

Comparison of Serum Calcium Level in Preeclamptic and Normotensive Pregnant Women in Ekiti State, Nigeria

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Abstract

Background: Pre-eclampsia is often referred to as disease of theories as the precise factors involved in its pathogenesis are unclear. While alterations in calcium metabolism have been linked with preeclampsia, the role of calcium in the development of the disease remains uncertain.

Objectives: This study aimed to compare the clinical features and serum calcium levels of pre-eclamptic women with normotensive controls.

Patients and methods: The study was a case-control study among patients with pre-eclampsia and healthy normotensive women.

Results: Ninety-five preeclamptic patients and 95 matched controls participated in the study. More than half (61.1%) of the pre-eclamptic women were unbooked while only about one-third (30.5%) of the normotensive women were unbooked ($P < 0.001$). Pre-eclamptic women had significantly shorter duration of cohabitation with biological fathers of their foetuses than the normotensive controls. Pre-eclamptic patients were thrice more likely to have family history of hypertension than the control group (14.7% vs 4.2% $P = 0.013$). Similarly, the mean serum calcium levels were statistically significantly lower in preeclamptic patients (1.87 ± 0.27 mmol/L) compared to the pregnant normotensive controls (2.33 ± 0.28 mmol/L).

Conclusion: Serum calcium levels were significantly lower in pre-eclamptic women compared to the normotensive controls in the study.

Keywords: Serum calcium; Pre-eclampsia; Pregnant women.

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Introduction

Hypertension is the second most common medical condition in pregnancy and it occurs in up to 10% of all pregnancies. Pre-eclampsia contributes significantly to maternal mortality, premature birth, intrauterine growth restriction (IUGR), and perinatal mortality (Salako et al.,2003; Oladapo et al.,2016; Onyirinka and Okolo,2004). While the exact cause of pre-eclampsia has not been determined, many theories abound regarding the condition. However, the precise factors involved in the pathogenesis of pre-eclampsia are unclear and several alterations in calcium metabolism have been identified (Mohieldein et al.,2007; Indumati et al.,2011). Although calcium deficiency cannot be described as the sole factor for the aetiology of pre-eclampsia, its relationship with pre-eclampsia cannot be denied (Atallah et al.,2006). Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signalling, and hormonal secretion. However, less than 1% of total body calcium is needed to support these critical metabolic functions.

Calcium metabolism shows that decreased serum calcium levels lead to an increase in the parathyroid hormone levels, thereby increasing the intracellular calcium levels, which in turn leads to an increase in the vascular smooth muscle contraction and thus, an increase in the blood pressure. Despite low circulating calcium levels, the intracellular level of calcium ions is high, which may lead to hypertension. Some authors also showed that an increased intracellular calcium concentration and

increased sensitivity of these cells lead to increased angiotensin II in women with pre-eclampsia (Idogun et al.,2007; Indumati et al.,2011). Epidemiological and clinical studies have shown that an inverse relationship exists between calcium intake and development of hypertension in pregnancy although the effect varies based on baseline calcium intake and pre-existing risk factors.⁸ There is evidence that calcium supplementation for women at high risk may be useful in reducing the risk of pre-eclampsia (Atallah et al.,2006; Imdad et al.,2011). A meta-analysis of studies from developing countries found calcium supplementation to be associated with a reduction in the risk of pre-eclampsia (Imdad et al.,2011; Chiu et al.,2015). While identification of low serum calcium levels as contributing factors for development of pre-eclampsia in Nigerian pregnant women will lead to a better understanding of this disease condition and improvement in its management, there is paucity of studies in literature on this study. Therefore, this comparative study was conducted to determine serum calcium levels in pre-eclamptic patients and compare them with normal pregnant women in the study environment.

Patients and methods

Study design

A hospital-based case-control study.

Study population

The study population comprised pre-eclamptic patients and healthy normotensive

pregnant women who had antenatal care at the Departments of Obstetrics and Gynaecology of Federal Teaching Hospital Ido-Ekiti and Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria. These two centers serve as referrer hospitals for people living in Ekiti State and its environs.

