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Original Article

Biochemistry Section

Comparison of Serum Calcium, Magnesium, and Zinc amongst Preeclampsia and Normotensive Pregnant Women attending a Tertiary Care Teaching Hospital in Tripura, Northeast India

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ABSTRACT

Introduction: Preeclampsia is one of the most frequently encountered medical complications of pregnancy. If left untreated, it exerts serious medical complications for both the mother as well as baby. As a multifactorial progressive disease, identifying potential biomarkers for predicting preeclampsia is crucial for disease stratification and targeted therapy. There is a growing interest in early detection of micronutrient deficiencies, such as calcium, magnesium, and zinc, to understand the causes of preeclampsia development.

Aim: To compare the serum levels of calcium, magnesium, and zinc in women with preeclampsia and normotensive pregnant women attending Agartala Government Medical College and Govind Ballabh Pant Hospital, Agartala, Tripura, India.

Materials and Methods: This cross-sectional observational study was conducted at Agartala Government Medical College, Agartala, Tripura, India, from January 2020 to December 2021. The study included primigravida women aged between 18 and 35 years, in their third trimester of pregnancy, with a singleton pregnancy. Sixty preeclampsia patients and 60 normotensive pregnant women were enrolled, and various biochemical parameters like serum calcium, magnesium, zinc, uric acid, urea, creatinine, Alanine Transaminase (ALT), and Aspartate Transaminase (AST) were analysed. Data were statistically analysed using the student t-test and Chi-square test.

Results: The mean age (in years), gestational age (in weeks), and Body Mass Index (BMI) (Kg/m^2) of the study subjects and control group were 26.02±4.69 and 23.4±3.81, 34.78±2.41 and 33.51±2.79, and 27.97±3.82 and 26.03±4.26, respectively. The authors observed that the levels of biochemical parameters like serum creatinine, AST, ALT, and uric acid were increased in preeclampsia. Furthermore, the serum concentrations of calcium, magnesium, and zinc were significantly decreased in preeclampsia.

Conclusion: This study demonstrated that preeclamptic women have reduced levels of serum calcium, zinc, and magnesium compared to normal pregnant women. Therefore, dietary supplementation of these essential nutrients, either individually or in combination, may help prevent preeclampsia at an early stage and improve foetal outcomes.

Keywords: Foetal outcome, Hypertension, Micronutrients, Oxidative stress, Pregnancy

INTRODUCTION

Preeclampsia, one of the most frequently encountered medical complications of pregnancy, is a leading cause of maternal and perinatal morbidity and mortality worldwide. This progressive multifactorial disorder is characterised by the development of new-onset hypertension, with blood pressure reaching 140/90 mmHg or higher, along with proteinuria ≥300 mg per 24 hours or urinary protein to creatinine ratio ≥0.3, or persistent dipstick 1+ proteinuria after 20 weeks of gestation in a previously normotensive and non-proteinuric pregnant woman [1].

In developing countries, a woman is seven times more likely to develop preeclampsia as a woman in a developed country, and 10%-25% of these cases are likely to result in maternal death [2]. India's third National Family Health Survey (NFHS 3) reported that the eastern and northeastern states had the highest incidence of preeclampsia, with prevalence ratios for preeclampsia symptoms showing almost a threefold variation between the lowest prevalence state (Haryana 18.5%) and the highest prevalence state (Tripura 49.4%) [3].

Although the exact aetiology of preeclampsia remains enigmatic to date, a growing body of evidence supports the understanding that the disease begins in the uteroplacental unit, is amplified by oxidative stress, and results in vascular endothelial dysfunction and vasospasm [4]. Several dietary deficiencies have also been implicated in the development of preeclampsia and in harming the pregnant mother and growing foetus, especially in developing countries with a high prevalence of preeclampsia [5,6]. Possible reasons for the association of low serum calcium levels with preeclampsia may include the stimulation of renin and parathyroid hormone release, which elevates the intracellular concentration of calcium in vascular smooth muscles, inducing generalised vasoconstriction [7].

