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Effect of calcium on preeclampsia among pregnant women in Osogbo, South Western Nigeria

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ABSTRACT

Preeclampsia is a public health problem with devastating foetomaternal consequences. It has been tagged a disease of theories with numerous postulations suggested to unravel its aetiopathogenesis. The need to continuously review the disorder, its pathogenesis, factors responsible for the severity of its presentation and means of preventing its occurrence will revolutionize the modern-day obstetric practice. A case-controlled study was conducted on 104 pregnant patients that attended antenatal clinic at three major hospitals in Osogbo, Osun State, Nigeria. Statistical analysis was done using SPSS version 22. Statistical significance was set at p-value less than 0.05 for all values of test statistic. The mean age of the participants was 29.84±5.60 but 44.2% of them fell within the age bracket of 30-39 years. The mean age of women with preeclampsia was higher than normotensive patients (30.71±5.69 versus 28.96±5.54 years). The mean plasma calcium level was significantly low in the preeclamptic group with mean calcium value of 1.65±0.37 mmol/L. There was a significant statistical relationship of mean plasma calcium level between the study and control groups (p<0.001). The mean plasma calcium level was inversely proportional to increasing age, though not statistically significant (p= 0.445). There was decreasing mean plasma calcium with severe hypertension and proteinuria but there is no significant statistical relationship between the mean plasma calcium level and the degree of hypertension and proteinuria. This study has shown that plasma calcium level was significantly lower in the preeclamptic group compared to the normotensive (control) group and calcium supplementation to all pregnant women may be of benefit.

INTRODUCTION

Preeclampsia is one of the most common causes of maternal and perinatal morbidity and mortality that are still bedeviling Sub-Saharan African region (Dalley, 2009). It is a systemic failure that affects about 10-20% of all pregnancies worldwide and is the most common yet least understood disorder of pregnancy. In developing nations, the incidence of the disease is reported to be 4-18%, with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries (Villar et al., 2001). Also, available evidence shows that most of the outcome measures considered in the previous studies done (for example, preterm labour, renal failure, severe preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, abruptio placenta, disseminated intravascular coagulopathy)

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occurred more severely in our environment compared with developed nations (Mohieldein et al., 2007). The disease is usually rapidly progressive and characterized by high blood pressure, platelet aggregation, proteinuria and swelling of the lower extremities (Villar et al., 2001; Davey, 2012). Blood pressure in this condition starts to elevate in the late 2nd and 3rd trimester (Villar et al., 2001; Dutta, 2011). Early detection and prompt management helps in reducing the complications of the condition. The need to continuously review the disorder, its pathogenesis, factors responsible for the severity of its presentation and means of preventing its occurrence will revolutionize the modern-day obstetric practice.

Despite its prevalence and severity, the pathophysiology and aetiology of this disease is still not fully understood. It has been tagged a disease of theories with numerous postulations suggested to unravel its aetiopathogenesis. One of the theories to explain preeclampsia is its relationship with the plasma calcium level with the postulation that plasma calcium level bears an inversely proportioned relationship to the development of preeclampsia (Pepke and Villar, 1991) (for example, the lower the plasma calcium level, the higher the risk of developing preeclampsia). Studies have shown that calcium prevent pregnancy induced hypertension by influencing the production of vasodilatory agents such as Nitric oxide (NO) and prostaglandin and prevent the production of vasoconstrictive agents like thromboxane A2 and endothelin (Dulley et al., 2004; Myatt, 1992; Hofmeyr et al., 2010).

Observational studies have found an inverse association between the maternal calcium intake and serum level on one side and hypertensive disorders of pregnancy on the other side (Villar et al., 1983; Nasar et al., 2001; Dulley et al., 2004; Seely et al., 1992). However, this is contradictory to some studies which reported no difference between the two groups (Golmohammed et al., 2015; Fatemeh et al., 2008). Trumbo and Ellwood (2007) also reported that the relationship between calcium and the risk of pregnancy induced hypertension and preeclampsia is highly unlikely, inconsistence and inconclusive. The possible explanation for these opposing findings in the literature is uncertain. However, it is known that some factors affect the results of the estimation of calcium in serum. These include albumin level, method of sample collection, postural changes of patient during sample collection and method of analysis (Wells, 1998). The negative results of the other studies may also be caused by underlying chronic hypertension or renal disease during pregnancy. The difference in the serum calcium values obtained in different studies may be due to the difference in the population studied.

