



# **A Comparative Study of Serum Calcium Levels between Pre-eclamptic and Normotensive Singleton Pregnancies in Federal Medical Centre, Owerri**

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## **Authors' contributions**

*This work was carried out in collaboration between both authors. The first author designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. The second author managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

**Aim:** To compare the serum level of calcium between pre-eclamptic and normotensive pregnant women carrying single fetuses.

**Study Design:** A comparative cross-sectional study.

**Place and Duration of Study:** Department of Obstetrics and Gynaecology (Maternity unit), Federal Medical Centre, Owerri, Imo state, from 1<sup>st</sup> November 2013 to 30<sup>th</sup> April 2014.

**Methodology:** One hundred and sixty women carrying singleton pregnancies were consecutively enrolled in this study (80 women with pre-eclampsia and 80 women without pre-eclampsia at a similar gestation were the control). Serum calcium concentration was estimated. The data were analysed using the SPSS software for Windows version 17.0, and the age, parity, gestational age, weight and serum calcium levels of subjects from both groups were compared using the analysis of variance. A P-value of <0.05 was considered significant.

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**Results:** The mean serum calcium level was significantly lower in pre-eclamptic women compared with the mean serum calcium level for normotensive women [ $7.20 \pm 0.92$  mg/dl vs  $8.99 \pm 0.88$  mg/dl respectively with  $P < .001$ ]. Also, serum calcium showed significant negative correlation with systolic blood pressure and diastolic blood pressure ( $r = -0.684$ ,  $r = -0.633$  respectively, with both having  $P < .001$ ). There was no statistical difference between the socio-demographic characteristics of both groups of pregnant women.

**Conclusion:** This study concludes that serum calcium was significantly lower among pre-eclamptic than normotensive pregnant women. However, the actual role of calcium supplements needs further investigation.

*Keywords: Serum calcium; pre-eclamptic women; singleton pregnancy.*

## 1. INTRODUCTION

Pre-eclampsia is defined as gestational hypertension of at least 140/90mmHg on two separate occasions  $\geq 4$  hours apart accompanied by significant proteinuria of at least 300mg in a 24-hour collection of urine, arising de novo after the 20<sup>th</sup> week of gestation in a previously normotensive and non-proteinuric woman resolving completely by the 6<sup>th</sup> postpartum week [1,2]. The pregnant woman's body provides daily doses of 50 to 330mg of calcium to support the developing foetal skeleton [3]. This high foetal demand for calcium is facilitated by profound physiological interaction between mother and fetus [4]. This additional calcium is normally provided by an increase in maternal intestinal calcium absorption. There may not be a necessary increase in dietary calcium intake [4].

Several studies have linked calcium to the aetiopathogenesis and prevention of pre-eclampsia, however, the precise mechanism involved is unclear [5-7].

Normal Serum total calcium is 2.2-2.6mmol/L(8.6-10.3mg/dl) [8]. Thus values less than 2.2mmol/L (<8.6mg/dl) indicates low serum calcium.

Epidemiological data suggest an inverse correlation between dietary calcium intake and incidence of pre-eclampsia [9]. This led to the hypothesis that the incidence of pre-eclampsia can be reduced in populations of low calcium intake by calcium supplementation [10]. The biochemical mechanism responsible for the possible increase in intracellular  $Ca^{2+}$  and a concomitant decrease in extracellular  $Ca^{2+}$  is unclear. Some have suggested that the protective effect of calcium on blood pressure can be explained by the influence of calcitropic hormones on intracellular calcium. Some have

suggested that low calcium intake (< 600 mg/day, corresponding to less than two dairy serving per day) may harm by causing vasoconstriction, either through increasing magnesium levels or stimulating release of parathyroid hormone or renin, thereby increasing vascular smooth muscle intracellular calcium [10].

Some studies have shown that changes in the level of serum trace elements in pre-eclamptic patients may be implicated in its pathogenesis [11].

There is paucity of studies on the relationship between serum calcium and pre-eclampsia in Nigeria and none from Imo State. Thus, this study will give a baseline of the relationship between serum calcium and pre-eclampsia in pregnant women carrying singleton fetus in Imo State.

## 2. MATERIALS AND METHODS

### 2.1 Study Area

This study was carried out in the maternity unit of the Department of Obstetrics and Gynaecology of the Federal Medical Centre, Owerri, Imo State, South East Nigeria.

Federal Medical Centre Owerri is a tertiary health facility which provides health service delivery to citizens of the state and neighbouring states.