Generally, magnesium has been known as an essential cofactor for many enzyme systems. Hence, deficiency of this element may hamper the proper functioning of antioxidant enzymes, leading to oxidative stress. Decreased levels of magnesium during pregnancy might increase the vasoconstrictor response of numerous neurohormonal agents, including epinephrine, norepinephrine, angiotensin-II, serotonin, and bradykinin, thereby increasing blood pressure [8]. Zinc is one of the trace elements directly involved in lipid peroxidation and oxidative stress, culminating in endothelial dysfunction, the hallmark of preeclampsia. Additionally, zinc deficiency may induce high blood pressure by promoting sodium reabsorption through increased Na+ Cl- co-transporter expression [9,10]. Hence, screening blood tests during antenatal check-ups to evaluate the concentration of these micronutrients might prove beneficial in preventing the occurrence of preeclampsia and reducing the disease burden to some extent.

Studies and data regarding the association between preeclampsia and changes in micronutrient levels are very infrequent in the North East (NE) region of our country. From this perspective, the present study was conducted to assess the levels of calcium, magnesium, and zinc amongst preeclamptic and normotensive pregnant women attending Agartala Government Medical College and Gobinda Ballabh Pant Hospital, Agartala, Tripura, India. The study also aimed to determine whether there were any alterations in the concentration of these nutrients based on the socioeconomic status [11] of the pregnant women. Such information may be helpful for early detection of preeclampsia and timely management thereof.

MATERIALS AND METHODS

This was a hospital-based observational cross-sectional study conducted at Agartala Government Medical College and Govind Ballabh Pant Hospital (AGMC and GBP Hospital) in collaboration between the Department of Biochemistry and the Department of Obstetrics and Gynaecology, Agartala Government Medical College and Govind Ballabh Pant Hospital, Agartala, Tripura, India. The study took place from January 2020 to December 2021 after receiving approval from the Institutional Ethics Committee (Ref.No.4(6-11)-AGMC/Medical Education/Ethics Com./2018 Dated 2nd December 2019). The institution serves as the tertiary care teaching hospital of Tripura and receives referrals from all other hospitals in the state.

Inclusion criteria: The study group comprised of primigravida women aged between 18 and 35 years, with alive singleton pregnancies in their third trimester (beyond 28 weeks), diagnosed with preeclampsia according to the guidelines by the ACOG task force on hypertension in pregnancy, and willing to participate in the study [1]. The comparison group included normotensive pregnant women in the same age group, parity, and gestational period, who were also willing to participate in the study.

Exclusion criteria: Patients were excluded if they had one or more of the following conditions: i) chronic hypertension, diabetes mellitus, or any major systemic illness; ii) patients admitted with obstetric emergencies; and iii) patients unwilling to participate in the study.

Sample size: The authors planned to study three variables, namely serum calcium, magnesium, and zinc, in preeclampsia patients, with an equal number of normotensive individuals in the same age group, parity, and gestational period. For sample size calculation, one of the three continuous response variables (serum zinc) from independent control and study subjects with a 1:1 ratio was taken into consideration. In a study conducted by Al-Jameil N et al., the response for serum zinc in each subject group was normally distributed with a standard deviation of 0.83 [9]. If the mean difference between the study and control groups is 0.6, it would be necessary to study 58 subjects in each group to be able to reject the null hypothesis that the means of both groups are equal with a power of 90%. The type 1 error associated with the test of this null hypothesis is considered 1%.

The sample size calculation was performed using the formula:

$$n=\frac{2[(a+b)^2\sigma^2]}{(\mu_1-\mu_2)^2}$$

Where:

n=the sample size in each group

μ_1=mean in Group-1

μ_2=mean in Group-2

s=standard deviation (SD)

a=conventional multiplier for alpha (2.58)

b=conventional multiplier for power (1.28)

Data collection: After obtaining written informed consent from each participant, a thorough history was taken, followed by a general physical examination. Blood pressure was measured on the right arm with the patient lying on her side at a 45° angle to the horizontal. An obstetrical examination was then carried out, and all the data and findings were recorded in a pre-structured case record sheet. Preeclampsia patients were categorised into mild (Systolic Blood Pressure [SBP] 140-149 mmHg or Diastolic Blood Pressure [DBP] 90-99 mmHg), moderate (SBP 150-159 mmHg or DBP 100-109 mmHg), and severe (SBP ≥160 mmHg or DBP ≥110 mmHg) according to the National Institute for Health and Care Excellence (NICE) guidelines from 2011 [12].