The conclusion of the observational study about the relationship between the maternal plasma calcium level and hypertensive disorder in pregnancy was similar to the conclusion of a meta-analysis that was performed by Xingmei (2006), which showed significant inverse relationship between the maternal plasma calcium and the development of hypertensive disorder in pregnancy. Kanagal et al (2014) in a double blinded case-controlled analytical study of sixty preeclampsia women and their corresponding control in Southern Indian showed that the calcium concentration was significantly lower in the preeclamptic group compared to the normotensive. He also noticed that the level of serum magnesium showed a marginal difference in both groups. He concluded that intake of oral calcium may help in the reduction of incidence of preeclampsia especially in the population of a developing countries where nutritional intake is poor. He also observed that not many studies have been done in the developing countries to assess the role of elements, including calcium, in the development of preeclampsia and thereby recommended that the roles of magnesium and calcium supplementation need further investigations.

Assessments of the maternal serum calcium and evaluation for calcium supplement have been confirmed to prevent hypertensive related disorder. This has been a veritable tool in reducing foetomaternal morbidity and mortality (Sanchez-Ramos et al., 1994; Aemer et al., 2011; Lovren and Janet, 2000). The reference ranges for plasma calcium level in non-pregnant women ranges between 8.7-10.2 mg/dl (2.18-2.55 mmol/L). The plasma calcium level in pregnancy varies in the three trimesters with values of 8.8-10.6 mg/dl (2.2-2.65 mmol/L), 8.2-9.0 mg/dl (2.05-2.25 mmol/L) and 8.2-9.7 mg/dl (2.05-2.43 mmol/L) in the first, second and third trimesters respectively (Abbassi–Ghamarati et al., 2009). Direct measurement of calcium however, is limited by difficulties in accurate analysis, lack of standardization and need for special handling; and all these result in increased cost. Therefore, strategies have been developed to estimate ionized calcium from total calcium adjusted for albumin which is more available and relatively less expensive (Moore, 1970).

The research problem aimed at lowering preeclampsia by the unique properties of calcium in its aetiopathogenesis as research now focuses on prevention rather than treatment. The frequency of calcium deficiency in pregnancy and the role of hypocalcaemia in the development of complications and adverse pregnancy outcome formed the basis for this study. This study explored the effectiveness of calcium in reducing preeclampsia in our locality, where study is minimal. Numerous studies have been published in this field from other regions of the world with lots of controversies, but there is paucity of studies in our environment, hence, reviewing the literatures and coming out with new discoveries in the grey areas will go a long way in preventing preeclampsia (Feleke et al, 1999). The study aimed at determining the plasma calcium level

in patients with preeclampsia and normotensive pregnant patients and also to compare mean plasma calcium level to degree of hypertension and proteinuria in preeclamptic patients.

METHODOLOGY

This was a case-controlled study of patients that attended antenatal clinic at three major hospitals in Osogbo, Osun State, Nigeria viz: Ladoke Akintola University of Technology Teaching Hospital (LTH), State Specialist Hospital, Asubiaro, and Our Lady of Fatimah Catholic Hospital. One hundred and four (104) participants were recruited for this study, based on the calculation of sample size, from the antenatal clinics of the previously mentioned hospitals. Fifty-two (52) patients who developed preeclampsia (from blood pressure and urinalysis findings) were recruited as case (study group) while the other 52 normotensive pregnant women of corresponding age, gestational age, tribe and parity were recruited as control. Patients with medical disease, for example, diabetes mellitus, renal disease, thyroid dysfunctions, chronic hypertension, patients on calcium containing supplements while receiving antenatal care, and those with multiple gestation were excluded from the study.

At recruitment, an informed consent was obtained from all the participants who met the criteria for inclusion and the mobile telephone numbers were also documented. Patients were counselled about the nature of the study, the amount of blood to be drawn, the detail of the subsequent follow up and the time of termination of the study. The blood samples for plasma calcium estimation of both the study and control groups were taken as they were being recruited. Urine protein and blood pressure of the study group were also noted.