Inclusion criteria

Cases: Patients who had pre-eclampsia

Eligible patients included pregnant women with an onset of hypertension i.e. more than or equal to 140/90 mmHg from the 20 weeks to 42 weeks of pregnancy with significant proteinuria. significant proteinuria was defined as: i) Excretion of 300 mg or more of urinary protein per 24 hours; ii) Urinary protein of \geq two + urinary on dipstick; or iii) Urinary protein of one + on dipstick with pH less than 8 and specific gravity of less than 1.030 on at least two occasions \geq 4 hours apart. There may be associated oedema and or rapid weight gain.

Controls: Healthy normotensive pregnant women. The controls for the study were chosen from healthy pregnant women who were similar to the cases in terms of age, parity, and gestational age but who did not have hypertensive disorder, being cared for. They were normotensive, with a systolic blood pressure of less than 140 mmHg and diastolic blood pressure of less than 90 mmHg, and fulfilled the study criteria.

Exclusion criteria

Patients suffering from any of the following were excluded from the study: i) Diabetes mellitus; ii) Chronic renal disease; iii) Any

other systemic disease that can alter calcium metabolism; iv) Women on calcium supplement; v) Patients with essential hypertension; vi) Women with known recent history of burns; vii) Bone disease; viii) Liver disease; ix) Parathyroid disease; x) History of recent transfusion of blood or blood products; and xi) History of administration of magnesium sulphate therapy. Pregnant women with multiple gestations were also excluded from the study.

Sample size determination

The sample size was determined using the formula for the comparison of two group means (**Charan and Biswas,2013**). With 0.05 as the significance level, 0.20 the type 2 error probability, 0.8 the statistical power of the study, 1.96 the 95% confidence level for a two-tailed test, 0.56 mmol the anticipated difference in serum calcium between controls and cases, and 1.38 the standard deviation of the serum calcium in a similar study (**Chukwunyere et al.,2020**), the sample size used for the study was 190 (95 cases and 95 controls).

Data collection

The recruited participants were informed and counseled about the study. Then the researcher and the research assistants interviewed each patient with a designed questionnaire. The research assistants were trained and educated before the administration of the questionnaire consisting of age, parity, educational status, and occupation. Items on clinical factors including blood pressure, dietary sources of

calcium, and serum calcium levels were also collected. Data was collected with the aid of interviewer-administered questionnaires following informed consent.

History and clinical examination

Clinical history was taken to be sure that the patients fulfilled the selection criteria and a thorough clinical examination was also conducted. To diagnose hypertension, the blood pressure was measured by a mercury sphygmomanometer while the patient was lying on a couch on her back. The systole and diastole readings were determined using Korotkoff sounds I and V respectively. Two readings of 140/90 mmHg and above at least four hours apart, or a single reading of 160/110 mmHg, and above were diagnostic of hypertension following at least 30 minutes of rest.

Identification of proteinuria

To diagnose significant proteinuria, midstream urine was collected and tested. A urinalysis result showing protein "++" or more using urinalysis dipstick reagent or "+" dipstick if specific gravity was less than 1.030 and pH less than 8 was considered significant. A total urinary protein of 300 mg and above in 24 hours urine collection was also used to diagnose significant proteinuria.

Measurement of serum calcium concentration

Five milliliters (5 ml) of blood samples were drawn from the forearm vein. The collected blood samples were allowed to clot spontaneously in a plain and subjected to

centrifugation at 1500 rpm for five minutes. The serum separated and frozen (-20°C) until analysis. Calcium levels were determined by a colorimetric method using using Randox CA590; Randox Limited, United Kingdom.

The plasma albumin concentration was also assayed for the correction of calcium albumin using the formula: Corrected Calcium (mmol/L) = Plasma measured Calcium + (40 - Plasma [albumin]) (g/L) × 0.02 (Crook, 2012). The normal serum calcium level is 2.1-2.6 mmol/l.