For the study, blood samples were collected to estimate serum calcium, magnesium, and zinc, along with routine antenatal hematological and biochemical tests. Using aseptic measures, 5 mL of blood was drawn preferably from the antecubital vein using a sterile needle and syringe. The blood samples were placed in different sterile containers (EDTA/Fluoride/Clot activator) and allowed to clot at room temperature. Serum was then separated from the cells by centrifuging at 3000 rpm for 3-5 minutes. The analysis of the samples was done on the same day. Various biochemical parameters like Serum urea, creatinine, uric acid, ALP, and ASP were performed on a fully automated clinical chemistry analyser (XL-640, Transasia Biomedicals Ltd., Mumbai), while special tests like serum calcium, magnesium, and zinc were analysed using a spectrophotometer (Eppendorf BioPhotometer D30) [Table/Fig-1] [13-19].

Parameters	Method of estimation	Cut-off range
S.Urea (mg/dL)	Urease-GLDH method [13]	15-40 mg/dL
S.Creatinine (mg/dL)	Enzymatic method [14]	0.6-1.1 mg/dL
S.Uric acid (mg/dL)	Uricase UV method [15]	2.6-6 mg/dL
S.AST (U/L)	Ultraviolet (UV) with PLP method [16]	Up to 31 U/L
S.ALT (U/L)	UV with PLP method [16]	Up to 34 U/L
S.Calcium (mg/dL)	O-Cresolphthalein Complexone (OCPC) method [17]	9-11 mg/dL
S.Magnesium (mEq/L)	Calmagite method [18]	1.6-2.2 mEq/L
S.Zinc (µg/dL)	Nitro-PAPS colorimetric method [19]	60-120 (µg/dL)

[Table/Fig-1]: Different biochemical parameters, methods and their cut-off range [13-19].
S.: Serum

Urine samples were also collected from the study subjects for urinalysis and protein measurement. A 10-12 mL freshly voided urine sample was collected in clean, sterile universal containers. In this study, proteinuria was determined using multiple reagent strips (dipstick) for all participants and interpreted as shown in [Table/Fig-2] [20].

Colour	Dipstick protein reading
	Negative
	Trace (±) 0.1 g/L
	1+ 0.3 g/L
	2+ 1.0 g/L
	3+ 3.0 g/L
	4+ 10.0 g/L

[Table/Fig-2]: Determination of concentration of protein in urine by dipstick [20].

STATISTICAL ANALYSIS

The results were analysed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Categorical data were presented as mean±standard deviation. The significance of the difference between the groups was compared using the Student t-test. The chi-square test was used to compare the socioeconomic status and clinical characteristics between the groups. A p-value of <0.05 was considered statistically significant. Karl Pearson correlation was used to study the correlation of variables in preeclampsia cases.

RESULTS

This study revealed that the majority of the normotensive group belonged to the middle class, whereas in the case of preeclamptic patients, the majority was from the poor economic class. The comparison of gestational age between the cases and the control group showed a statistically significant difference. There was also a significant difference in age between both groups [Table/Fig-3].

	Control group (n=60)	Cases (n=60)	p-value
Socioeconomic status			
Upper (I)	3 (5%)	1 (1.7%)	0.013
Upper-middle (II)	18 (30%)	12 (20%)	
Lower-middle (III)	30 (50%)	21 (35%)	
Upper-lower (IV)	8 (13.3%)	20 (33%)	
Lower (V)	1 (1.7%)	6 (10%)	
Proteinuria			
Nil	52 (87%)	3 (5%)	<0.01
1+	5 (8%)	21 (35%)	
2+/3+	3 (5%)	36 (60%)	
Mean gestational age (mean±Std. Dev.) (years)	**33.51±2.79**	**34.78±2.41**	**0.008**
Mean age (in years)	**23.4±3.81**	**26.02±4.69**	**0.001**
Preeclampsia			
Mild preclampsia		20 (33%)	
Moderate preclampsia		27 (45%)	
Severe preeclampsia		13 (22%)	
Headache	5 (8%)	16 (27%) 8 (50%)=Severe PE 6 (38%)=Moderate PE 2 (12%)=Mild PE	0.008
Blurring of vision	2 (3%)	11 (18%) 5=Severe PE 6=Mod PE	0.008

[Table/Fig-3]: Comparison of socioeconomic status and clinical characteristics in the control group and cases.

