limit its severity [4].

Proper implantation and angiogenesis are essential for the maintenance of a healthy pregnancy. The invading cells of embryo are called cytotrophoblasts. The process of invasion of cytotrophoblasts requires enzymatic digestion of the extracellular matrix (ECM) by matrix metalloproteinase enzyme (MMP-9) which is a zinc endopeptidase [5]. A study proves that zinc chelation diminishes the activity of MMP-2 and MMP-9 [5]. Deficient concentrations of

zinc during pregnancy may cause impairment of antioxidant potential of cells by decreasing superoxide dismutase activity, as well as increased lipid peroxidation. Lipid peroxides formed at a primary site are then transported through the circulation by lipoproteins causing damage at distant tissues. The endothelial cells lining the high-pressured arterial vessels are particularly vulnerable to oxygen free radical initiated lipid peroxidation. Impaired function of generalized vascular endothelium may, in turn, cause vasospasm and an increase in sensitivity to vasopressors occurring in preeclampsia. This suggests the possibility of zinc deficiency in the incidence of preeclampsia [6,7].

In recent years, it was estimated that over 80% of pregnant mothers worldwide have inadequate zinc intake due to increased demand, low-zinc diets, and the consumption of foods that interfere with zinc absorption (WHO, 2016) [8]. Several groups of researchers emphasized the contribution of zinc deficiency in the aetiology of preeclampsia [9,10,11]. Meanwhile, some studies found that the serum zinc concentrations were not significantly different between the preeclampsia patients and the healthy pregnant women [12,13]. So, this study has been designed to estimate the serum zinc level and determine its association with preeclampsia in women of our country.

Materials and Methods

This prospective case control study was conducted in the department of Obstetrics & Gynecology of Bangabandhu Sheikh Mujib Medical University (BSMMU), during March 2020 to February 2022 after obtaining Institutional Review Board approval. A total of 100 study subjects were enrolled upon fulfilling inclusion and exclusion criteria attending the outpatient and inpatient department of Obstetrics & Gynecology BSMMU. The study population was divided into two groups: case (n=50) consisting of patients with preeclampsia and control (n=50) comprising women without preeclampsia matched for age and gestational age. Inclusion criteria for cases were: singleton pregnancy with preeclampsia within the age range of 18 to 40 years with gestational age between 28 to 40 weeks. Control group bear the above-mentioned same characteristics except normotensive as determined by measurement of BP. Exclusion criteria are: multiple pregnancy, previous history of preeclampsia, pregnant women with raised uric acid level, diagnosed cases of chronic renal disease, diagnosed case of chronic hypertension, diagnosed case of cardiovascular disease, and patients who were taking zinc supplementation. Detailed medical, family, and socioeconomic histories were taken and recorded. Thorough physical examination of the subjects was done. Blood pressure was measured and recorded carefully. Urine analysis was done to measure the degree of proteinuria. Maternal blood samples were tested for serum zinc level in the Department of Biochemistry & Molecular Biology of BSMMU. Unpaired t-test, chi square test and Pearson's correlation coefficient test were done for statistical analysis. Odds ratio (at 95%CI) was calculated to see the association of maternal serum zinc level with preeclampsia. A 'p' value <0.05 was considered as statistically significant.

Results

The clinical characteristics as age, socioeconomic status, gravidity, gestational age, body mass index (BMI) and family history of hypertension are shown in table - I and table – II respectively. The mean maternal zinc level of the respondents is shown in table -III which revealed that the zinc level of the cases was low (59.58 ± 31.79 μg/dl) than the control (89.02 ± 31.14 μg/dl) which is significant (p = 0.025). Table IV shows that the pregnant women with zinc level <68 μg/dl had 6.05 times more chance to have preeclampsia compared to those of the pregnant women with zinc level ≥ 68 μg/dl (p<0.001; OR=6.048; 95% CI=2.540-14.399). Negative correlation (r= -0.340,) was observed between maternal serum zinc level and

systolic blood pressure in the study subjects which is statistically significant (p=0.001) (Fig. 1). Similar negative correlation (r= -0.404) was observed between maternal serum zinc level and diastolic blood pressure which is also statistically significant (p<0.001) (Fig. 2).