Plasma calcium assay was carried out in the Department of Chemical Pathology of the teaching hospital. For all participants, socio-demographic data which includes age, parity, occupation and level of education of the patient and her spouse, estimated gestational age, as well as relevant clinical parameters were entered into a data extraction sheet.

Ethical approval for this work was obtained from the research ethical committee of the Ladoke Akintola University Teaching Hospital, Osogbo.

In this study, the normal plasma calcium levels that were used are 8.2-9.0 mg/dl (2.05-2.25 mmol/L) and 8.2-9.7 mg/dl (2.05-2.43 mmol/L) in the second and third trimester respectively (Abbassi–Ghamarati et al., 2009). Hypocalcaemia for this study was plasma calcium level of less than 8.2 mg/dl (2.05 mmol/L).

Systolic blood pressure of lesser than 120 mmHg and diastolic of lesser than 80 mmHg was taken as a normal blood pressure (Giles et al., 2009). Prehypertension was systolic blood pressure between 120-139 mmHg and diastolic of 80-89 mmHg. Stage 1 hypertension was systolic blood pressure of 140-159 mmHg and diastolic of 90-99 mmHg, while stage 2 hypertension was systolic blood pressure of 160 mmHg and above with diastolic blood pressure of 100 mmHg and above. Stage 3 hypertension was stage 2 with any organ damage according to the Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure (JNC7) (National Heart, Lung, and Blood Institute, 2013). The normal urine protein excretion per day is less than 300 mg. Dipstick proteinuria of 1+ is equivalent to 300 mg/L, 2+ to 1 g/L, 3+ to 3 g/L and 4+ to 5 g/L. Excretion greater than 300 mg is significant and excretion of 5 g/L and above is adjudged as severe proteinuria (Balakrishna, 2013).

All results were entered into the proforma. The data was analyzed using Statistical Package for Social Sciences (SPSS) version 22. The results were presented in summary frequency distribution tables, charts and graphs. Categorical variables were expressed in proportions and the variables were compared between the study and controls using Chi-square while continuous variables were expressed as means (± standard deviation). The arithmetic means of the study and control groups were compared using the *t*-test. Statistical significance was set at p-value less than 0.05 for all values of test statistic.

RESULTS

Table 1 shows the Socio-demographic distribution of both the study and control groups. It shows that 46 women, which represents 44.2%, fell within the age bracket 30-39 years and represent the largest age bracket for the study (Figure 1) with mean age of 29.84±5.60. The mean age of women with preeclampsia was higher than normotensive patients (30.71±5.69 years vs 28.96±5.54 years). There were 92 patients (88.5%) from Yoruba ethnicity, this was expected due to the location of the study; majority of the women (51.9%) were Christians.

The mean plasma calcium level was significantly low in the preeclamptic group with mean calcium value of 1.65±0.37 mmol/L as shown in Table 2. Forty-four respondents (84.6%) had hypocalcemia compared to the control group with mean calcium level of 2.09±0.36 mmol/L. There was a significant statistical relationship of mean plasma calcium level between the study and control groups ($p<0.001$). The mean body mass index (BMI) was significantly higher in preeclamptic respondents compared to the controls (28.96±4.24 vs 25.38±5.19 $p<0.001$). The mean plasma calcium level in normotensive (control) group matched for age, parity, estimated gestational age and tribe is shown in Table 3. It shows that mean plasma calcium level was inversely

