Serum Zinc Profile In Pre-Eclamptic Patients In Federal Medical Centre, Umuahia, Abia State, Nigeria

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ABSTRACT

Background: Pre-eclampsia is a common medical complication of pregnancy associated with increased maternal and perinatal mortality and morbidity. The exact cause is still unknown. The trace element zinc, possesses antioxidant activity and also acts as a peroxynitrite scavenger. The disturbance in the metabolism of this element may be a contributing factor in the development of pre-eclampsia.

Objective: The study was aimed at determining the mean serum zinc level in pre-eclamptic patients in comparison with pregnant women without pre-eclampsia,in Federal Medical Centre, Umuahia, Abia State, Nigeria and evaluating the relationship between serum zinc level and severity of pre-eclampsia.

Methods:A cross-sectional comparative study was carried out. Fifty seven pre-ecclamptic and fifty seven (57) normotensive pregnant women were used in the study. Serum zinc level was determined by flame atomic absorption spectrophotometry. The data obtained from the study were analyzed statistically using students' t-test and chi square with P-value less than 0.05 was taken to be significant.

Results: The mean serum zinc level was significantly lower ($p < 0.01$) in pre-eclamptics than the normotensives with values of 8.16 ± 0.78 μmol/L, and 10.63 ± 1.06 μmol/L respectively. Also serum zinc was found to be significantly lower ($p=0.001$) in those with severe pre-eclampsia compared to those with mild pre-eclampsia, with values of 7.93 ± 0.81 μmol/L, and 8.66 ± 0.36 μmol/L respectively.

Conclusion: The result of the study showed a positive correlation between serum zinc levels and pre-ecclampsia in women.

Keywords: Zinc, Pre-Ecclampsia, Pregnancy, Maternal mortality and morbidity, Umuahia, Atomic absorption spectrophotometry.

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INTRODUCTION

Pre-eclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension with proteinuria after the 20th week of gestation in a previously normotensive and non-proteinuric woman [1]. It is severe if the elevated blood pressure is greater than or equal to $^{160}/_{110}$ mmHg, and/or proteinuria of ≥5g in a 24 hour urine collection. When complicated with convulsion, it is known as eclampsia [2].

Pre-eclampsia is one of the leading causes of maternal and newborn morbidity and mortality all over the world, and affects approximately 5 to 7 percent of pregnancies.[3]

Its incidence is about 10% in primigravidae, and about 5% in multigravidae. [4] Women in developing countries are seven times more likely to develop pre-eclampsia than women in developed countries, of which 10-25% will result in maternal death. [5]

In Nigeria, it is estimated that 5-10% of pregnancies are complicated by pre-eclampsia.[6] Pre-eclampsia-eclampsia was reported to have contributed to 28.2% of maternal deaths in Nigeria. [7]

Several theories exist on the pathogenesis of pre-eclampsia, but at present it is suggested that the placenta is the primary agent in the development of pre-eclampsia, hence delivery of the placenta is the sole method of treating the condition. [8]

Placental oxidative stress has been shown to be a key feature in the pathogenesis. [9] Some studies have indicated that pre-eclampsia is associated with an imbalance of increased lipid peroxides (LPO) and decreased antioxidants [10,11]. Trace elements such as zinc, copper and selenium display antioxidant activity. [12] Deficiency of zinc may cause increasing lipid peroxidation. [13] Nutritional deficiencies are common during pregnancy. It has been reported that 82% of pregnant women worldwide are likely to have inadequate dietary intake of

zinc.[14]Several studies have demonstrated an association of zinc deficiency with increased incidence of pre-eclampsia. [15,16,17] Women of low socioeconomic status and those who smoke may have an increased risk of zinc deficiency. [15] Several researchers from different countries have observed significantly lower serum zinc levels in pre-eclamptic women compared to healthy pregnant women.[15,16,17.] Some studies did not support this relationship.[18,19] However results from a meta-analysis indicated that serum zinc level in pre-eclamptic patients is significantly lower than that in healthy pregnant controls.[20]

It should be noted that the adverse effects of pre-eclampsia and eclampsia are not only limited to the mother but also do affect the fetus with several complications ranging from intrauterine growth restriction to intrauterine fetal death. [21] Pre-eclampsia is associated with oxidative stress in the maternal circulation. There is substantial evidence to suggest that the diverse manifestations of pre-eclampsia, including altered vascular reactivity, vasospasm, and discrete pathology in many organ systems, are derived from pathologic changes within the maternal vascular endothelium. The imbalance between oxidative damage and antioxidant defences in pre-eclampsia leads to endothelial cell dysfunction which appears to be a central feature in the pathophysiology of pre-eclampsia[22]. The free radicals produce cellular injury by lipid peroxidation, enzyme inactivation, DNA damage and degradation of structural proteins[22].

