Original Article

Comparison of Serum Calcium Level in Hypertensive and Normotensive Pregnant Women

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Abstract

Background: Calcium deficiency in pregnancy is linked to the risk of development of hypertensive disorders of pregnancy. At present, hypertensive disorders of pregnancy are among leading causes of maternal death in Nigeria. This study was aimed to compare the serum calcium level of women with hypertensive disorders of pregnancy and normotensive controls. **Methodology:** This was a comparative descriptive study among patients with hypertensive disorders of pregnancy (45 pre-eclampsia [PE] and 45 gestational hypertension [GH]) and comparative group of 45 normotensive pregnant women at Federal Medical Center, Abeokuta. **Results:** The serum calcium level in normotensive controls (mean ± standard deviation) was 2.64 ± 1.38 mmol/l, women with GH was 2.39 ± 1.15 mmol/l, and PE was 2.08 ± 0.76 mmol/l ($P = 0.065$). Hypocalcemia was found to have an incidence rate of 33% in normotensive controls, 51.1% among GH, and 51.1% among PE. **Conclusion:** Pregnant women with hypertensive disorders of pregnancy showed nonsignificant difference in mean serum calcium level.

Keywords: Calcium, gestational hypertension, hypertensive, normotensive, preeclampsia

Introduction

Hypertension in pregnancy is among the leading factors in etiology of maternal mortality,[1] and therefore, more studies on the possible role of serum calcium in either preventing or reducing the burden of hypertensive disorder of pregnancy will ultimately help reduce maternal mortality.

The first report on the relationship of hypertension in pregnancy with intake of calcium was made in 1980.[2] This was due to the finding that Mayan Indians that lived in Republic of Guatemala,[2] usually prepare their corn by dipping it in lime before cooking as part of their custom, were noticed to have a low incidence of preeclampsia (PE) and eclampsia and much consumption of calcium. Furthermore, the incidence rate of PE had been reported to be low from Ethiopia where most of the diet comprised high levels of calcium.[2]

Studies are ongoing on the effect of calcium in pregnant women with hypertension, especially on the prevention of PE as a way of decreasing the risk of hypertension in pregnancy and therefore maternal death.[3-5]

Calcium is involved in mediating the vasoconstriction and vasorelaxation of blood vessels, excitation contraction coupling in muscle contraction, and transmission of nerve impulses.

Studies have shown the possible relationship between nutrition and prevention of hypertensive disorders of pregnancy in dietary approaches towards stoppage of hypertension study.[5] Due to the economic downtown in Sub Saharan Africa and our region, pregnant women may not have good nutrient intake and this may be casual in most pregnant women with hypertension. This study is, therefore, designed within our locality to establish the basal calcium level among the pregnant population and to investigate its probable role in gestational hypertension (GH) without proteinuria and PE in our environment. It is also designed to evaluate the proportion of our pregnant women with hypocalcemia. This may provide

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possible evidence for routine calcium supplementation for our antenatal population as a way of decreasing the risk of hypertensive disorders of pregnancy and maternal mortality.

The objective of the study was to compare calcium level of pregnant women with hypertensive disorders of pregnancy (GH and PE) and that of pregnant women with normal blood pressure.

Methodology

This was a comparative, cross-sectional study among patients diagnosed with hypertensive disorders of pregnancy at the Federal Medical Center, Abeokuta (FMCA) during the study period. The comparative group was pregnant women with normal blood pressure and no history of chronic hypertension or proteinuria. The ratio of cases to comparative group ratio was 2:1. The present study was carried out at the maternity section of the hospital. FMCA is one of the public tertiary hospitals in Ogun State that usually receive referrals from other hospitals. FMCA offers specialist maternal-fetal services and has a dedicated maternofetal medicine unit with consultant obstetricians.

Inclusion criteria

(1) Selected pregnant women with singleton gestation, age ≥18 years of age, with documented normal blood pressure before the 20th week of pregnancy; (2) Pregnant women with confirmed gestational age (GA) ≥20 weeks from the last menstrual period or ultrasound determined GA; and (3) consenting pregnant women were included in the study.