Statistical analysis

Categorical variables were described in frequencies and percentages and continuous variables in terms of means and standard deviation. Continuous variables were compared with the student's t-test while categorical variables were analysed using Pearson's chi-square. The serum calcium was correlated with systolic and diastolic blood pressure using correlation analysis. Statistical analyses were carried out using Statistical Package for Social sciences (SPSS) version 18 and a significance statistical level was determined at a critical value of $p < 0.05$.

Ethical considerations

In conducting this study ethical issues were put into consideration. Ethical clearances for the study were obtained from the Ethical and Research Committees of the Federal Teaching Hospital, Ido-Ekiti, and Ekiti State Teaching Hospital, Ado-Ekiti. Willing participants were made to sign informed

consent forms after providing them with adequate information concerning the study. Participants were informed of their freedom to withdraw or refuse to take part in the study without prejudice to their expected standard of care. All information obtained from the participants was kept strictly confidential. Blood sample collection was done with precautions to minimize pain and avoid multiple needle pricks as much as possible. The study was financed by the researcher. Hence, no financial cost was borne by the participants. However, the sponsorship for this study was partially from a dissertation grant from the hospital and the hospital also gave laboratory support for the study. The study lasted about seven months. The patients and the controls were adequately counseled and informed consent was obtained before each participant was recruited into the study.

Results

One hundred and ninety pregnant women participated in the study, with 95 cases (preeclamptic women) and 95 controls (healthy normotensive pregnant women). In both case and control groups, women aged 25-29 years made up the largest proportion (42.1% vs 41.1%) of the participants. Majority of both pre-eclamptic women and the control were married (87.4% vs 95.8%) and almost all the women in both the case and the control groups (92.6% vs. 96.8%) had formal education, at least primary

school education. Both also groups had a similar pattern of religious and tribal distribution with more than three-quarters of the cases and the controls (76.8% vs.75.8%, $P=0.809$) belonging to the Yoruba ethnic group. More than four-fifths of the participants were Christians (87.4% vs. 85.3%). The occupational distribution pattern (unemployment) between the cases (22.1%) and the controls (17.9%) was similar. More than half (61.1%) of the pre-eclamptic presented as unbooked while less than one-third (30.5%) of normotensive women presented as unbooked patients. The participants in the cases and the control groups in the study were essentially similar (**Table 1, Table 2, Fig.1**). However, the pre-eclamptic patients were significantly more likely to have a shorter duration of sexual relationships with the biological fathers of their fetuses (mean duration= 24.9 ± 20.7 months vs. 34.1 ± 26.1 months $P=0.007$) than the healthy normotensive pregnant women (**Table 2**). Comparison of clinical factors including the previous history of preeclampsia and family history of hypertension between the cases and the controls reveals notable findings. The pre-eclamptic patients were significantly more likely to have a family history of hypertension compared to the controls (14.7% vs. 4.2%, $p=0.013$). Although cases were more likely to have a previous history of pre-eclampsia (5.3%) compared to controls (0%), this difference was statistically insignificant.