There was a significant statistical difference in BMI (kg/m^2), SBP, and DBP between the two groups. Regarding the biochemical analysis, the serum urea, uric acid, creatinine, AST, and ALT levels were found to be increased in preeclamptic women. However, no statistically significant difference was observed in serum creatinine content or the activities of transaminases. The levels of mean serum total calcium, magnesium, and zinc in preeclampsia patients were significantly lower in comparison to normotensive pregnant women [Table/Fig-4].

The comparison of nutrient deficiencies between both groups showed a higher number of hypocalcemia, hypomagnesemia, and hypozincemia in the preeclampsia patients compared to the normotensive controls. The presence of these nutrient deficiencies was also found to be more common in individuals belonging to comparatively lower socioeconomic classes [Table/Fig-5].

The preeclamptic patients in this study were categorised into three different categories (mild, moderate, and severe) of preeclampsia. Hypocalcemia and hypozincemia were present in the majority of

Variable	Control group (n=60) (mean±SD)	Cases (n=60) (mean±SD)	p-value
BMI (kg/m^2)	26.03±4.26	27.97±3.82	0.01
SBP (mmHg)	112.9±8.35	154.7±13.44	<0.001
DBP (mmHg)	73.0±5.06	99.0±8.64	<0.001
S.Urea (mg/dL)	24.14±7.56	28.03±11.47	0.03
S.Creatinine (mg/dL)	0.67±0.12	0.95±0.34	0.116
S.Uric acid (mg/dL)	3.60±0.75	4.42±1.37	0.0001
S.AST (U/L)	37.11±16.01	78.84±50.18	0.08
S.ALT (U/L)	41.23±20.27	80.07±43.95	0.12
S.Calcium (mg/dL)	9.06±0.48	8.70±0.49	0.0001
S.Magnesium (meq/L)	1.70±0.21	1.53±0.24	0.01
S.Zinc (μg/dL)	62.69±10.99	52.81±16.35	0.0001

[Table/Fig-4]: Comparative analysis of demographic, anthropometric profile and biochemical parameters of study participants.
*p<0.05=statistically significant, p<0.01=statistically highly significant

Deficiency of nutrients	Control group (n=60)	Case (n=60)
Hypocalcaemia	17 (28%) Upper-middle (II)=6 Lower-middle (III)=4 Upper-lower (IV)=6 Lower (V)=1	40 (67%) Upper-middle (II)=4 Lower-middle (III)=14 Upper-lower (IV)=18 Lower (V)=4
Hypomagnesemia	13 (21%) Upper-middle (II)=1 Lower-middle (III)=10 Upper-lower (IV)=1 Lower (V)=1	32 (53%) Upper-middle (II)=4 Lower-middle (III)=15 Upper-lower (IV)=13
Hypozincaemia	12 (20%) Upper (I)=1 Upper-middle (II)=2 Lower-middle (III)=6 Upper-lower (IV)=2 Lower (V)=1	47 (78%) Upper-middle (II)=6 Lower-middle (III)=19 Upper-lower (IV)=19 Lower (V)=3

[Table/Fig-5]: Comparison of deficiency levels of serum calcium, magnesium and zinc among the study subjects.

subjects with severe preeclampsia. The deficiency levels of each of the study nutrients in various categories were highlighted in [Table/Fig-6].

The Pearson correlation of SBP and DBP individually with serum calcium, magnesium, and zinc levels showed a negative correlation between blood pressure and the study nutrients [Table/Fig-7-13].