### 2.2 Study Population

This study population comprised pregnant women with singleton fetus with a diagnosis of pre-eclampsia as cases and women with normal singleton pregnancies (without pre-eclampsia) as controls all at gestational ages above 20 weeks from LMP.

### 2.3 Study Design

It is a comparative cross-sectional study of pre-eclamptic as cases and normotensive pregnant women as controls.

### 2.4 Sampling Techniques

Consecutive, eligible and consenting pre-eclamptic women were enrolled from among ante-natal clinic attendees after obtaining ethical approval from the institution's Research and Ethical Committee. Eligible normotensive women were enrolled from the same antenatal population to serve as a control.

The cases and controls were women of similar gestation.

### 2.5 Data Collection

The procedure was explained to all the subjects, and written consent was obtained. Data were recorded from each subject using a well-designed questionnaire.

Before the blood pressure measurement, the woman would have rested for 5 minutes and seated at a 45 degree angle. The mercury sphygmomanometer appropriate sized cuff was applied around the upper arm at the level of the heart. The korotkoff sound V was used to get the diastolic blood pressure as it is more reproducible than the fourth sound [8]. Two blood pressure measurements were taken at least 5 minutes apart, and the average of these was used. Sustained elevation of blood pressure was confirmed by repeating the above procedure at least 4 hours later.

All blood pressure measurements were carried out by the researcher or trained assistants. The subjects were weighed and Urine Protein estimation was carried out using the Dipstick measurement of clean catch midstream specimens. The trained assistants and researcher did the later measurement estimation.

### 2.6 Sample Collection

Two millilitres of the blood sample for calcium estimation was drawn from the cubital vein using a heparinised syringe and needle without using a tourniquet by the researcher or trained assistants. The blood was dispensed into a plain specimen bottle. The sample was left to stand for fifteen minutes, after clot retraction, the sample

was spun at 3000 rpm for 5 minutes. The supernatant was collected and stored at -15 degree Celsius until analysis.

### 2.7 Biochemical Analysis

The Laboratory estimation of serum calcium was done in the Federal Medical centre Owerri laboratory by a spectrophotometric manual method using O-cresolphthalein-complexone as the colour indicator. The calcium kits were manufactured by Giese Diagnostics. The analysis was carried out by a laboratory scientist while the researcher assisted.

This method is highly sensitive as it accurately measured calcium levels as low as 0.15mmol/L and up to 5.5 mol/L.

Normal Serum total calcium is 2.2-2.6mmol/L(8.6-10.3mg/dl) [8]. Thus values less than 2.2mmol/L (<8.6mg/dl) indicates low serum calcium.

### 2.8 Statistical Methods

Data were analysed using the SPSS software for Windows version 17.0 (SPSS Inc., Chicago, IL). The mean and standard deviation of age, parity and gestational age, weight and serum calcium levels of subjects from both groups were compared using the analysis of variance. A *P*-value of < 0.05 was considered significant.

## 3. RESULTS

Out of 160 pregnant women studied, 80 were pre-eclamptic, and 80 were normotensive.

There was no significant socio-demographic difference between the pre-eclamptic and normotensive women (see Table 1). There was no statistically significant difference between the mean age of the pre-eclamptic cases (28.9± 5.2 years) and that of the normotensive cases (29.7± 4.8 years) (*P*= 0.354; *t*-test = 0.929) (see Table 2).

The mean gestational age for pre-eclamptics involved in the study was 36.0± 3.6 weeks and that of normotensive 36.0± 3.6 weeks. There was no significant difference (*P*=1.000, *t*-test =0.000).

The mean parity for pre-eclamptics was 1.2± 1.3 and normotensives 1.4± 1.5. There was also no significant difference (*P*=.282, *t*-test =1.079).

The mean systolic blood pressure was 152.0± 9.3mmHg for pre-eclamptics and 106± 10.3mmHg for normotensive. There was a significant difference ( $P < .001$ , t-test = 29.5).

The mean Diastolic blood pressure was 98.0± 8.2 mmHg for pre-eclamptics and 67.6± 7.9mmHg for normotensives. There was also a significant difference ( $P < .001$ , t-test= 23.7).

In Table 3 below there was an inverse relationship between serum calcium and systolic blood pressure( $r = -0.684$ ,  $P < .001$ ).

There was also an inverse correlation between serum calcium and diastolic blood pressure

( $r = 0.633$ ,  $P < .001$ ). These negative correlations suggest a strong relationship between deficiency of calcium and risk of pre-eclampsia.