Current concepts of the genesis of pre-eclampsia that include endothelial dysfunction, inflammatory activation, oxidative stress and predisposing maternal factors provide targets for nutritional aspects[21]. Maternal zinc level has been found to be lower in low birth weight newborns than in those with normal weight[23]. Also, serum zinc concentration has been described to have relationship with the severity of pre-eclampsia, hence its assessment as an index for predicting the severity of pre-eclampsia.[19]

In recent times, there has been an increasing prevalence in the incidence of pre-eclampsia globally, but there are conflicting reports on the relationship between serum zinc and pre-eclampsia globally. In south eastern part of Nigeria, despite the high incidence of pre-eclampsia, there is paucity of studies on this element, considering the fact that zinc is readily available and affordable both in food items as well as supplements. Establishment of relationship of serum zinc level with pre-eclampsia in this population may suggest its supplementation in pregnancy and will go a long way in reducing the incidence of pre-eclampsia as well as its complications.

This study therefore was aimed at comparing maternal serum zinc level in normal pregnancy and in those complicated with pre-eclampsia in a tertiary institution in Southeastern Nigeria-Federal Medical Centre Umuahia- and to find out the relationship between serum zinc level and pre-eclampsia in this population.

METHODS

This was a cross-sectional comparative study to evaluate the serum levels of zinc in pregnant women with pre-eclampsia and those without pre-eclampsia. This study was carried out in the Obstetrics and Gynaecology

department of Federal Medical Centre, Umuahia the capital city of Abia State, South-eastern Nigeria. The State is bounded on the North/North East by Anambra, Enugu and Ebonyi States, on the West by Imo State, on the South by Rivers State and on the East by Cross River and Akwa Ibom States. The study populationcomprised pregnant women who attended antenatal clinic, or were admitted into antenatal ward, and labour ward of the hospital. The inclusion criteria were: Pregnant women with singleton pregnancy between gestational ages of 20 and 40 weeks; Blood pressure of $^{140}/_{90}$ mm Hg or more measured twice, 6 hoursapart; Proteinuria of at least 2+ on dipstick testing; for the control groups, normotensive and non-proteinuric women were recruited.Exclusion criteria were**:** A history of systemic hypertension; pregnant women with multiple or molar pregnancy; History of chronic renal disease. Informed consent was obtained from all the participants of this study. Prior to commencement of the study, ethical approval was obtained from the ethics committee of the institution.

Sample size

Sample size was calculated using the formula for comparative studies;

$$n = \frac{r+1 SD^2 (Z_b + Za_{/2})^2}{rd^2}$$

n = Sample size in each group (assumes equal sized groups)

r = Ratio of control to case (which is 1in this study)

SD = Standard deviation of the outcome variable

Z_b = Represents the desired power (typically .84 for 80%power).

$Za_{/2}$= Represents the desired level of statistical significance(typically 1.96).

d = Expected mean difference between case and control.[12]

From the formula, the sample size was calculated to be 60 for each group, giving rise to a total of 120.

Study period

Following approval by the Health Research Committee, the study lasted for nine (9) months (April 2017 to December 2017).

Data collection Tool

A structured study proforma designed for the study was used for data collection. The information recorded included socio-demographic data, as well as the height, weight and blood pressure. The result of urinalysis was documented. Interviews were conducted in English and/or Igbo where applicable. Each participant's oral response to the proforma was recorded.

Blood sample collection

Blood (5ml) was drawn from the antecubital vein, after cleaning the puncture site with methylated spirit, using a sterile needle and syringe into an appropriate tube. The samples in plain tubes were taken to the laboratory and allowed to clot undisturbed. The serum was separated using a centrifuge (Thermo Fischer Scientific, UK)at 4000 rpmfor 10 minutes, collected into plain tubes and stored at-20°C in the laboratory until time of analysis[24]. Analysis was done using an Atomic absorption spectrophotometer (Hitachi, Japan).

