RESEARCH ARTICLE

COMPARATIVE EVALUATION OF SERUM CALCIUM LEVEL IN PREECLAMPTIC AND NON-PREECLAMPTIC WOMEN IN A TERTIARY HOSPITAL IN SOUTHERN NIGERIA

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ABSTRACT

Background: Preeclampsia is one of the commonest complications of pregnancy. Calcium deficiency is implicated in the development of preeclampsia especially in developing Countries. There is paucity of studies on the role of serum levels of calcium in preeclampsia in Southern Nigeria.
Objective: The main objective of this study was to determine the serum level of calcium in women with preeclampsia and those without preeclampsia.
Methodology: This was a comparative study in which 52 preeclamptic and 52 non preeclamptic women who satisfied the eligibility criteria were recruited for the study.
Data entry and statistical analysis was done using statistical software (IBM SPSS® for windows version 21.0.) Data were analyzed for mean and standard deviation. Comparison of serum levels of calcium between the two groups was performed by student t-test and P value < 0.05 was considered as statistically significant.
Results: The serum calcium level was statistically lower in women who had preeclampsia compared to those who did not (8.37 ± 0.91 mg/dl vs 9.33 ± 1.15mg/dl respectively, p<0.001).The systolic and diastolic blood pressure showed a significant negative correlation with serum calcium level in those that developed preeclampsia
Conclusion: This study showed that women with preeclampsia demonstrated a significantly reduced serum calcium level. This support the hypothesis that hypocalcaemia is a possible aetiology of preeclampsia.

INTRODUCTION

Preeclampsia is one of the commonest complications of pregnancy; it is transient but potentially life threatening (Carson and Changpeng, 2014). It is a disease of theories because of the multiple hypothesis put forward to explain its occurrence, however the underlying aetiology remains obscure (Gol Mohammed *et al.*, 2008). The relationship between preeclampsia and nutritional deficiencies has been well established, studies have persistently and consistently shown that a relationship exist between the two (Belinzan *et al.*, 1988; Hofmer *et al.*, 1994; Onyegbule *et al.*, 2014; Carroli *et al.*, 1994).

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The results of clinical trials showed the aggravation of hypertensive complication and the change in concentration of various trace elements. (Belinzan *et al.*, 1988; Hofmer *et al.*, 1994; Onyegbule *et al.*, 2014; Carroli *et al.*, 1994; Hofmer *et al.*, 2010) Calcium have a relaxant effects on blood vessels of pregnant women and changes in the concentration of these elements can lead to alteration of blood pressure causing preeclampsia (Carroli *et al.*, 1994; Hofmer *et al.*, 2010). Family history of preeclampsia, extreme reproductive age, primigravidity, diabetes, renal diseases, hypertension prior to pregnancy and black race are some of the risks factors for preeclampsia (Shennan, 2007; Kenny, 2011; Miller, 2007). Other risk factors include antiphospholipid syndrome, multiple pregnancy, oocytes donation or donor insermination, stress, hydatidiform mole, a new partner and the use of barrier contraception (Shennan, 2007; Kenny, 2011; Miller, 2007; Omole-Ohonsi and Ashimi, 2008; Luealon and Phupong, 2010).

The prevention of preeclampsia is difficult, because the aetiology of the disease is not fully understood (Carson and Changpeng, 2014). However there is interest in supplementation with low dose aspirin, calcium, and anti–oxidants like vitamins C and E. Some trials of the use of calcium and antioxidant vitamins in high doses have reported improvements in biochemical makers of endothelial activation together with a reduction in preeclampsia (Shennan, 2007; Kenny, 2011; Miller, 2007; Sibai, 2003). Preeclampsia is a progressive disorder that is associated with the following complications; eclampsia, cerebral haemorrhage, cerebral oedema and cortical blindness. Others include pulmonary oedema, disseminated intravascular coagulopathy, HELLP syndrome and abruption placenta (Shennan, 2007; Kenny, 2011). Fetal complications are also common: These include prematurity, preterm birth and intrauterine fetal death (Shennan, 2007; Kenny, 2011; Miller, 2007). Deficiencies of trace elements like calcium have been implicated in the aetiology of preeclampsia. There is paucity of studies on the role of serum levels of calcium in preeclampsia in Southern Nigeria. This study therefore proposes to determine the serum level of calcium level in preeclamptic and non preeclamptic women. The studies was also aimed at determining if any difference in the serum calcium levels between preeclamptic and non preeclamptic women is statistically significant and also contribute to the understanding of the role of serum levels of calcium in preeclampsia.