The eligible participants were assigned into the three groups of GH, PE, and normotension. One in every three normotensive pregnant women was selected until 45 normotensive participants were recruited while pregnant subjects that met the criteria for GH or PE as stated above were consecutively recruited until 45 participants were recruited in each group. The eligible participants were recruited until the required numbers of 135 pregnant women were gotten.

Exclusion criteria

(1) Unbooked pregnancy presenting after the GA of 20 weeks (2) pregnant women without documented blood pressure before the 20th week of gestation, those with renal disease, thyroid or metabolic disorders, multiple gestation, intrauterine fetal death, chronic hypertension, diabetes mellitus, or liver disorders. (3) Pregnant women who were already on calcium supplements before or during the index pregnancy.

The sample size was determined by applying the formula for the comparison of two mean. A total number of 45 participants with GH without proteinuria, 45 participants with PE, and 45 healthy controls were recruited for the study.

Study procedure

This study was carried out among the consenting antenatal subjects who presented at FMCA for their routine antenatal care during the study period. Pregnant women with new diagnosis of hypertension in pregnancy at GA of ≥20 weeks with maternal age ≥18 years, blood pressure measurement of systolic ≥140 mmHg and or diastolic ≥90 mmHg repeated at least 4–6 h apart, and also normotensive participants were recruited for the study. Significant proteinuria was defined as 2+ proteinuria on reagent strip, or 1+ proteinuria with a PH >8 and specific gravity <1.030 or 24-h urinary protein measurement ≥300 mg.[6-8]

After adequate counseling was offered by the investigator with other clinicians trained on the study, and informed written consent obtained from the pregnant subjects presenting to the maternity section of FMCA, data concerning each subject were collected using a questionnaire except those excluded from the study with the criteria listed above. Brachial systolic and diastolic blood pressures were determined using sphygmomanometric auscultatory method at the arm level with the subject sitting down relaxed at least 5 min prior to the measurement. Systolic blood pressure was recorded as the beginning of the Korotkoff sounds (phase 1) whilst diastolic blood pressure was recorded as the vanishing point of the Korokoff sounds (phase V).[9-12] The blood pressure was measured using aneroid sphygmomanometer made by Accoson, United Kingdom. During the study period, 5–6 mL of venous blood sample was withdrawn from the forearm without the use of a tourniquet to prevent disturbance in albumin concentration that would occur with venous stasis which may lead to a momentary local alteration of serum calcium concentration. Blood samples were collected for both serum albumin and total plasma calcium assay.

Laboratory methods

Blood sample collection and clinicopathological analysis

Blood was collected into sterile vacutainer blood collection sample tubes (BD, Franklin Lakes, NJ, USA) which was analyzed by the Chemical Pathology unit of FMCA Laboratory Service within 12 h of taking the specimen. The serum was separated from the cells by centrifuging at 3000 rpm for a period of 3–5 min which was done within 30 min of receiving the sample, the assay of total plasma calcium and albumin done from the lithium heparin container using the ortho-cresolphthalein complexone method.

The plasma albumin concentration was also assayed for the correction of calcium albumin using the formula below;

Corrected Calcium (mmol/L) = Plasma measured Calcium + (40 − Plasma [albumin]) (g/L) × 0.02.[11] The normal reference range of total serum calcium is 2.1–2.8 mmol/L.

Urine samples were also collected for urinalysis and protein measurement from the study subjects. Ten to twenty milliliters of freshly voided urine was collected in clean, sterile universal containers for urinalysis was done using dipstick strips.

Summary of test principle and clinical relevance of ortho-cresophalein method

In the serum, calcium exists both in free ionized form and in bound form with albumin, therefore a reduction in

albumin causes lower calcium levels and vice versa. The assay of calcium is based on the reaction of calcium with O-cresolphtalein complexone in alkaline solution that will produce a purple coloured complex. The intensity of the color formed is directly proportional to the calcium concentration in the sample. The absorbance of calcium-O-Cresolphtalein complex is measured at 570 nm.[12]

Pregnant women were given information concerning the study at the antenatal clinic by the investigator. The participants who met the inclusion criteria were referred to the investigator and consent obtained.