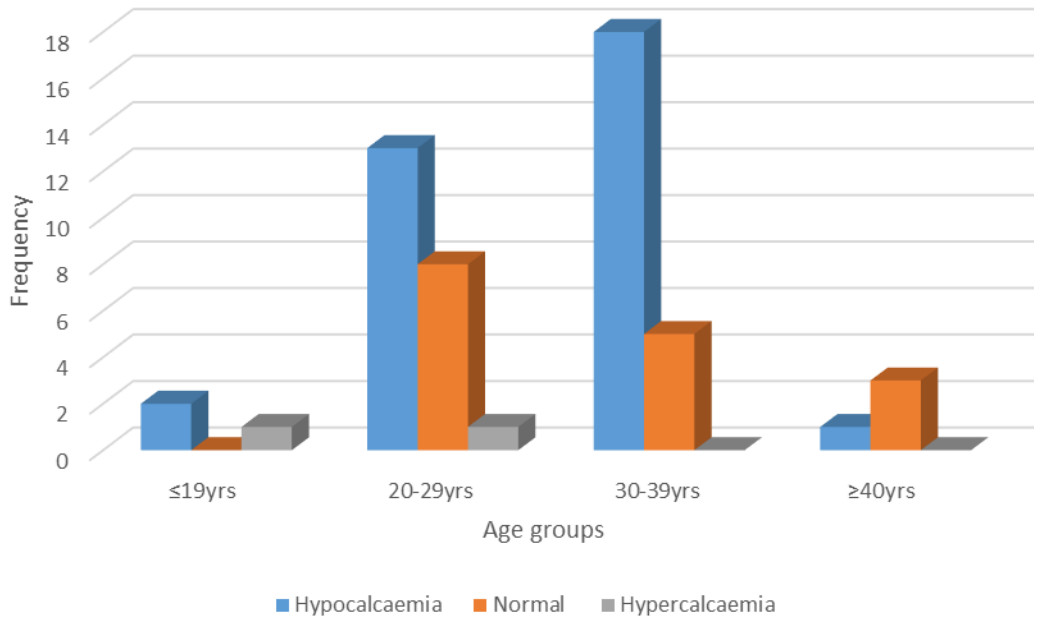

Figure 1. Showing age group of preeclampsia patients in calcium taking; age 19 years and below have low hypocalcaemia and hypercalcaemia patients while age 30-39 years had highest hypocalcaemia.

Table 1. Social demographic data of preeclamptic and normotensive patients.

Variable	Frequency	Percentage
Age group		
≤19 years	6	5.8
20-29 years	44	42.3
30-39 years	46	44.2
≥40 years	8	7.7
Tribe		
Yoruba	92	88.5
Hausa	1	1.0
Igbo	6	5.8
Others	5	51.9
Religion		
Christianity	54	51.9
Islam	49	47.1
Traditional	1	1.0
Parity		
Primigravida	51	49.0
Primiparous	25	24.0
Multiparous	28	27.0
Occupation		
Unemployed	18	17.3
Self employed	23	22.1
Civil servant	32	30.8
Traders	31	29.8
Educational level		

Table 1. Contd.

Primary education	1	1.0
Secondary education	34	32.7
Tertiary education	69	66.3
Husband occupation		
Artisan	14	13.4
Trader	11	10.6
Civil servant	44	42.3
Self-employed	35	33.7
Social class		
1	4	3.8
2	34	32.7
3	36	34.6
4	30	28.9

Table 2. Relationship between the preeclamptic and normotensive patients' parameters.

Variable	Mean ±SD (case)	Mean ±SD (control)	t value	P value
Age	30.71±5.69	28.96±5.54	1.588	0.115
Height	1.62±0.04	1.60±0.07	1.120	0.266
Weight	75.96±13.16	64.95±12.76	4.332	<0.001
BMI	28.96±4.24	25.38±5.19	3.843	<0.001
Gestational age at diagnosis in weeks	34.06±2.39	35.65±1.96	1.885	0.154
Gestational age at recruitment in weeks	34.25±2.24	35.65±1.96	1.575	0.741
Calcium level in mmol/l	1.65±0.37	2.09±0.36	6.190	<0.001
Systolic blood pressure mmHg	157.42±11.07	106.85±10.71	23.679	<0.001
Diastolic blood pressure mmHg	105.73±6.96	67.31±7.44	27.226	<0.001

Table 3. Relationship between calcium levels in normotensive pregnant women controlled for age, parity, estimated gestational age and tribe.

Variable	N	Mean ±SD	F value	P-value
Age				
30-34yrs	18	2.18±0.39		
35-39yrs	32	2.05±0.35	0.822	0.445
Above 39yrs	2	2.00±0.01		
Tribe				
Yoruba	51	2.09±0.36	0.949	0.335
Igbo	1	2.44±0.00		
Parity				
Primigravida (nulliparous)	23	2.24±0.42		
Primiparous	23	1.98±0.27	3.738	0.031
Multiparous	6	1.97±0.23		

proportional to increasing age with value of 2.18±0.39 in the age bracket of 30-34 years, 2.05±0.35 in age bracket of 35-39 years and 2.00±0.01 in age bracket 39 years and above, although there is no significant relationship between the mean plasma calcium level and the maternal age (p= 0.445).