MATERIALS AND METHODS

Study area

This study was carried out in the University of Port Harcourt Teaching Hospital. It is a 650-bed hospital located at Alakhahia in Obio -Akpor local government area of Rivers state South-South Nigeria, about 15 kilometers from Port Harcourt city along the East-West road. It is a tertiary health center that provides all levels of health care services for Rivers, Bayelsa, Delta, Imo, Abia and Akwaibom states. The obstetrics and gynaecology department is a key department in the hospital with 18 Consultants staff. On average between400 and 450 pregnant women are booked for antenatal care services in the hospital every week and primidravidae constitute about 41% of total attendance. Follow up attendance rate is between 250 and 300 patients per week. The annual delivery rate in the hospital is about 3500 which gives an average of 290 deliveries monthly. The hospital has a chemical pathology department staffed by consultants, resident doctors, Laboratory scientists and interns. Over 40 different tests are conducted in the chemistry laboratory including serum calcium quantitation. The Ethical approval for the study was obtained from the Ethical committee of the Hospital.

Study design

This was a comparative case study designed to evaluate the levels of serum calcium in pregnant women with and without preeclampsia in the University of Port Harcourt Teaching Hospital. This study was performed between 1st of July 2015 to 22nd of February 2016. The control and study group was chosen from women attending ante natal care in the University of Port Harcourt Teaching Hospital. The control group was chosen from women who fulfilled the inclusion criteria and were followed up from booking till delivery but did not develop preeclampsia in the third trimester, while the study group was those that were followed up from booking and on development of preeclampsia in the third trimester and fulfilled other selection criteria were enrolled in the study. A proforma developed for the study was used to record the socio-demographic characteristics, clinical and laboratory data of the patients. The content of the questionnaire include age, marital status, occupation, educational status, religion, parity, booking status, last menstrual period, gestational age, past history of diabetes or hypertension, family history of diabetes or hypertension, presence or absence of pedal oedema, serum calcium level, onset of delivery, mode of delivery, birth weight, Apgar score and admission into special care baby units.

Inclusion criteria

- **All those who developed preeclampsia based on:** Blood pressure equal to or greater than 140/90 mm Hg on two occasion 6 hours apart and proteinuria greater than 300mg in 24 hours urine sample or one plus of protein in 2 mid-stream urine sample collected 6 hours apart in the 3rd trimester.
- Singleton fetus
- Gestational age: third trimester
- Primigravida
- No history or evidence of urinary tract infection
- Age range 18 to 35 years
- Non diabetics

Exclusion criteria

- Multiple pregnancy
- Diabetics
- Pregnancy with renal diseases
- Gestational trophoblastic diseases
- Chronic hypertension
- Pregnancy with heart disease
- Maternal age greater than 35 years

Sample size determination

The sample size was calculated using the formula for comparison of two means

$$n = \frac{(U+V)^2(SD_1^2 + SD_1^2)}{(U_1 - U_2)^2}$$

Where:

n= minimum sample size required

U=one sided percentage point of the normal distribution corresponding to 100% minus the power. Thus were power is 90% then U=1.28 V= percentage point of the normal distribution corresponding to the two sided significance level. Thus at 5% significance level V=1.96