Category of preeclampsia	Hypocalcaemia	Hypomagnesemia	Hypozincaemia
Mild (n=20)	11 (55%)	6 (30%)	13 (65%)
Moderate (n=27)	18 (67%)	18 (67%)	22 (81%)
Severe (n=13)	11 (85%)	8 (61%)	11 (85%)
Total n=60	n=40 (67%)	n=32 (53%)	n=46 (78%)

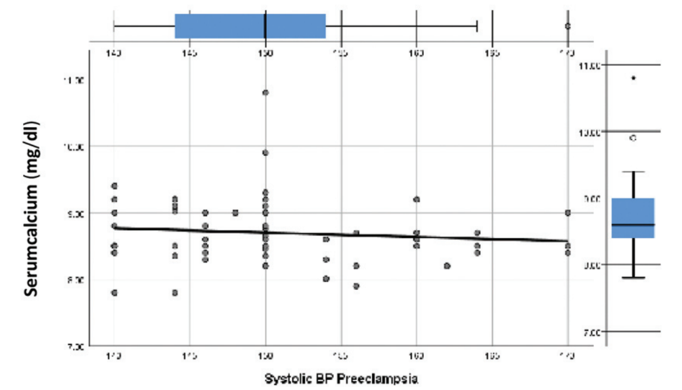
[Table/Fig-6]: Stratification of the nutrients' deficiency in different categories of preeclampsia (cases).

Parameter	SBP (mmHg)		DBP (mmHg)	
	R value	p-value	R value	p-value
Serum calcium	r=-0.107	0.41	r=-0.135	0.30
Serum magnesium	r=-0.202	0.12	r=-0.162	0.21
Serum zinc	r=-0.152	0.24	r=-0.184	0.15

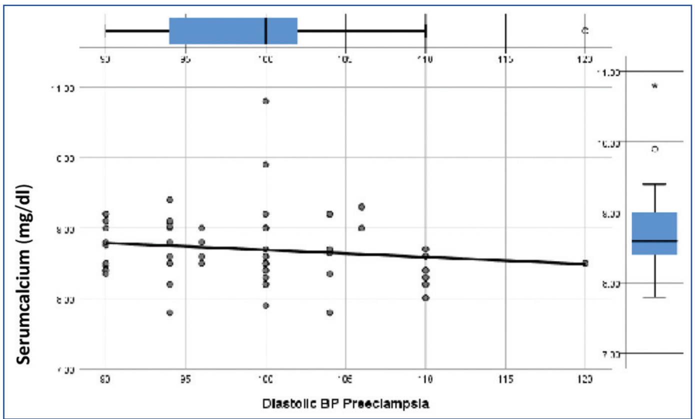
[Table/Fig-7]: Correlation of S.calcium, magnesium and zinc levels individually with blood pressure.
Here, r=Karl Pearson correlation Co-efficient

DISCUSSION

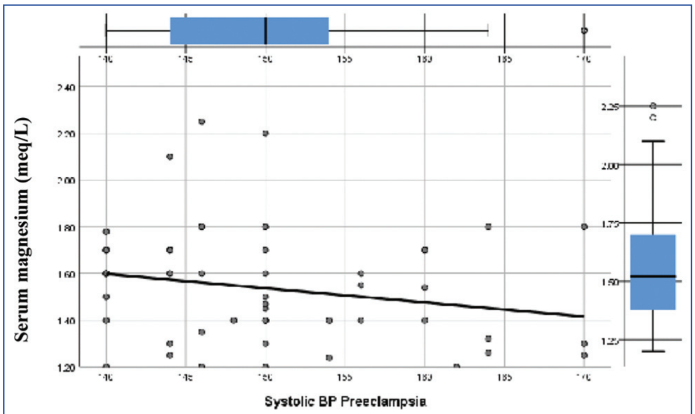
Considering the socioeconomic profiles, it can be inferred that lower socioeconomic status may be a risk factor for preeclampsia, which is consistent with a study conducted by Mostafe HM [21]. In the present study, 8 normotensive women had proteinuria, out of which six women were at 37-40 weeks gestation. Three of the