Statistical Analysis

The data obtained from this study was analyzed with the statistical package for the social sciences (SPSS) version 20.0, (IBM Corporation, Armonk, New York, USA). Continuous variables obtained from this study were expressed as means and standard deviation while categorical variables were summarized using frequency and percentages. Comparison of proportions of Socio-demographic characteristics of the pre-clamptic and normotensives were done using chi square while means of continuous variables e.g serum zinc, BMI, BP e.t.cwere compared between pre-clamptic and normotensives using student's t-test. P-value less than 0.05 were taken as significant.

RESULTS

Of the 114 pregnant women that participated in the study, 57 were pre-eclamptic, while 57 were non pre-eclamptic. Table 1 shows the socio-demographic characteristics of the study population. There was no significant difference in the mean age of cases compared to that of the control (P=0.091). Also there was no significant difference in social status and parity between the two groups (P= 0.132) and (P=0.462) respectively, with most of the respondents in social class 1. However there was significant difference in marital and booking status between the two groups (P=0.022) and (P=0.001) respectively.

Table 2 shows significant difference in the mean BMI (body mass index) and blood pressure between the groups (P=0.031) and (P< 0.001) respectively. The BMI and blood pressure were significantly higher in the pre-eclamptic subjects than the normotensives. There was also significant difference in the mean arterial blood pressure between the two groups, being higher in the pre-eclamptic group.

Table 1: Socio-demographic characteristics of the study population

	Pre-eclamptic n (%)	Normotensive n (%)	χ^2	P value
Age group(Mean ± SD)	***30.40 ± 5.99***	***28.82 ± 3.58***	-	0.091
16 – 20	5 (8.8)	0 (0.0)	16.418	0.006

21 – 25	5 (8.8)	12 (21.1)		
26 – 30	16 (28.1)	25 (43.9)		
31 – 35	20 (35.1)	18 (31.6)		
36 – 40	9 (15.8)	2 (3.5)		
41 – 45	2 (3.5)	0 (0.0)		
Marital status				
Married	52 (91.2)	57 (100.0)	5.229	0.022
Single	5 (8.8)	0 (0.0)		
Social status				
1	40 (70.2)	47 (82.5)	5.619	0.132
2	13 (22.8)	5 (8.8)		
3	3 (5.3)	5 (8.8)		
4	1 (1.8)	0 (0.0)		
GA group				
20 - <28	5 (8.8)	5 (8.8)	0.000	1.000
28 - <32	4 (7.0)	4 (7.0)		
32 – 36	8 (14.0)	8 (14.0)		
37 – 41	40 (70.2)	40 (70.2)		
Parity				
0	38 (66.7)	33 (57.9)	1.543	0.462
1	8 (14.0)	13 (22.8)		
2 – 5	11 (19.3)	11 (19.3)		
Booking Status				
Booked	44 (77.2)	56 (98.2)	11.726	0.001
Unbooked	13 (22.8)	1 (1.8)		

Table 2: Mean Body Mass Index, mean Blood Pressure, and mean arterial blood pressure.

	Pre-eclamptic	Normotensive	T	P value

	Mean ± SD	Mean ± SD		
BMI (kg/m^2)	30.05 ± 6.43	27.84 ± 4.16	2.181	0.031
Systolic B.P mmHg	161.58 ± 16.83	111.84 ± 7.88	20.206	< 0.001
Diastolic B.P mmHg	101.93 ± 9.39	70.79 ± 6.87	20.212	< 0.001
Mean arterial blood Pressure mmHg	121.82 ± 10.97	84.47 ± 6.39	22.207	< 0.001

Table 3 shows that the mean serum zinc levels in pre-ecclamptic subjects are 8.16 ± 0.78 with range 6.26 – 9.08μmol/L. The mean serum zinc levels in normotensives is 10.63 ± 1.06 μmol/L with range 8.01 – 12.59μmol/L.

Figure 1 shows the mean serum zinc levels as obtained from table 3. These were significantly lower in pre-eclamptic patients when compared to the normotensives (t = 14.176, P < 0.001).

The serum zinc level of subjects with mild pre-eclampsia is 8.66 ± 0.36μmol/L while that of those with severe pre-eclampsia is 7.93 ± 0.81μmol/L. Serum zinc levels decrease significantly with severity of preeclampsia as shown in table 4 (t = 3.650, P = 0.001).