SD_1= standard deviation in study group= 0.37
SD_2= standard deviation in control group= 0.69
U_1= mean of observation in study group= 1.92
U_2= mean of observation in control group=2.29

$$n = (1.28+1.98)^2(0.37^2 + 0.69^2)$$

$(1.92-2.29)^2$

n= (10.4976) (0.1369+0.4761)

     0.1369

n= (10.4976) (0.613)

     0.1369

n= 6.4350

   0.1369

n= 47. Therefore a minimum sample size of 47 patients is required in each group. Adjusting for a drop out of 10%, this study will require a total of 104 patients. (52patients in each group)

Data collection and processing

The participants in this study were followed up from booking in the second trimester (the minimum gestational age at booking was 16 weeks). And informed consent was obtained from each participant before recruitment into the study. A detailed history was taken to ensure each patient fulfilled the selection criteria. Data regarding socio-demographic characteristics, clinical, family history and laboratory results were recorded in the Proforma. A through clinical examination was done for each patient. The Height and weight of each participant was measured (using a weighing scale ZT-120, METLAR) and the body mass index calculated by dividing the weight in kilogrammes by the square of the height in meters. Those in the control group were all normotensive from booking and did not develop preeclampsia. While those in the study group were followed up from booking and on development of preeclampsia in the third trimester for the first time and fulfillment of the selection criteria were recruited for the study. Patients in both groups were followed up till delivery. Blood pressure was measured with the use of manual sphygmomanometer while the patient was in supine position on a couch with a left sided tilt. An appropriate size cuff that covers at least $2/3^{rd}$ of the upper arm was used. The systolic blood pressure was taken at the first point the sound was heard while, the diastolic blood pressure was taken as Korotkoff V. (the absence of sound). A patient was said to be hypertensive when her blood pressure was equal to or greater than 140/90 mmHg measured at least 6 hours apart. Urine collection was done in the ante natal clinic between 8 to 9 am. Urine samples were collected under the supervision of trained Nurses. Patients were given clean, dry, wide-mouthed, leak-proof containers with their names and number on it. Patients were instructed to clean their vulva with copious clean water, and then part their labia and the first part of the urine voided and to collect the next stream of urine into the urine containers provided. Samples were analyzed for protein estimation using dip stick. Protein estimation was made based on the colour change of the dip stick compared to the corresponding colour chart on the reagent container. The diagnosis of proteinuria was made when two samples of mid-stream urine collected atleast four hours apart showed one or more plus of albumin. Urine microscopy culture and sensitivity test was routinely done in suspicious cases to exclude infection. Therefore a patient was said to be preeclamptic when her blood pressure was equal to or greater than 140/90mmHg measured at least six hours apart accompanied by proteinuria of atleast one plus. Blood samples (5mls) was taken from the ante cubital vein and sent to the laboratory for calcium estimation. Blood samples was taken for women in the control group at the time of presentation in the labour ward after an informed consent, while for patients with preeclampsia blood samples was collected at the time the diagnosis was first made. Then they were followed up till delivery. At the laboratory the samples were centrifuged to get the serum which was stored in the refrigerator until the time of analysis. Serum calcium measurement was done using quantitative spectrophotometric analysis. Serum albumin binds to calcium hence to calculate the correct serum calcium level this formula below was used. Corrected total calcium (mg/dl) = Total calcium measured (mmol/L) + 0.2(40-albumin mmol/L). At birth data were collected regarding onset of labour, mode of delivery, birth weights, Apgar score and information on whether the baby was admitted in to the special care baby or not were entered in to the Proforma and the development of any complication.

Statistical analysis

Statistical analysis was done using statistical software (IBM SPSS^R for window version 21.0.) Data were analyzed for mean and standard deviation. Comparison of serum levels of calcium between the two groups was performed by student t-test and p value < 0.05 at 95% was considered statistically significant.