Table 4. Association between the preeclamptic and normotensive patients with hypocalcaemia.

Variable	Case	Control	Df	Chi-square	P-value
Hypocalcaemia	44(84.6)	30(57.7)			
Normal	8(15.4)	14(26.9)	2	12.285	0.002
Hypercalcaemia	0	8(15.4)			

Table 5. Relationship between the blood pressure and proteinuria with mean plasma calcium among the preeclamptic patients.

	N	Mild hypertension (Mean ± SD)	N	Severe hypertension (Mean ± SD)	t-value	P-value
Systolic BP	21	1.67 0.35	31	1.64±0.38	0.278	0.782
Diastolic BP	24	1.69±0.35	28	1.63±0.39	0.597	0.553
Proteinuria	37	1.66±0.36	15	1.62±0.39	0.342	0.734

Table 6. Logistic regression showing demographic data on calcium level.

Independent variables	B	SD	EYP (β) O.R	95% CI	P values
Age	-0.041		0.960	0.867-1.063	0.431
Parity	0.351		1.421	0.682-2.963	0.349
BMI	0.161		0.85	0.771-0.940	0.001

$Y = 0.960_{Age} + 1.421_{Parity} + 0.852_{BMI}$

The mean calcium in primigravida, primiparous and multiparous are 2.24±0.42, 1.98±0.27 and 1.97±0.23 respectively. There is a significant statistical relationship between mean calcium level and the parity in the control group (p<0.031).

In Table 4, 44 respondents (84.6%) of the study group had hypocalcaemia, 8 patients (15.4%) had normal plasma level with no case of hypercalcaemia. In the control group, 30 patients (57.7%) had hypocalcaemia with 14 patients (26.9%) having normal plasma calcium value and 8 cases (15.4%) of hypercalcaemia recorded. There is a significant statistical relationship between the plasma calcium level in preeclamptic and normotensive pregnant women (p<0.002).

Table 5 depicts the relationship between the mean plasma calcium level and the degree of hypertension and proteinuria in the study group. Twenty-one (40.4%) patients had mild systolic blood pressure with mean plasma calcium of 1.67±0.35, 31(59.6%) respondents with severe blood pressure had a mean plasma calcium level 1.64±0.38(p=0.782), 24(46.1%) preeclamptic women with mild diastolic blood pressure had a mean plasma calcium level of 1.69±0.35 while 28(53.9%) with severe diastolic blood pressure had a mean calcium level of 1.63± 0.39(p=0.553). The mean calcium level of 1.66±0.36 was found in 37(71.1%) patients with mild proteinuria while 15(28.9%) patients with severe proteinuria had a mean calcium level of 1.62±0.39(p=0.734).

There was decreasing mean plasma calcium with severe hypertension and proteinuria but there is no significant statistical relationship between the mean plasma calcium level and the degree of hypertension and proteinuria.

Table 6 shows that the relationship between hypocalcaemia on one side, and maternal age and parity on the other side appears as a coincidence while the p-value of 0.001, which is significant, showed that there is a true association between hypocalcaemia and BMI.

DISCUSSION

Hypertensive disorders in pregnancy ranks among the leading causes of maternal morbidity and mortality, complicating 10-20% of pregnancy worldwide with preeclampsia and eclampsia being the major causes of maternal and perinatal morbidity and mortality (Millner, 2007; NDHS, 2008; Alkema and Chou, 2016). Despite the volume of knowledge on hypertension in pregnancy, no preventive measure has been found (Dalley, 2009). Recent studies have shown that calcium may have a role to play in its occurrence.