Table 1. Sociodemographic characteristics of cases and controls in the study

Variables	Pre-eclampsia (n=95)%	Control (n=95)%	χ^2value	P-value
Educational levels				
None	7(7.4%)	3(3.2%)	5.830*	0.120
Primary	17(17.9%)	13(13.7%)		
Secondary	53(55.8%)	48(50.5%)		
Post-secondary	18(18.9%)	31(32.6%)		
Marital status				
Single	11(11.6%)	4(4.2%)	4.498*	0.065
Married	83(87.4%)	91(95.8%)		
Separated	1(1.1%)	-		
Tribe				
Yoruba	73(76.8%)	72(75.8%)	1.095*	0.809
Igbo	5(5.1%)	8(8.4%)		
Hausa	6(6.3%)	2(2.1%)		
Others	11(11.6%)	13(13.7%)		
Religion				
Christianity	83(87.4%)	81(85.3%)	<0.001	0.960
Islam	12(12.6%)	14(9.7%)		
Occupation				
Student	5(5.3%)	3(3.2%)	8.681*	0.067
unemployed	21(22.1%)	17(17.9%)		
Housewife	14(14.7%)	14(14.7%)		
Unskilled worker	43(45.3%)	33(34.7%)		
Skilled worker	12(12.6%)	28(29.57%)		
Booking status				
Booked	37(38.9%)	66(69.5%)	17.832	<0.001
Un-booked	58(61.1%)	29(30.5%)		
Age(years)				
≤19	2(2.1%)	2(2.1%)	0.12*	0.998
20-24	24(25.3%)	26(27.4%)		
25-29	40(42.1%)	39(41.1%)		
30-34	11(11.6%)	11(11.6%)		
≥35	18(18.9%)	17(17.9%)		
EGA at contact (weeks)				
< 34	12(12.6%)	18(19.0%)		
34-36	43(45.3%)	40(42.1%)	1.43	0.490
37-42	40(42.1%)	37(39.0%)		
* Fisher's exact test				

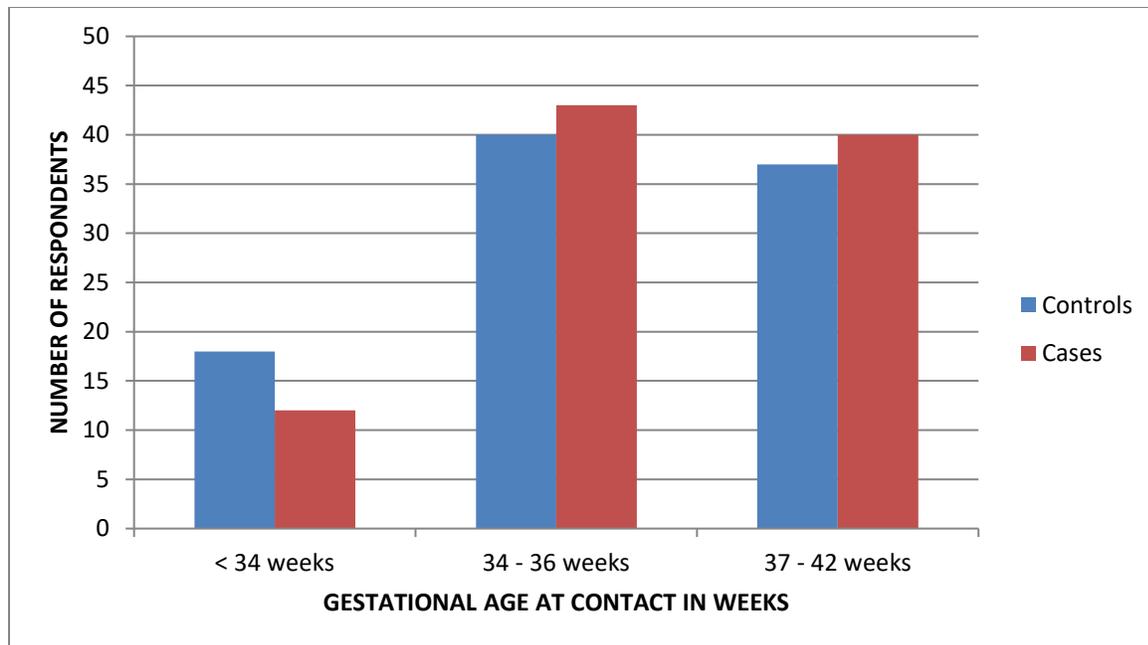


Fig.1. Estimated gestational ages of cases and controls at first contact with antenatal care