RESULTS

A total of one hundred and four booked women were enrolled in the study, the socio-demographic characteristic of the patients were shown in tables 1, 2, 3 and 4. In the cases group the age range of women was 18 to 35 years and the mean age was 27.58 ± 7.34 years. While in the control group the age range of women used in this study was 18 to 35 years and the mean age was 26.71 ± 4.21 years. The difference was not statistically significant, the P value was 0.45. In the cases group 11 % were singles while 87% and 2% were married and divorced respectively while in the control group 8% were singles while 88% and 4% were married and divorced respectively. In the cases group 27% had primary education, while 44% and 29% were educated up to secondary and tertiary level respectively. In the control group 11.5% were educated up to primary level while 46.2% and 42.3% had secondary and tertiary education respectively. In the cases group 94.2 % of were Christians and 5.8% Muslems. While in the control group 90.4% were Christians and 9.6% Muslems. The mean gestational age was 36.54 ± 2.69 weeks for preeclamptic patients. In the non preeclamptic group the mean gestational age was 38.67 ± 1.10 weeks. There was a significant difference between the two groups. The p value was 0.01. The mean body mass index range of the cases group was 28.09 ± 3.50 Kg/m^2. The mean body mass index of the control group was 26.42 ± 2.42Kg/m^2. There was a statistical difference in body mass index between the two groups. The p value was < 0.01. The mean systolic blood pressure of the cases group was 158.88 ± 11.80 mmHg. The mean systolic pressure of the control group was 113.65 ± 7.15 mmHg. There was a statistical difference in systolic blood pressure between the two groups. The p value was 0.01.The mean diastolic blood pressure for the cases group was 101 ± 8.20mmHg. The mean diastolic blood pressure of the control group was 71.35 ± 6.57mmHg. There

was a statistical difference in diastolic blood pressure between the two groups. The p value was 0.01. The mean serum calcium level in preeclamptic women was 8.37±0.91 mg/dl. The mean serum calcium level in non preeclamptic women was 9.33±1.15mg/dl. The p value was 0.01. There was a statistical difference in the mean serum calcium level between the two groups. There was a negative correlation between systolic blood pressure and serum calcium level. Pearson correlation = - 0.335, p< 0.01.There was also a negative correlation between diastolic blood pressure and serum calcium level. Pearson correlation = - 0.256, p< 0.01. The onset of labour was spontaneous in 32.7% of patients with preeclampsia, while it was 73.1% in the non preeclamptic group.

Labour was induced in 28.8% of the study group while in the control group 15.4% of women had their labour induced. In the control group 38.5% had no labour while in the control group 11.5% had no labour. In the study group 44.2% had vaginal delivery as against 88.5% in the control group. Caesarean section was performed for 55.8% of women in the cases group while 11.5% of women in the control group had caesarean section as their mode of delivery. The mean birth weight in the preeclamptic women was 2.71±0.70Kg.The mean birth weight in non preeclamptic women was 3.10±0.43Kg. The p value was 0.01. There was significance in birth weight between the two groups. In the cases group 30.8% of babies were admitted in the special care baby unit, while in the control group 7.7% were admitted.

Table 1. Social and demographic characteristic of the cases and control

Age (yrs)	Cases	Percentage (%)	Control	Percentage (%)
15-19	10	19.2	4	7.7
20-24	12	23.1	14	26.9
25-29	11	21.2	18	34.6
30-35	19	36.5	16	30.8

Table 2. Educational status of cases and control

Educational status	Cases	Percentage (%)	Control	Percentage (%)
Primary	14	27.0	6	11.5
Secondary	23	44.0	24	46.2
Tertiary	15	29.0	22	42.3
No formal education	0		0	

Table 3. Marital status for cases and control

Marital status	Cases	Percentage (%)	Control	Percentage (%)
Single	6	11	4	8.0
Married	45	87	46	88.0
Divorced	1	2	2	4.0