Table I. Sociodemographic data of the respondents

Characteristics	Case (n=50)	Control (n=50)	p-value
Age (Mean ± SD)	27.18 ± 6.03	26.56 ± 5.46	0.591[a]
Monthly family income (in taka) *			
Lower class (≤ 7,378)	8 (16.0)	4 (8.0)	0.363[b]
Lower middle class (7,379–28,810)	26 (52.0)	25 (50.0)	
Upper middle class (28,811–89,280)	16 (32.0)	21 (42.0)	

[a]Chi square test was done to measure the level of significance.
[b]Un-paired t-test was done to measure the level of significance.
Figure within parentheses indicates in percentage.
* World Bank Data Team on July 2020

Table II. Clinical characteristics of the respondents

Characteristics	Case (n=50)	Control (n=50)	p-value
Gravida			
Primigravida	31 (62.0)	28 (56.0)	0.542[a]
Multi gravida	19 (38.0)	22 (44.0)	
Gestational age in weeks (Mean ± SD)	32.94 ± 1.86	33.54 ± 2.19	0.143[b]
Family history of hypertension			0.068[a]
Present	17 (34.0)	9 (18.0)	
Absent	33(66.0)	41 (82.0)	
BMI (kg/m^2) Mean ± SD	26.68 ± 1.78	26.02 ± 1.56	0.053[b]

[a]Chi square test was done to measure the level of significance.
[b]Un-paired t-test was done to measure the level of significance.
Figure within parentheses indicates in percentage.

Table III. Mean maternal zinc level of the respondents

Mean maternal zinc level (µg/dl)	Case (n=50)	Control (n=50)	p-value
Mean ± SD	59.58 ± 31.79	89.02 ± 31.14	<0.001[a]

[a]Un-paired t-test was done to measure the level of significance.

Table IV. Odds ratios (OR) and 95% confidence intervals (CI) for preeclampsia according to maternal serum zinc level in pregnancy

Maternal	Case	Control	p-value	Odd's Ratio	95% CI (lower-

serum zinc level (µg/dl)	(n=50)	(n=50)			upper
< 68 µg/dl	34 (68.0)	13 (26.0)	<0.001[a]	6.048	(2.540-14.399)
≥ 68 µg/dl	16 (32.0)	37 (74.0)			

[a]Chi-square test was done to measure the level of significance.
Figure within parentheses indicates in percentage