Table 2. Comparison of demographic data in the studied groups

Variables	Preeclampsia mean \pm s.d	Control mean \pm s.d	t – value	P – value
Mean age (years)	28.5 \pm 6.3	28.1 \pm 6.1	0.407	0.684
Mean gestational age (weeks)	35.9 \pm 2.7	35.4 \pm 2.9	1.340	0.182
Mean parity	0.71 \pm 1.2	0.65 \pm 1.2	0.307	0.760
Mean duration of sexual relationship with biological fathers of the foetuses (months)	24.9 \pm 20.7	34.1 \pm 26.1	2.697	0.007
Mean gestational age at booking (weeks)	22.3 \pm 4.0	22.4 \pm 4.2	0.207	0.836

Table 3 shows pregnancy drug history. There were significant differences in the pattern of use of routine antenatal drugs. The Iron, Folate, Vitamin B complex, and Vitamin C supplements were taken by all the normotensive women except one while the pre-eclamptic women had a different pattern of use of these routine drugs. These differences in drug use between the two groups were statistically significant ($P < 0.05$). The frequency of consumption per week of high calcium containing dietary foods by pre-eclamptic and normotensive women was low because only a few in both groups ate frequently food items like milk (38.9% vs 36.8%, $P = 0.881$), yogurt

(22.1% vs 20.0%, $P = 0.589$) and cheese (15.8% vs 17.9%, $P = 0.846$) respectively, which are rich in calcium (**Table 4**).

The mean (\pm SD) systolic blood pressure (SBP) among cases was 167 ± 22.6 mmHg compared to 114.1 ± 9.4 mmHg among controls while the mean (\pm SD) diastolic blood pressure (DBP) at contact among pre-eclamptic patients and normotensive pregnant women were 102.5 ± 14.8 mmHg and 68.9 ± 7.6 mmHg respectively.

The pre-eclamptic women had significantly lower mean serum calcium levels compared to the healthy normotensive women ($P < 0.001$).

Table 3. Comparison of the use of haematinic drugs in pregnancy between preeclamptic and normotensive women

Type of drug	Cases N(%)	Control N(%)	X ²	P – value
Fesolate use				
Yes	75(78.9%)	94(98.9%)	17.346	<0.001
No	20(21.1%)	1(1.1%)		
Folate use				
Yes	81(85.3%)	94(98.9%)	10.423	<0.001
No	14(14.7%)	1(1.1%)		
Vitamin C use				
Yes	81(85.3%)	94(98.9%)	10.423	<0.001
No	14(14.7%)	1(1.1%)		
Vitamin Bco use				
Yes	84(88.4%)	94(98.9%)	7.205	0.005
No	11(11.6%)	1(1.1%)		

Table 4. Comparison of pattern of consumption of dietary sources of calcium between the studied groups

Food items	Preeclamptic group n=95		Control group n=95		χ^2	P value
	Frequently Consumed N (%)	Not frequently Consumed N (%)	Frequently Consumed N (%)	Not frequently Consumed N (%)		
Milk	37(38.9%)	58(61.0%)	35(36.8%)	60(63.2%)	0.022	0.881
Yogurt	21(22.1%)	74(77.9%)	19(20.0%)	76(80.0%)	0.032	0.859
Cheese	15(15.8%)	80(84.2%)	17(17.9%)	78(82.1%)	0.038	0.846
Vegetables	92(96.8%)	3(3.2%)	95 (100%)	0(0%)	1.355	0.246
Grains	94(98.9%)	1(1.1%)	93(97.9%)	2(2.1%)	0.000	1.000

Discussion

Pre-eclampsia is a multi-factorial disease and multi-organ dysfunction with no individual factor strictly essential or sufficient for causing it (Sunitha et al.,2012). The age range of pre-eclamptic women in this study was 17-46 years, and this is similar to 16-45 years reported in a study in Benin (Ebeigbe and Aziken,2010). This similarity is because pre-eclampsia is a disease of women of reproductive age group. This study also showed that pre-eclampsia occurred most frequently among women aged 25-29 years, unlike 20-24 years found in another study done on pre-eclampsia in Benin (Onyiriuka and Okolo,2004). This dissimilarity might be due to differences in sociocultural influence on age of marriage between the two study populations. The mean gestational age at the diagnosis of pre-eclampsia was 35.9±2.7 weeks. This was similar to 35.5± 1.1weeks found in a similar study among 60 pre-

eclamptic patients in Iran (Farzin and Sajadi, 2012). This similarity may be because pre-eclampsia occurs more frequently in the third trimester especially close to the end of pregnancy.