Table 4. Religion of cases and control

Religion	Cases	Percentage (%)	Control	Percentage (%)
Christianity	49	94.2	47	90.4
Muslims	3	5.8	5	9.6
Others	0		0	

Table 5. Age of cases and control group

Parameter	Cases Mean ±SD	Control Mean ± SD	'p' value	Significance
Age (yrs)	27.58±7.34	26.71±4.21	0.45	Not significant

Table 6. Gestational age of cases and control

Parameter	Cases Mean ±SD	Control Mean ± SD	'p' value	Significance
Gestational age	36.54±2,69	38.67±1.10	0.01	Significant

Table 7. Body mass index of cases and control

Parameter	Cases Mean ±SD	Control Mean ± SD	'p' value	Significance
Body mass index (kg/m^2)	28.09±3.50	26.42±2.42	0.01	Significant

Table 8. Blood pressure of cases and control

Parameter mmHg	Cases Mean ±SD	Control Mean ±SD	'p' value	Significance
Systolic blood pressure	158.88±11.80	113.65±7.15	0.01	Significant
Diastolic blood pressure	101±8.20	71.35±6.57	0.01	Significant

Table 9. Serum calcium levels of cases and control

Parameter	Cases Mean ±SD	Control Mean ±SD	'p' value	Significance
Calcium (mg/dl)	8.37±0.91	9.33±1.15	0.01	Significant

Table 10. Onset of labour in cases and control

Onset of labour	Cases	Percentage (%)	Control	Percentage (%)
Induced	15	28.8	8	15.4
Spontaneous	17	32.7	38	73.1
No labour	20	38.5	6	11.5

Table 11. Mode of delivery of cases and control

Mode of delivery	Cases	Percentage (%)	Control	Percentage (%)
Vaginal	23	44.2	46	88.5
Caesarean section	29	55.8	6	11.5
Forceps/vacuum				

Table 12. Maternal complications of cases and control

Complications	Cases	Control
Abruption	3	0
Intrauterine growth restriction	6	2
Eclampsia	2	0

Table 13. Birth weight of cases and control

Parameter	Cases Mean ±SD	Control Mean ±SD	'p' value	Statistical Significance
Birth weight (kg)	2.71±0.70	3.10±0.43	0.01	Significant

Table 14. Admission in to special care baby unit

Parameter	Cases	Percentage (%)	Control	Percentage (%)
Admission into special care baby unit	16	30.8	4	7.7

DISCUSSION

Preeclampsia is one of the most common complications of pregnancy. It is one of the most common causes of maternal and fetal morbidity and mortality (Anorlu *et al*., 2005). Nutritional deficiencies are commonly seen during pregnancy when requirement increased. This is observed more in pregnant women in developing countries with a diet deficient in essential minerals and vitamines (Akinloye *et al*., 2010). Our study did not show any statistical significance in age between the preeclamptic and non preeclamptic patients. The result of our study was supported by the work done in Nnewi South East Nigeria and Osogbo South West Nigeria by Onyegbule *et al*. (2014) and Akinloye *et al*. (2010) respectively. The similarity in outcome with our study may be due race, diet and studied population. The findings in this study correlated with other previous reports. (Gol Mohammed *et al*., 2008; Ugwuja *et al*., 2016; Naser and Ziad, 2000) However the findings in our study was at variance with the work done in India by Kanagal *et al*. (2014). Here there was a significant difference in age between the two groups. Evidence has consistently and persistently shown that obesity is a risk factor of preeclampsia and other hypertensive disorders of pregnancy. (Kaklina *et al*., 2009; Jido and Yakasai, 2014) This was supported by this study. The results of this study showed that preeclamptic women had a higher body mass index. The result of our study was consistent with other similar studies (Kanagal *et al*., 2014; Akinloye *et al*., 2010). However, the result of this study was not in keeping with the findings of other earlier studies (Gol Mohammed *et al*., 2008; Onyegbule *et al*., 2014; Ugwuja *et al*., 2016).