A semi-structured pretested questionnaire was administered by the researcher along with trained clinicians to obtain information on the sociodemographics, consumption of dietary sources of calcium, cardiovascular and anthropometric measurements, as well as the laboratory test results of the consenting study participants. Anthropometric measurements, the height (meters) of the subjects were measured without shoes using a stadiometer and the weights (kilograms) were measured with the subject standing barefoot in light clothing using a weighing scale. Data entry and analysis were done using IBM Corp. International Business Machines Statistical Package for Social sciences Statistics for Windows, Version 22.0. Armonk, New York, USA: IBM; Released 2013.[13] The data were presented as frequency tables and graphs. The continuous variables that are normally distributed were presented as mean (±standard deviation [SD]) while those continuous variables not normally spread were presented as median (±interquartile range). The one-way analysis of variance (ANOVA) was used to test the differences in the mean values for the numerical variables across three groups. The Chi-square test was used to test the differences in the proportion of categorical variables. The level of significance was set at <0.05 (5%). The study was carried out after the ethical approval was granted by the Research Ethics Committee of the FMCA. The ethical approval protocol number was FMCA/470/HREC/10/2016/08.

Results

Within the period of this study, a total of 135 participants (45 in normotensive group, 45 in gestational hypertension group, and 45 in PE group) that met the eligibility criteria for the study were recruited following counseling and informed consent. During this study, a total of 58 gestational hypertension cases were seen, 13 cases were excluded from the study to get 45 eligible gestational hypertension subjects. A total of 3220 pregnant women were seen, giving an incidence rate of 1.80%. Out of 66 cases of PE seen, 21 cases were excluded for not meeting the inclusion criteria, giving an incidence rate of 2.06% [Table 1].

The mean age ± SD of the mothers in the normotensive group was 31.89 ± 4.71 years, while the mean age ± SD among GH and PE groups were 31.42 ± 4.72 years and 31.89 ± 5.23 years, respectively. In the mean ages across the three groups, there was nonsignificant statistical difference (P = 0.638).

The mean body mass index (BMI) in the normotensive subjects was 27.32 ± 3.87 kg/m^2 while the mean BMI among the gestational hypertension and the PE groups were 29.78 ± 5.45 kg/m^2 and 31.02 ± 5.64 kg/m^2 respectively. In the BMI across the three groups, there was significant statistical difference with P= 0.003* [Table 1].

The corrected mean serum calcium (mmol/l) ± SD among the normotensive control was 2.64 ± 1.38 mmol/l (n = 45), while the corresponding values among the GH was 2.39 ± 1.15 mmol/l (n = 45) and in PE was 2.08 ± 0.76 mmol/l (n = 45). The findings showed nonsignificant statistical difference (P = 0.065) in mean serum calcium level across the three groups using ANOVA [Table 2].

A total of 24 (53.3%) of gestational hypertension had early onset (GA <34 weeks) while 21 (46.7%) had late onset GH (GA ≥ 34 weeks). Among the PE group, 22 (48.9%) had early onset PE while 23 (51%) had late onset PE [Table 3].

The mean serum calcium level ± SD (mmol/L) in mild GH was 2.41 ± 1.22 and in severe GH was 2.29 ± 0.71 with P = 0.687.

There was no significant statistical difference in the mean serum calcium levels across mild and severe gestational hypertensions [Table 4].

The mean serum calcium level ± SD (mmol/L) in mild PE was 2.12 ± 0.74 and in severe PE was 2.01 ± 0.82 with P = 0.640 [Table 4].

Across the groups revealed nonsignificant statistical difference in the mean serum calcium levels among women with mild and those with severe PE.

Overall, the incidence of hypocalcemia across the three groups was 45.2% (61 out of the 135 participants in this study). Among the normotensive group, the incidence of hypocalcemia was 15 (33.3%), while in the gestational hypertension and PE groups, the incidence of hypocalcaemia were 23 (51.1%) and 23 (51.1%), respectively.

Discussion

In this study, the incidence rate of GH was 1.80% while that of PE was 2.06%. This is similar to the findings by Monica *et al*.[14] in Harare Zimbabwe, who found 1.7% of cases of PE in their population but lower than that by Singh *et al*.[8] in Sokoto who found 6% of PE among mothers. In this study, PE is more common than GH contrary to the findings by Melamed *et al*.[15] in Toronto Canada, where GH was stated to be the most common form of hypertensive disorder of pregnancy.