Table 3: Serum zinc levels in pre-eclamptic and normotensive patients

Group	Minimum	Maximum	Mean	Std. Deviation

	(µmol/L)	(µmol/L)	(µmol/L)	
Pre-eclampsia	6.26	9.08	8.16	0.78
Normotensive	8.01	12.59	10.63	1.06

(n=57 for each group)

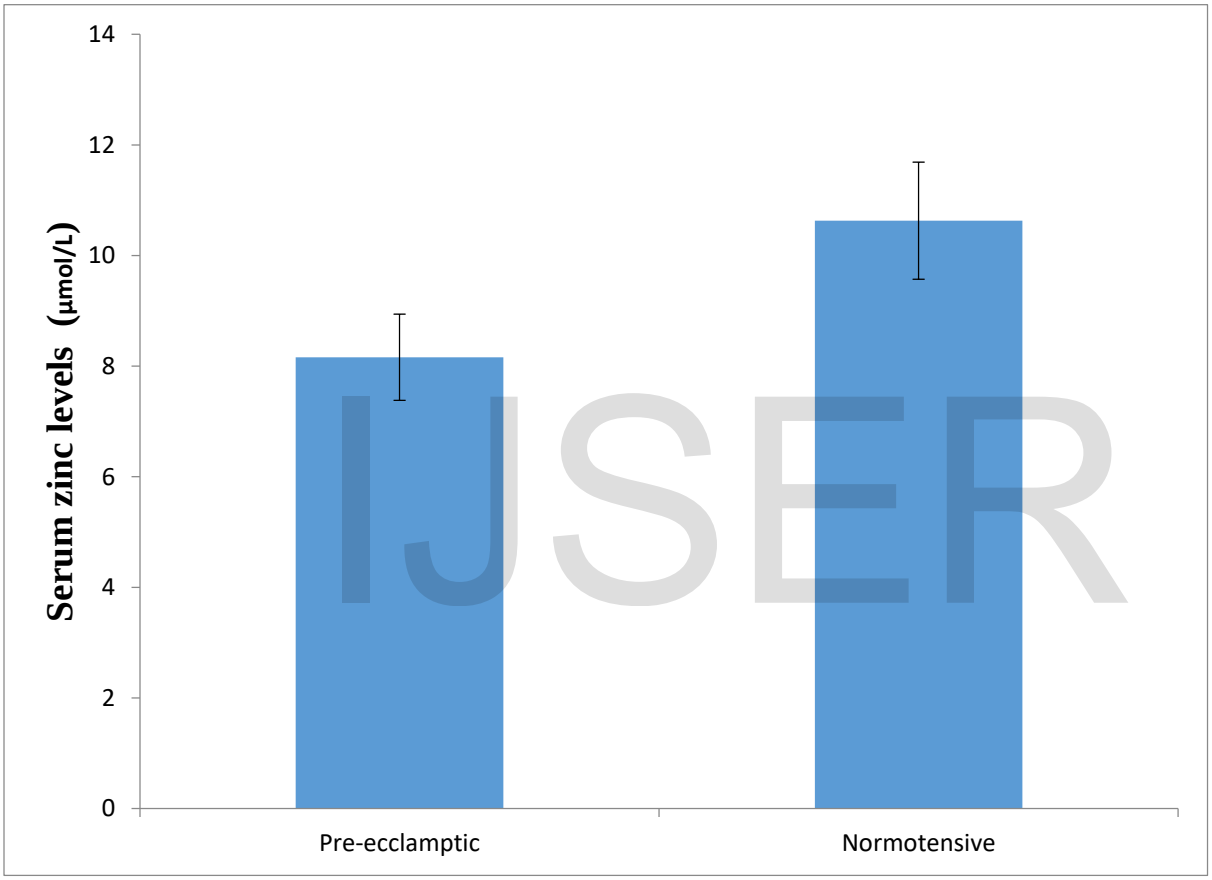

Figure 1: Mean serum zinc profile values of pre-ecclamptic and normotensive patients

(n=57 for each group)

Table 4: Comparison of mean serum zinc levels between subjects with mild and severe pre-eclampsia

	Severity of pre-eclampsia

	Mild n=24 Mean ± SD (μmol/L)	Severe n=33 Mean ± SD (μmol/L)	T	P value
Mean serum zinc levels	8.66 ± 0.36	7.93 ± 0.81	3.650	0.001

DISCUSSION

The mean serum zinc level observed in this study is similar to the findings of Akinloye et al. [12] and Onyegbule et al. [25]. In developing countries, nutritional deficiencies of both macro and micro nutrients are common health problems among women of reproductive age. The risk is further increased with pregnancy because of increased requirements of various nutrients like zinc, calcium, etc. to satisfy the needs of the growing fetus.[15]Hypoalbumineamia resulting from albuminuria could be a factor contributing to the more decline in the level of serum zinc in pre-eclamptic women. This is because greater percentage of serum zinc is bound to albumin.[26]In this study, there was significant decrease in the serum level of zinc in pre-eclamptic women compared to the non-pre-eclamptic counterparts. This finding agrees with Akinloye et al.[12], Leila et al.,[27] and Onyegbule et al.[25], who also observed reduced serum zinc levels in women with pre-eclampsia.