Our study reported that the babies of non preeclamptic women were delivered at a higher gestational age. The result of this study was in keeping with an earlier work (Kanagal *et al*., 2014). The outcome of our study was at variance with the work done by Ugwuja *et al*. (2016) in Abakaliki South East, Nigeria which did not report any significant difference in gestational age at delivery between the two groups. The results from this study showed a mean systolic blood pressure of 158.88±11.80 mmHg and a mean diastolic blood pressure of 101±8.20 mmHg in preeclamptic patients in contrast to a mean systolic blood pressure of 113.65±7.15 mmHg and a mean diastolic blood pressure of 71.35±6.57mmHg in control group. This was consistent with an earlier investigation by Sukonpan *et al* (Anorlu *et al*., 2005) who reported a mean systolic blood pressure of 155.50± 12.18 mmHg and a mean diastolic blood pressure of 108.18±10.89 mmHg in preeclamptic patients and a mean systolic and diastolic blood pressure of 108±6.50mmHg and 68.60±8.19 mmHg in the control group respectively. The slight differences may be due to ethnic differences. The implication of this, is that the pathogenesis and severity of complications following preeclampsia varies from one region to the other (Akinloye *et al*., 2010). Our study showed a statistical significant difference in birth weight between the two groups. The babies of non preeclamptic women had higher birth weight. The findings in our study was consistent with similar studies (Kanagal *et al*., 2014; Jido and Yakasai, 2014; Naser and Ziad, 2000). In this study the mean serum level of calcium in the control group was 9.33±1.15 mg/dl while the mean serum calcium level in the cases group was 8.37±0.91 mg/dl.Calcium is an important element as it is necessary for muscle contraction and neuronal activity.

The blood pressure changes evident in preeclampsia can be attributed to the change in serum calcium level. Decrease in serum calcium levels led to an increase in intracellular calcium. This led to constriction of blood vessels and increased in vascular resistance and resultant increase in blood pressure (Anorlu *et al*., 2005). The major finding in this study was the significant lower level of mean serum calcium level in preeclamptic women 8.37±0.91 mg/dl compared to non preeclamptic women 9.33±1.15 mg/dl. Akinloye *et al* (2010) had a similar finding which was supported by other previous reports (Kumru *et al*., 2003; Essom *et al*., 2010; Abdallah and Abdiabo, 2014). However this was in disagreement to the study by Gol Mohammed *et al*. (2008) that reported no difference in the level of serum calcium level between preeclamptic and non preeclamptic women[2].

The difference in serum calcium levels obtained in different studies may be due to the difference in the study design, analytical technique, difference in population characteristics such as age, race, ethnicity, socio-economic status as well as country and region of residency (Essom *et al*., 2010). This study supported the hypothesis that hypocalcaemia might be a factor in the development of preeclampsia. This study has potential limitations and issues attracting criticism. First the dietary intake of preeclamptic women was not taken prior to the commencement of the study to ascertain their calcium and magnesium level. Another limitation of this study is the non-use of quantitative method in detecting proteinuria. The direct (Calmagite) method which is easier and cheaper was used in this study instead of the ion-selective electrode which is better but expensive in the analysis of serum calcium level. However findings from this study remain relevant and add to evidence on the subject matter.

Conclusion

This study showed that in preeclamptic women serum calcium is significantly reduced. This study support the hypothesis that hypocalcaemia is a possible aetiology of preeclampsia. Hence dietary supplementation with calcium especially in developed countries may help in the reduction of incidence, morbidity and mortality associated with preeclampsia.

Recommendation

Educating women of reproductive age on the importance of micronutrients in the prevention of preeclampsia. Routine screening and close surveillance of micronutrients especially calcium during antenatal period. Dietary supplementation with calcium should be done at least in susceptible women especially in developing countries. More studies should be carried out in this field

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