This study revealed that 44 respondents (84.6%) from

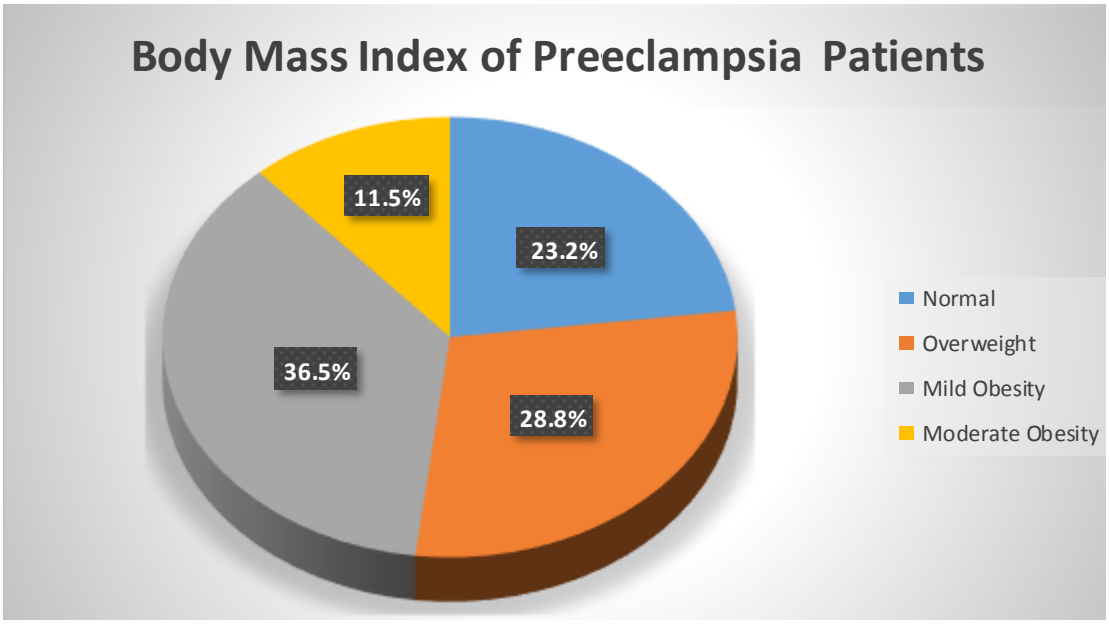

Figure 2. Showing the distribution of body mass index of preeclampsia patients with 23.2% were normal, 36.5% mild obesity, 11.5% were moderate obesity while 28.85% were overweight.

the study group had hypocalcemia, with the definition of hypocalcemia set as plasma calcium level below 2.05 mmol/L. This was similar to several studies done on level of plasma calcium in preeclamptic patients (Villar et al., 1983; Nasar et al., 2001; Dulley et al., 2004; Seely et al., 1992). The study also showed that women with a higher BMI are more likely to become hypertensive (Figure 2) compared with those with lower value as BMI showed a significant relationship between the study and control groups ($p<0.001$). The BMI was significantly higher in the preeclamptic patients which is in tandem with the work done by Kanagal et al (2014) in costal India where 120 patients (60 preeclamptic patients as study and 60 normotensive patients as control) were involved. He discovered that the BMI was significantly higher in the study group (27.07±3.07 vs 24.9±2.32). He concluded that preeclamptic women were older with a higher BMI than the control group.

There was hypocalcemia in 30 patients (55.7%) in the control group. This may be accounted for by the high prevalence of malnutrition due to dietary insufficiency and short inter-pregnancy intervals in the developing world (Winkvist et al., 1992; Conde-Agudelo, 2005; Winikoff, 1983; Prentice et al., 1981). Although 8 patients (15.4%) of the control group had hypercalcemia with no case of hypercalcemia in the study group.

A noticeable result of the study also showed that plasma calcium level was decreasing with advanced maternal age, although there was no significance between the mean plasma calcium level and maternal age ($p=0.445$). There was a significant statistical relationship between plasma calcium level and parity ($p<0.031$), which is similar to the work done by Winkvist et al. (1992).