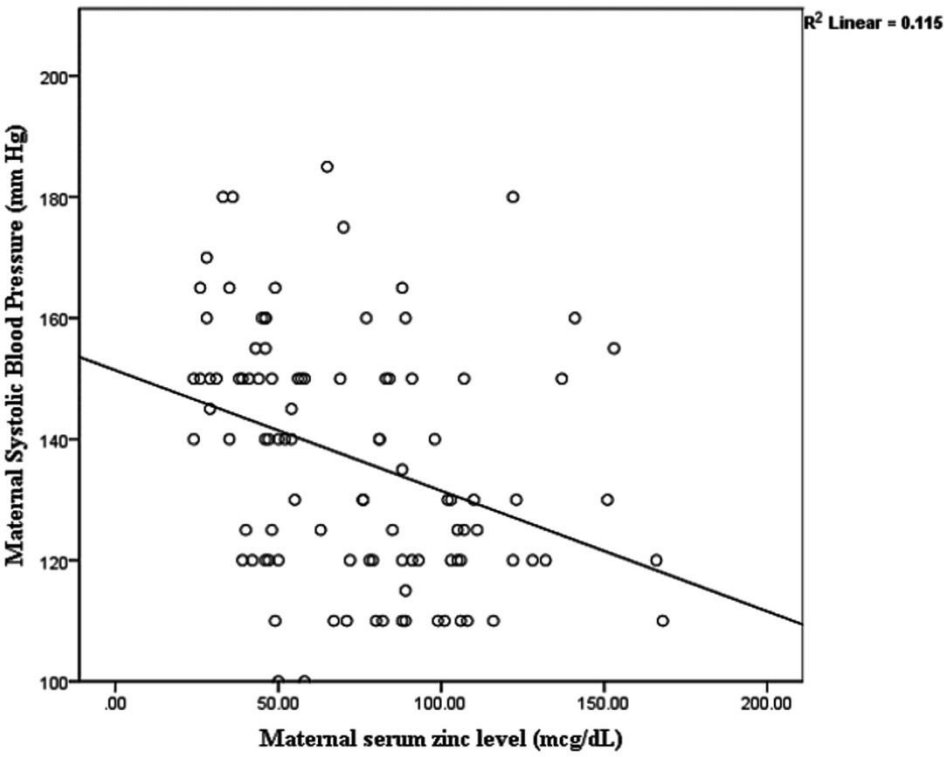

Figure 1: Scatterplot diagram showing correlation between serum zinc level and systolic blood pressure (SBP) in patients with preeclampsia.

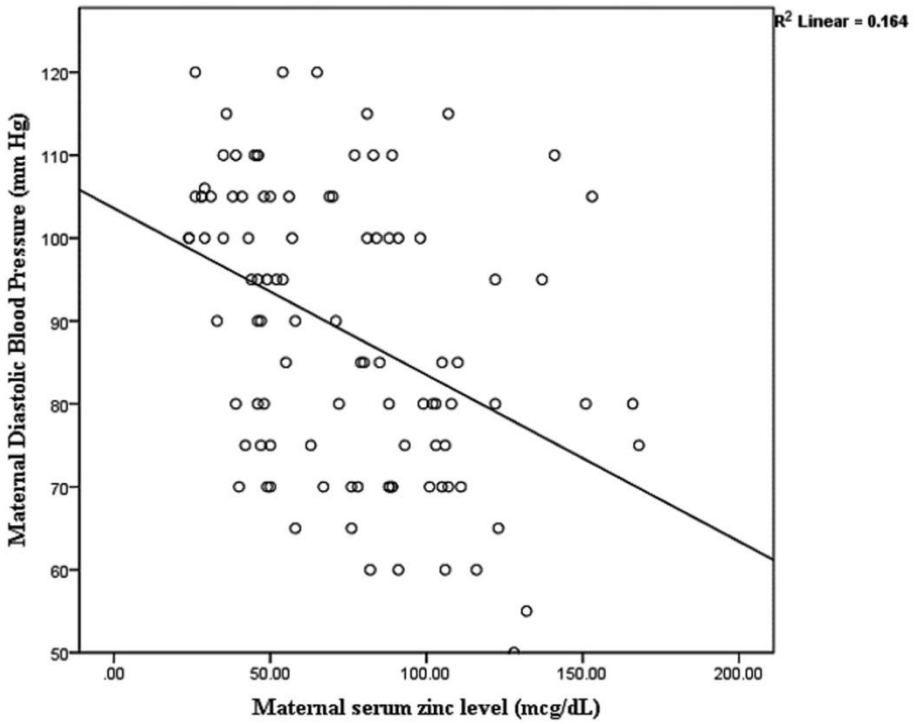

Figure 2: Scatterplot diagram showing correlation between serum zinc level and diastolic blood pressure (DBP) in the study subjects.

Discussion

In this study, the mean age of the respondents was 27.18 ± 6.03 years in cases and 26.56 ± 5.46 years in control. Majorities of the respondents from both the groups belonged to lower-middle-class social status (case: 52.0% and control: 50.0%). There was no significant difference in the distribution of the respondents in both groups regarding socio-demographic characteristics (p>0.05). This result is consistent with the study of Akhtar et al. where the mean age was 25.11±5.66 years in preeclamptic and 25.20±4.85 years in normotensive pregnant women [14]. However, these findings contrast with the results of Morikaw et al. who recognized that an advanced maternal age ≥ 35 years and increased pre-pregnancy BMI were risk factors for pregnancy induced hypertension among pregnant Japanese women [15]. Differences in the study design and the demographic characteristics of the population may account for these differences in the results.