Fig. 1 below that serum calcium was significantly higher in normotensive than pre-eclamptics ( $8.98 \pm 0.88$  vs  $7.20 \pm 0.92$  mg/dl respectively,  $P < .001$ , t-test 12.51).

#### 4. DISCUSSION

Pre-eclampsia is a pregnancy-specific complication associated with increased maternal and perinatal morbidity and mortality [12].

**Table 1. Socio-demographic characteristics of pregnant women**

Socio-demographic Characterisitcs	Pre-eclamptic (n = 80)%	Normotensive (n = 80)%	P – value
<b>Age</b>			
< 20	3 (3.8)	3 (3.8)	.731*
20 - 25	17 (21.3)	11 (13.8)	
26 - 30	34 (42.5)	31 (38.8)	
31 - 35	20 (25.0)	27 (33.8)	
36 - 40	5 (6.3)	7 (8.8)	
> 40	1 (1.3)	1 (1.3)	
<b>Level of education</b>			
Primary	4 (5.0)	2 (2.5)	.580*
Secondary	26 (32.5)	23 (28.8)	
Tertiary	50 (62.5)	55 (68.7)	
<b>Occupation</b>			
Housewife	27 (33.8)	23 (28.8)	.867*
Student	13 (16.3)	15 (18.7)	
Trader	18 (22.5)	16 (20.0)	
Self employed	6 (7.4)	8 (10.0)	
Civil servant	15 (18.7)	15 (18.7)	
Professional	1 (1.3)	3 (3.8)	
<b>Parity</b>			
Nullipara	35 (43.8)	30 (37.5)	.856*
Para 1	16 (20.0)	17 (21.3)	
Multipara	27 (33.8)	30 (37.4)	
Grand multipara	2 (2.4)	3 (3.8)	

Key \*= not statistically significant

**Table 2. Characteristics of the study participants**

Parameters	Pre-eclamptic (n = 80) Mean ± SD	Normotensive (n = 80) Mean ± SD	't' value	P – value
Age (years)	28.9 ± 5.2	29.7 ± 4.8	0.929	.354*
Gestational Age (weeks)	36.0 ± 3.6	36.0 ± 3.6	0.000	1.000*
Parity	1.2 ± 1.3	1.4 ± 1.5	1.079	.282*
Systolic BP (mmHg)	152.0 ± 9.3	106 ± 10.3	29.468	<.001**
Diastolic BP (mmHg)	98.0 ± 8.2	67.6 ± 7.9	23.760	<.001**

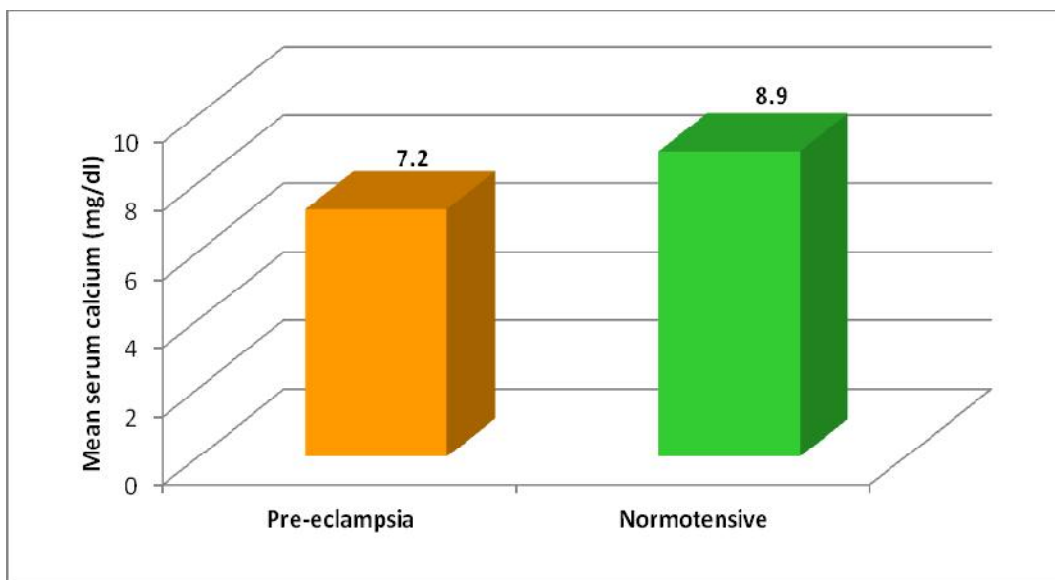
Key \*= not statistically significant

\*\*= statistically significant

**Table 3. Correlation Analysis between serum calcium and blood pressure**

Variable	Systolic BP	Diastolic BP
<b>Serum calcium (mg/dl)</b>		
Pearson correlation coefficient (r)	-0.684	-0.633
P-value	<.001**	<.001**

Key \*\*= statistically significant



**Fig. 1. Mean serum calcium value of the pregnant women**

*P* = .001

Although many pathophysiological factors have been implicated in the aetiology of pre-eclampsia, its aetiology is still under investigation.