The findings showed nonsignificant relationship across the mean serum calcium level of 2.64 ± 1.38 mmol/L (mean ± SD) in normotensive pregnant women, 2.39 ± 1.15 mmol/L in gestational hypertensions, and 2.08 ± 0.76 mmol/L in PE (P = 0.065) [Table 2]. The findings are also different from that of Ositadinma *et al*.[16] in Nnewi who compared 60 preeclamptic/eclamptic women and 60 normotensive

pregnant women and found significant differences in the mean serum calcium of 1.91 ± 0.28 mmol/l in preeclamptics/eclamptics and 2.32 ± 0.21 mmol/l in normotensive counterparts (P = 0.02). Furthermore, the serum calcium level found by Ositadinma *et al*.[16] in preeclamptics/eclamptics was quite lower than that found in this study. The reason could be that eclampsia which was included as part of the study.

Olusanya *et al*.[17] in a study in the role hypocalcemia may have a role in the Aetiopathogenesis of PE, found mean serum calcium of 2.05 ± 0.4 mmol/L in PE, 1.9 ± 0.2 mmol/L in eclamptics, and 2.6 ± 0.4 mmol/L in normotensives (P < 0.001) and significantly lower mean serum calcium level in cases with hypertensive disorders of pregnancy.

A study by Owusu Darkwa *et al*.[18] revealed statistically non-significant difference in the mean serum calcium level in preeclamptic and normotensive pregnancy, with P = 0.092. Possible reasons for the association of low calcium level with hypertensive disorders of pregnancy are the stimulation of renin and parathyroid hormone release that elevates

Table 1: Sociodemographic features of subjects

Variable	Normotensives	GH	PE	*P*
Age (years)	*n*=45 (%)	*n*=45 (%)	*n*=45 (%)	0.638
Mean±SD	31.89±4.71	31.42±4.72	31.89±5.23	
Parity	*n*=45 (%)	*n*=45 (%)	*n*=45 (%)	0.737
Mean±SD	1.96±0.85	2.02±0.84	2.02±0.81	
Interpregnancy interval (years)	*n*=45 (%)	*n*=45 (%)	*n*=45 (%)	0.520
Mean±SD	1.71±0.63	1.80±0.69	1.76±0.53	
BMI (kg/m^2)	*n*=45 (%)	*n*=45 (%)	*n*=45 (%)	0.003*
Mean±SD	27.32±3.87	29.78±5.45	31.02±5.64	
New paternity	*n*=45 (%)	*n*=45 (%)	*n*=45 (%)	
Yes	3 (6.7)	2 (4.4)	1 (2.2)	0.593
No	42 (93.3)	43 (95.6)	44 (97.8)	
Family history of hypertensive disorders	*n*=45 (%)	*n*=45 (%)	*n*=45 (%)	
Yes	6 (13.3)	13 (28.9)	13 (28.9)	0.134
No	39 (86.7)	32 (71.1)	32 (71.1)	

BMI: Body mass index, SD: Standard deviation, GH: Gestational hypertension, PE: Preeclampsia

Table 2: The mean serum calcium and albumin, diastolic blood pressure and systolic blood pressure in normotensive, gestational hypertension, and preeclampsia groups

Variable	Normotensive (control), mean±SD	GH, mean±SD	PE, mean±SD	*P*
Mean corrected serum calcium (mmol/l)	2.64±1.38	2.39±1.15	2.08±0.76	0.065
Mean serum albumin (mg/dl)	5.26±3.04	6.93±8.02	5.53±2.79	0.195
DBP (mmHg)	63.56±8.02	88.89±8.59	96.22±14.62	<0.001*
SBP (mmHg)	106.62±8.46	143.42±9.22	153.00±23.02	<0.001*

GH: Gestational hypertension, PE: Pre-eclampsia, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, SD: Standard deviation. *Statistically significant < 0.05

Table 3: The mean serum calcium level in early onset and late onset preeclampsia as well as early onset and late onset gestational hypertension using the analysis of variance