The significant statistical relationship found in the mean plasma calcium level in preeclamptic compared to that in normotensive pregnant women in this study was similar to the study by Nasar et al. (2001) at the King Hussein Medical Centre in Saudi Arabia which was conducted among 80 patients (50 patients who developed pregnancy induced hypertension, PIH) as study group and 30 normotensive patients as control). He found out that the mean serum calcium level was lower in the study compared to control (8.22±0.12 vs 9.50±0.16, $p<0.005$). He also noticed a higher parathyroid hormone in the study group and concluded that maternal serum total calcium and parathyroid hormone are implicated in the PIH, with the low calcium having a role in the development of PIH. He recommended that calcium supplement during late pregnancy may be used to help in the prevention of PIH. This was also corroborated by the work done by Seely et al. (1992) and Kanagal et al (2014). It was noticed from the study that the level of calcium in this study was much lower in severe preeclamptic patient compared to mild cases. However, there was no significant statistical relationship between the mean plasma calcium level and the degree of hypertension and proteinuria (for example, the degree of severity of preeclampsia). A meta-analysis that was performed by Xingmei (2006) showed significant

inverse relationship between the maternal plasma calcium and the development of hypertensive disorder in pregnancy. Mohieldein et al. (2007) in a case control hospital-based study in Sudan also concluded that a low level of maternal total calcium has a role in the development of hypertensive disorder in pregnancy (inverse relationship) and recommended calcium supplementation during pregnancy. However, this was in contrast to the work done by Trumbo and Ellwood (2007) which concluded that the relationship between calcium and risk of hypertension is inconsistent and inconclusive, and that the relationship between both is highly unlikely. The possible reasons for his result and conclusion could be the method of sample collection, postural changes of patients during sample collection, method of analysis and serum albumin level measurement.

The mean age of women with preeclampsia was 30.71±5.69years which was higher than the mean age of control of 28.96±5.54years. This corroborated the earlier work done by Kanagal et al (2014) but was in sharp contrast to the work of Golmohammed et al. (2015) in Iran in which serum calcium, magnesium, copper and zinc levels were measured in 52 preeclamptic (study) and corresponding 52 normotensive patients (control). He concluded that there was no significant difference between the serum levels of the mineral in the study and control groups. He also concluded that there were no significant differences in BMI and maternal ages between the two groups. This might probably be due to the fact that he recruited only the primigravida as study group, with all patients recruited in the third trimester.

There was a higher frequency of mean plasma calcium deficiency with increasing parity with a significant association ($p<0.031$) among the control group from the study (nulliparous 2.24±0.42, primiparous 1.98±0.27 and multiparous 1.97±0.23). Similar finding was noted in the work of Winkvist et al. (1992) who stated that women with extremely inadequate diet have lesser weight gain during pregnancy and may suffer deficiency of vital minerals including calcium. This was also noticed in the work of Conde-Agudelo et al. (2004) and Lindsday et al. (2012). This can be explained as a result of frequent pregnancy and short inter-pregnancy intervals among women in Sub-Saharan Africa. The high prevalence of malnutrition in this environment (dietary insufficiency), coupled with short inter-pregnancy intervals are two prominent factors responsible for hypocalcaemia during pregnancy with attendant preeclampsia and its sequelae (Winkvist et al.,1992; Conde-Agudelo, 2005; Winikoff, 1983; Prentice et al., 1981; Lindsday et al., 2012).

LIMITATIONS OF THE STUDY

Conduct of this study was limited to the hospitals in Osogbo, the capital city of the state and so might have been opened to only a selected group in the population. All the participants were literate and most of them were gainfully employed.

The use of frozen sample might have introduced some variability in the assay of plasma calcium compared with immediate determination using freshly centrifuged blood sample. Direct measurement of calcium is limited by difficulties in accurate analysis, lack of standardization and need for a special handling. Hence, we resorted to estimation of ionized calcium from total calcium adjusted for albumin.

Conclusion

The study showed that plasma calcium level was significantly lower in the preeclamptic group compared to the normotensive (control) group. This supports the hypothesis that hypocalcemia may have a role in the aetiopathogenesis and progression of preeclampsia. If there is a significant level of difference in plasma calcium levels between the preeclamptic and normotensive pregnant women, then elemental calcium administration, especially in this environment, may be beneficial.

It is recommended that patients should be counselled on the need for a balanced diet and diet rich in calcium. Dietician can also be invited on regular basis for counseling during the ANC (antenatal care) visit. Supplementation of calcium to all pregnant women to prevent the occurrence or further progression of preeclampsia and its foeto-maternal complications as a result of calcium deficiency may be of benefit.

There is a need to conduct a cohort study to strengthen the findings of this study as this will involve a larger population and a longer period of monitoring which is likely to be more representative.

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