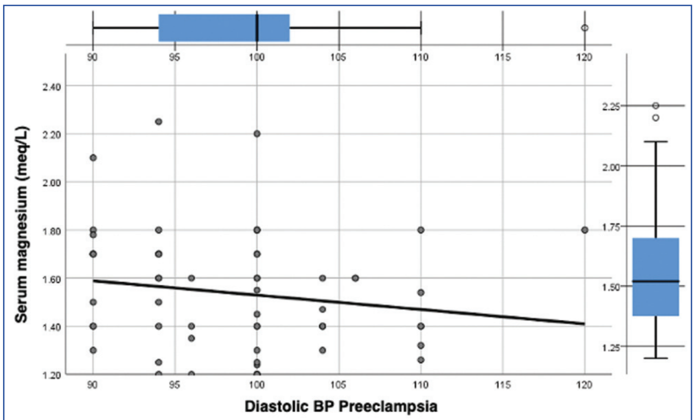
[Table/Fig-8]: Correlation of serum calcium with Systolic Blood Pressure (SBP).



[Table/Fig-9]: Correlation of serum calcium with Diastolic Blood Pressure (DBP).

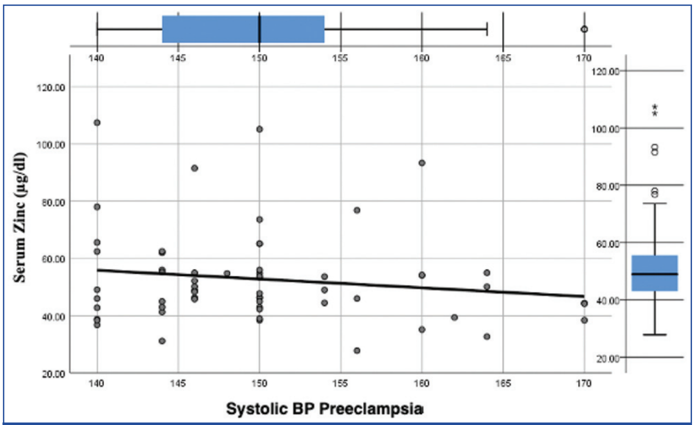


[Table/Fig-10]: Correlation of serum magnesium with Systolic Blood Pressure (SBP).

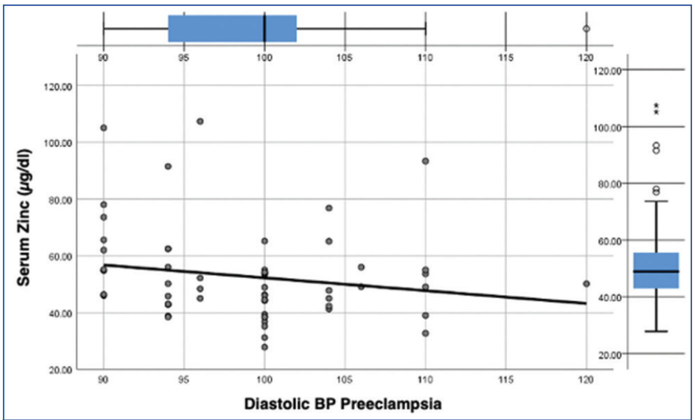


[Table/Fig-11]: Correlation of serum magnesium with Diastolic Blood Pressure (DBP).

women with proteinuria were suffering from urinary tract infections. Furthermore, in the present study, the majority (50%) of the preeclampsia patients belonged to the older age range compared to normotensive pregnant women, which supports previous reports that advanced maternal age may be a risk factor for the development of preeclampsia [22,23].



[Table/Fig-12]: Correlation of serum zinc with Systolic Blood Pressure (SBP).



[Table/Fig-13]: Correlation of serum zinc with Diastolic Blood Pressure (DBP).

When analysing the BMI among the study participants, it was found that women with preeclampsia had a significantly higher BMI compared to the normotensive group, which is consistent with the study by Motedayen M [24]. In this study, the majority of preeclamptic women (48%) were overweight (BMI ≥25 kg/m^2), 27% were obese (BMI ≥30 kg/m^2), and only 25% had a normal BMI (18.5-24.9 kg/m^2). On the other hand, in the control group, the majority of pregnant women (60%) had a normal BMI, 27% were overweight, and only 8% were obese.