The present study revealed slightly lower gestational age among the cases (32.94±1.86 weeks) compared to the controls (35.54±2.19 weeks). About three-fifths (62.0%) of the preeclamptic patients and 56.0% healthy pregnant women were found primigravida but these were not statistically significant. In a similar study, Martadiansyah et al. also exhibited no difference in terms of gestational age (p = 0.347) and parity (p = 0.940) between cases and controls [16].

Family history of hypertension was present among 34.0% of the cases compared to 18.0% of the control group of respondents, this difference was found statistically not significant (p=0.068) in the present study. In another study it was observed that the proportion of participants did not significantly differ with regards to family history of preeclampsia (p=0.704) [17]. The mean BMI of the cases and control were 26.68±1.78 kg/m^2 and 26.02±1.56 kg/m^2 respectively which was not statistically significant (p>0.05). In a systematic review and meta-analysis Tesfa et al. also noted a nonsignificant relation of BMI

between preeclampsia and the control group of patients (p=0.057) [18]. In contrast to this study, Al-Sakarneh and Mashal observed that during pregnancy the BMI of preeclamptic women was significantly higher than the normotensive women (34.4±1.1 kg/m2 vs. 30.08±1.0 kg/m^2, p=0.02) [19].

The mean (±SD) serum zinc level was much lower in the case (59.58±31.79 μg/dl) than the control (89.02±31.14 μg/dl), which was statistically highly significant. Patients having zinc level < 68 μg/dl had 6.05 times more chance to develop preeclampsia compared to those with zinc level ≥ 68 μg/dl (OR=6.048, 95% CI = 2.540-14.399; p value < 0.001). Kumru et al. reported a significant reduction (43%) of serum zinc level in Turkish females with preeclampsia than in controls (p<0.001) [6]. A study by Akhtar et al. observed that there was a significant difference in zinc levels between pregnant women with preeclampsia and normal pregnancies (902.50±157.15 μg/L vs. 1153.33±67.09 μg/L; p <0.001) [14]. Mohamed et al. exhibited zinc levels in the control group at 95.7 μg /dl and in the preeclamptic group at 60.8 μg dl with highly significant statistical difference (p<0.001) [20]. Emam and Attia evidenced that significantly lower levels of zinc (PE group: 58.94±11.19 μg/dl vs. control group 85.92±13.8 μg/dl, p<0.001) was associated with the development of preeclampsia (OR 4.47, 95% CI 3.05-6.52; p value <0.001) and were inversely and significantly correlated with systolic (r= -0.493, p=0.01) and diastolic blood pressure (r= -0.520, p=0.01) [21]. In this study we also observed negative correlation (r=-0.340) between maternal serum zinc level and systolic blood pressure which was statistically significant (p=0.001). Similar negative correlation (r= -0.404) was observed between maternal serum zinc level and diastolic blood pressure which is also statistically significant (p<0.001).

In contrast, Adam et al. found no significant difference (p>0.05) in the mean serum zinc levels between preeclamptic (31.2±5.2 μg/dl) and normal pregnant women (34.1±4.4 μg/dl) [22]. Another study conducted by Magri et al. did not find a relationship between the serum levels of calcium, magnesium and zinc and gestational hypertension; therefore, they proposed that these elements might not clinically participate in the pathogenesis of the gestational hypertension [23]. These discrepancies of the study findings might be due to methods for measuring serum zinc not being sensitive or specific enough, variations in sample sizes and other demographic factors.

Most of the studies with few exceptions revealed low serum zinc level among the preeclampsia patients. So, we can take some measures like proper food consumption containing adequate micronutrients, zinc supplementation to overcome zinc deficiency to prevent preeclampsia and thereby improve the maternal and perinatal outcome.

Conclusion

This study finding suggests that low maternal serum zinc level is significantly related with an increased risk for preeclampsia. The serum zinc level was found inversely correlated with both systolic and diastolic blood pressure. Therefore, this study concludes that a low level of serum zinc can be considered an important risk factor for developing preeclampsia.

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