It has been documented that reduction in serum zinc is associated with obstetric complications including pre-eclampsia.[27]Zinc is an important trace element in metabolism, growth, development and reproduction. It plays important roles in nucleic acid metabolism and protein synthesis, as well as membrane structure and function.[28]It is a constituent of many enzymes including antioxidant enzymes which are involved in combating oxidative stress implicated in the aetio-pathogenesis of pre-eclampsia.[9]However, a study done by Parvin et al, showed no significant difference between the mean serum zinc concentration of the two groups (pre-eclamptic and normal pregnancy group), but there was significant reduction in serum zinc level in those with severe pre-eclampsia.[19]The disparity in their finding could not be explained as they used similar sample size, inclusion and exclusion criteria as well as method of analysis. However their definition of mild, and severe pre-eclampsia was not stated.

It was also shown in this study that serum zinc level is lower in severe pre-eclampsia when compared with mild pre-eclampsia. This further implicates zinc in this disease entity called pre-eclampsia. However, the exact role of zinc is not known as it is difficult to decipher cause from effect. Hence more studies are needed to elucidate the exact role of zinc deficiency in pre-eclampsia. This inverse relationship between serum zinc level and

severity of pre-eclampsia as observed in this study may also suggest the use of serum zinc assay as one of the indices in defining severity of pre-eclampsia; however, more studies are required to identify its prognostic value.

With the discovery of low serum zinc level in pre-eclamptic women, zinc supplementation in pregnancy could be advocated as a means of prevention of pre-eclampsia, and/or its complications. Unfortunately there is paucity of studies on zinc supplementation in pregnancy in Nigeria. However, available studies show conflicting results. A randomized double blind trial of supplementation of zinc and other anti-oxidants during pregnancy by Dewi, et-al, done on 60 respondents, where 15mg of zinc was used showed a protective effect against the development of pre-eclampsia.[29] Conversely, another randomized trial of zinc supplementation by Ziba, et-al, in Rasht, Iran that involved five hundred and forty respondents divided into two groups where one group was also given 15mg of zinc, and the other group was given placebo showed no protective effect.[30]Hence more studies on zinc supplementation in pregnancy is advocated.

CONCLUSION

The result of this study revealed an association between serum zinc level and pre-eclampsia, however it did not decipher cause from effect. Monitoring of serum zinc during antenatal period could be suggested; the effect of zinc supplementation to pre-ecclamptic women could also be investigated in further studies. In addition, it is suggested that serum zinc assay be used as one of the indices in defining severity of pre-eclampsia.

DECLARATION OF INTEREST

The authors have no conflict of interest.

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HEALTH RESEARCH ETHICS COMMITTEE (HREC)

13th July, 2016.

Full Committee Approval

Protocol's full title including official abbreviations:
SERUM ZINC PROFILE IN PRE-ECLAMPTIC PATIENTS AT FEDERAL MEDICAL CENTRE, UMUAHIA.

Health Research Committee assigned Number: FMC/QEH/G.596/Vol.10/189

Name of Principal Investigator: **Dr. NDUKWU NNAMDI CHUKWUNYEREUGO**

Address of Principal Investigator: **Department of Obstetrics and Gynaecology, Federal Medical Centre, Umuahia.**

Date of receipt of valid application: 27th April, 2016

Date of meeting when final determination of research was made: 30th June, 2016.

This is to inform you that the research described in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and given full approval by the Health Research Ethics Committee.

This approval dates from 1st July, 2016 to 30th June, 2017. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these date. *All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study.* In multi year research, endeavour to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National Code for Health Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserved the right to conduct compliance visit to your research site without previous notification.

You are please required to donate a copy of this research work to the Health Research Ethics Committee of the Federal Medical Centre, Umuahia.

Thank you.

Dr I.O. Iwegbu
Chairman, HREC
For: Medical Director

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