Our study shows a significant relationship between hypocalcaemia and pre-eclampsia. This is similar to the finding of Punthumapol C. et al. which showed that hypocalcaemia correlated with severe pre-eclampsia [13].

Although some studies showed an inverse relationship between calcium intake and pre-eclampsia [9,14]. This led to the hypothesis that the incidence of pre-eclampsia can be reduced in populations of low calcium intake by calcium supplementation [10]. Other studies [15,16] did not confirm a significant alteration of Calcium levels.

The biochemical mechanism responsible for the possible increase in intracellular  $Ca^{2+}$  and a concomitant decrease in extracellular  $Ca^{2+}$  is unclear.

Our study showed no statistically significant difference in maternal age between normotensive and pre-eclampsia (*P*= 0.354). This was similar to the findings in other studies [14,17]. It was, however, different from the findings of Macdonald-Wallis et al. [18]. Such difference may be due to the specificity of each population and hospital of the attendant patients.

This study showed a significant reduction in the levels of calcium in pre-eclamptic women compared to normotensive women (*P*< 0.001). This is consistent with the findings of other studies [14,19,20].

In contrast, some other investigators found that serum calcium in pre-eclamptic group did not differ significantly from the normal pregnant group [15,21]. This difference can be attributed to the different dietary habits and the different genetic pools of the population in which the study had been carried out as compared with the population in this study.

Serum calcium plays an important role in the uteroplacental blood flow as it lowers the resistance index in uterine and umbilical arteries and its deficiency is capable of producing smooth muscle contraction and increased vascular resistance according to some studies [22]. Various investigators suggested that calcium influences smooth muscle cell contractility. Low serum calcium in pregnancy increases the release of parathyroid hormones and rennin which in turn increases intracellular calcium in vascular smooth muscle. This increased smooth muscle calcium causes vasoconstriction and thereby increased vascular resistance leading to a rise in blood pressure on pre-eclamptic mother [23].

Imdad A. and his colleagues in a meta-analysis found hypocalcemia in pre-eclampsics. They suggested calcium supplementation and the dose of calcium were based on individual patient requirement [24]. Similarly, Hofmey GJ et al. [25] in an intervention review concluded that calcium supplementation appears to approximately halve the risk of pre-eclampsia, to reduce the risk of preterm birth and to reduce the occurrence of the composite outcome 'death or serious morbidity'. In 2006, a WHO multicentre randomised, placebo-controlled double-blind trial on nulliparous normotensive women recruited before 20 weeks of gestation who received supplements throughout pregnancy. It was evident that supplementation with 1.5 grams of calcium per day did not result in a statistically significant decrease in the overall incidence of pre-eclampsia, however, treatment significantly decreased the risk of its more serious complication [26].

However, in 2013, the WHO following two Cochrane systematic reviews stated that in populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia in pregnant women, particularly among those at higher risk of developing hypertension [27].

Similarly, a Cochrane review of 13 studies of good quality among 15,730 women indicated a reduction in the average risk of pre-eclampsia with calcium supplementation. This effect was most evident in groups with low baseline calcium intake [24].

Although the finding in our study may suggest a role of calcium in the development and

pathogenesis of pre-eclampsia and could form a basis for calcium supplementation, this result must be interpreted with caution as the study did not investigate the dietary intake of pre-eclamptic women to find out whether the reduced levels of serum calcium derives from nutritional deficiencies or not.

## **5. CONCLUSION**

In conclusion, the study showed that pre-eclamptic pregnant women of Imo State have lower levels of Serum Calcium compared with normotensive pregnant women. The study puts to light the need to monitor serum calcium during the antenatal period. It is hoped that this finding will contribute to the knowledge of the role of serum calcium in the pathogenesis of pre-eclampsia.

## **CONSENT**

Informed written consent was obtained from the subject before enrolment for the study.

## **ETHICAL APPROVAL**

The ethical clearance for this study was gotten from the Research and Ethical Committee of Federal Medical Centre Owerri. Informed written consent was obtained from the subject before enrolment for the study.

## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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