Mean corrected serum calcium level (mmol/L)	Early onset (GA at onset <34 weeks)	Late onset (GA at onset ≥34 weeks)	*P*
PE	2.29±0.78 (*n*=22)	1.87±0.70 (*n*=23)	0.064
GH	2.40±1.09 (*n*=24)	2.38±1.24 (*n*=21)	0.954

GA: Gestational age, PE: Pre-eclampsia, GH: Gestational hypertension

Table 4: Gestational age at onset of hypertensive disorder of pregnancy

Hypertensive disorder of pregnancy	Sub-class	GA at onset <34 weeks, *n* (%)	GA at onset ≥34 weeks, *n* (%)
GH	Mild	20 (44.4)	18 (40)
	Severe	4 (8.9)	3 (6.7)
PE	Mild	15 (33.3)	14 (31.1)
	Severe	7 (15.6)	9 (20)

GA: Gestational age, PE: Pre-eclampsia, GH: Gestational hypertension

the intracellular concentration of calcium in cells of the smooth muscles such as those of the blood vessels leading to generalized vasoconstriction.

Furthermore, ionized calcium is required for the synthesis of nitric oxide and prostacyclin, and deficiencies of these may lead to oxidative stress that increases the risk of developing PE. Sultana *et al*.[19] found the mean serum calcium in normotensive, mild, and severe pregnancy induced hypertension to be 9.64 ± 0.77 mg%, 9.18 ± 0.83 mg%, and 8.45 ± 0.58 mg%, respectively ($P < 0.05$).

Jain *et al*.[20] on the study of the role of calcium in PE found significant low mean serum calcium among pregnant women with PE when compared to normal pregnant group. A study by Jain *et al*.[20] indicates that the reduction of serum level of calcium may be implicated in the etiology of PE. Kumru *et al*.[21] found serum calcium to be lower in pregnant women with PE when compared to the healthy controls ($P < 0.0001$).

The mean serum calcium was 2.29 ± 0.78 mmol/L ($n = 22$) in early onset PE, 1.87 ± 0.70 mmol/L ($n = 23$) in late onset PE, 2.40 ± 1.09 mmol/L ($n = 24$) in early onset GH, and 2.38 ± 1.24 mmol/L ($n = 21$) in late onset GH [Table 3]. In this study, nonstatistically significant difference ($P = 0.064$) was found in the measured serum calcium level in the early and the late onset PE subgroups. In this study, majority of the participants were diagnosed with late onset PE 23 (51%. 1%) while the majority of those with GH was early onset 24 (53.3%). This is similar to the findings by Erez *et al*.[22] in Maryland USA, who found PE occurring later in pregnancy as the common form of this syndrome. The study by Erez *et al*.[22] also identified differences in hemodynamic status occurring as early as 24 weeks GA with PE occurring later in pregnancy having elevated cardiac output and almost stable total vascular resistance, whereas participants with early onset PE have reduced cardiac output and some elevated vascular resistance.

In the developing countries, physiologic changes of pregnancy are aggravated by under nutrition which worsens micronutrient deficiency.[23] There is evidence that hypocalcemia causes increased stimulation of the secretion of parathyroid hormone that leads to the release of renin from the renin angiotensin aldosterone system which leads to the elevation of blood pressure and hypertension in pregnancy.

Yeboah *et al*.[24] in Kumasi, Ghana, reported that >70% of pregnant women with PE who presented for antenatal care had low serum calcium, which is similar although relatively higher than the incidence of hypocalcemia in this study.

Limitations of the study

There is a possibility that some of the subjects might be on medication that may contain calcium supplements. However, adequate drug history was taken to ascertain that the subjects that were on drugs with calcium supplements were completely excluded during recruitment for the study.

Conclusion

The findings from the study showed that nonsignificant relationship exists in the mean serum calcium level among normotensive, gestational hypertension, and preeclamptic women.

The findings in this study suggest that the incidence of hypocalcemia among pregnant women with GH and PE was high within our environment.

Recommendations

More studies should be carried out in different settings to establish the mean serum calcium which may help understand the role of calcium in hypertension in pregnancy.

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Conflicts of interest

There are no conflicts of interest.

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