In preeclampsia, glomerular endotheliosis and spasms of glomerular arterioles result in reduced renal blood flow and glomerular filtration rate (25%), and impaired tubular reabsorption or secretory function [20]. This study indicates an association between preeclampsia and higher serum urea levels, which is consistent with an earlier study by Aslan Cetin B et al., [25].

An association between higher serum creatinine and uric acid levels and preeclampsia was observed in this study, which is similar to the observations made by Ambad RS and Dhok DA, and Skakarami A et al., [26,27]. In preeclampsia, elevated levels of uric acid are not only attributed to decreased renal excretion but also increased oxidative stress resulting from placental ischaemia and increased activity of xanthine oxidase. The findings of this study also indicate that both the mean serum AST and ALT levels are more than double in preeclamptic women compared to normotensive pregnant women, which is consistent with the findings of Anusha T and Sankaranarayana T [28].

In the present study, a significant reduction in mean serum calcium levels in preeclamptic women (67%) is evident compared to normal pregnant women, similar to the observations made by Kangal DV et al., and Saeed S et al., [7,29]. Two women in the control group with hypocalcemia had a history of polycystic ovarian syndrome, which may be a possible cause of vitamin D deficiency and subsequent hypocalcemia. Additionally, three women belonged to the Muslim community, in which hypocalcemia may be attributed to the practice of purdah and subsequent vitamin D deficiency. A study on a group of healthy pregnant women living in Dhaka reported that low vitamin D levels, classified as "deficiency," severely affected 2.1%, affected 60.7%, and classified as "insufficiency," affected 31.4% of the individuals studied, in which the practice of purdah may have played an important role [30]. Three normotensive women with hypocalcemia had a history of hyperemesis gravidarum, four women had a history of gastritis and constipation, leading to irregular intake of calcium and iron-folic acid (IFA) tablets. Additionally, one woman was allergic to milk and milk products.

Serum magnesium levels in preeclampsia patients in this study significantly decreased (53%) compared to normal pregnant women, which is consistent with the findings of Reddy HK et al., [31]. In the normotensive control group with hypomagnesemia, three women had a history of recurrent episodes of gastritis and had been taking proton pump inhibitors since the first trimester. Four women with hypomagnesemia were found to have anemia, and another woman had suffered from Coronavirus Disease-2019(COVID-19) pneumonia associated with a diarrhoeal episode, nausea, and vomiting.

A significant reduction in the mean serum zinc level is evident in the preeclamptic study group (78%) compared to normal pregnant women, which is similar to the findings of a previous study by Martadiansyah A et al., [32]. Among the control subjects with hypozincemia, four were found to have intrauterine growth retardation as suggested by ultrasonography reports. Stratification of data on serum calcium, magnesium, and zinc in various categories of preeclampsia revealed an association between the gradually decreasing levels of these nutrient elements with the increase in disease severity.

Considering the correlation of severity, when serum calcium, magnesium, and zinc levels of preeclamptic patients are individually correlated with Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), a negative correlation is obtained, emphasising the fact that hypocalcemia, hypomagnesemia, and hypozincemia may have a strong relationship with both the risk of developing preeclampsia and disease severity.

Limitation(s)

The dietary habits of study participants were not examined in depth; hence, more research is recommended in different settings to determine the predictive ability of these critical nutrients for the early detection of preeclampsia.

CONCLUSION(S)

The present study findings demonstrate a significant association between elevated maternal serum uric acid and preeclampsia. The study also identified reduced levels of serum calcium, zinc, and magnesium in preeclamptic women compared to normal pregnant women. These findings suggest that insufficient intake of these essential nutrients, either individually or in combination, may contribute to the development of preeclampsia. Additionally, the severity of the disease can be assessed using these indicators. Therefore, timely dietary supplementation of these nutrients could be explored to prevent preeclampsia and improve foetal outcomes. In conclusion, maternal serum calcium, magnesium, zinc, and uric acid levels show promise as indicators for predicting or detecting preeclampsia. Further studies evaluating hypocalcemia in normotensive pregnant women would be beneficial.

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