When pregnant women do not register for antenatal care, they are referred to as being un-booked. Majority of the pre-eclamptic women were un-booked. A similar finding was reported in a previous study in Ile Ife where more than three-quarters of pre-eclamptic women were unbooked (Makinde et al.2009). In the present study, most of the preeclamptic patients were referred from primary and secondary facilities in a catchment area similar to that of Ile Ife. Hence, the similarity in the findings of both studies. Furthermore, 62.5% of pre-eclamptic women were also un-booked in a similar study in India (Sultana and Aparna,2013). Pre-eclampsia often requires the care of a specialist for proper management. The high

rate of “unbooking” found in pre-eclamptic women in this study as well as in other studies in similar settings reflects the poor healthcare-seeking behavior of women in developing countries (Makinde et al.2009).

There was a significant shorter duration of sexual relationship with the biological fathers of the foetuses in the pre-eclamptic women than the normotensive controls in the present study. Previous studies have cited the concept of maternal–fetus immune maladaptation with the development of pre-eclampsia associated with short sperm exposure as a plausible explanation of this finding (Kho et al.,2009; Sultana and Aparna,2013).

A comparably higher prevalence of family history of hypertension among preeclamptic women was found in this study. On the other hand, there was no statistically significant difference in the prevalence of a family history of preeclampsia between healthy normotensive pregnant women and women with preeclampsia. This finding is in keeping with that of Gilles et al. (2013), further supporting the fact that preeclampsia in a pregnancy episode is associated with a family history of hypertension (Bezerra et al.,2010).

Some studies have shown that changes in serum levels of trace elements in pre-eclamptic patients may be implicated in its pathogenesis²³ while others have failed to show an association between serum levels of trace elements and prevalence of pre-eclampsia (Jain et al.,2010). In the present study, statistically significant lower serum levels of calcium were seen in pre-eclamptic women as compared to normotensive

controls. This finding is consistent with Akinloye et al. (2010), in Edo State, Nigeria as well as studies conducted in other similar settings (I Punthumapol and Kittichotpanich ,2008; kechukwu et al.,2012). The similarity between the study findings and other previous ones might be due to similarity in the study population characteristics in these settings. However, some authors reported contrary findings. Chanvitya et al²⁷ as well as Golmohammad et al. (2008) reported no difference in serum calcium levels between pre-eclamptic and normotensive pregnant women. The differences in dietary intake among different populations involved in these different studies may also account for the disparity in the findings.

Conclusion

This study showed that calcium serum levels were significantly lower in pregnant women with pre-eclampsia compared to the normotensive pregnant women. In addition, pre-eclampsia was associated with unbooked pregnancy status, family history of hypertension, and shorter duration of sexual relationships with the biological fathers of their foetuses. The lower serum calcium finding in pre-eclampsia in this study supports the hypothesis that hypocalcemia is a possible aetiology of pre-eclampsia. Longitudinal multicentre studies are needed on large scale in developing countries to confirm the low serum calcium and a possible link with pre-eclampsia observed in this study.

Limitations of the study

Although differences in body mass index of participants could affect serum calcium distribution and concentration, pre-eclamptic

women were not matched with the normotensive controls in terms of body mass index in this study because of effect of fluid retention on weight, especially in pre-eclamptic. Furthermore, fasting may affect serum calcium levels. However, random blood samples were collected at the presentation of the pregnant women regardless of the duration of fasting. This may have had some effects on serum calcium levels in a few patients.

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