ORIGINAL ARTICLES

CALCIUM SUPPLEMENTATION FOR THE PREVENTION OF PREGNANCY INDUCED HYPERTENSION/PREECLAMPSIA

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Abstract

Background: Pregnancy induced hypertension (PIH) and preeclampsia (PE) contribute significantly to maternal and perinatal morbidity and mortality. The role of calcium supplementation towards preventing PIH/PE however remains unclear.

Objective: To assess the efficacy of calcium supplementation in prevention of PIH and PE.

Materials and methods: An open label, randomized controlled trial conducted at the antenatal clinic of University of Abuja Teaching Hospital between July 2014 and June 2015. A total of 484 nulliparous women 16 weeks or less gestation and with normal blood pressures were randomly assigned to either receive 1200mg of calcium tablet daily (N=242) or not to receive calcium tablets (N=242) from 16weeks until delivery. Primary outcome measure was development of PIH or PE and secondary outcome measure was preterm birth.

Results: The incidence of PIH was 7.7% among the intervention group compared to 13.7% in the control, p=0.039 and calcium supplementation reduced the risk of PIH (RR=0.56 (95% CI: 0.32-0.98)), but not PE. It also prolonged the duration of pregnancy in women who developed PIH (p=0.02). Incidence of preeclampsia was not significant, RR-0.56 (95% CI: 0.21-1.52) so also was the incidence of preterm delivery between the two groups (RR-0.65 (95% CI: 0.32-1.31)). No serious maternal side effects of treatment were recorded.

Conclusion: Calcium supplementation during pregnancy reduced the risk of PIH and thus may have a role in the prevention of PIH amongst nulliparous women. Its role in the absolute prevention of PE was not demonstrated in this study.

Key Words: Calcium supplementation, pregnancy induced hypertension, preeclampsia, preterm delivery, Nigeria.

Introduction

The hypertensive disorders of pregnancy (pre-existing hypertension, gestational hypertension, and preeclampsia) remain important causes of maternal and perinatal morbidity and mortality, especially in low and middle-income countries[1]

Preeclampsia is a multi-systemic disorder with a poorly understood aetiology, pathogenesis and pathophysiology. However, recently it has been postulated that it is a two-stage disease with an imbalance between angiogenic and anti-antigenic factors[2]. Its pathogenesis is also suggested to be related to disturbances in placentation at the beginning of pregnancy, followed by generalized inflammation and progressive endothelial damage[3]. Although previous systematic reviews on the role of calcium supplementation in pregnancy had suggested a beneficial effect towards preventing pregnancy induced hypertension and preecampsia[4,5,6] its routine use in pregnancy has only recently been recommended by WHO for pregnant women in areas with low dietary calcium intake and especially in those at high risk of developing pre-eclampsia[7]. Studies from Nigeria suggests that the dietary intake of calcium by pregnant and non-pregnant populations are low[8,9,10]. The local application of the results of the aforementioned systematic reviews as well as implementation of the WHO recommendation is limited by the non-existence of supporting evidences or studies from African obstetric populations apart from Egypt and South Africa. This research gap formed the basis of this study. Information obtained from this study would be beneficial towards policy change as regards implementation or further evaluation of the WHO recommendation on calcium supplementation in pregnancy in Nigeria and other developing countries in Africa.

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Materials and Methods

This was an open label randomized controlled trial to assess the efficacy of calcium supplementation in the prevention of pregnancy induced hypertension/ preeclampsia in nulliparous women. The study was conducted at the Department of Obstetrics and Gynaecology of University of Abuja Teaching Hospital, Abuja, Nigeria between June 2014 and July

2015.Healthy nulliparous women at gestational ages of 16 weeks or less and with blood pressures less than 140/ 90 mm Hg were enrolled into the study. Exclusion criteria included patients with blood pressure ≥140 and/or 90 mm Hg at first antenatal visit, history of diabetes mellitus, chronic hypertension, hyperparathyroidism, renal calculi or renal disease, twin gestation, report of frequent use of calcium supplements or antacids and refusal to give consent. Random numbers were computer generated and allocation concealed by use of sequentially numbered, opaque, sealed envelopes. The eligible women were randomly assigned into the treatment arm or control arm of the study. Those in the intervention arm received 1.2 g of elemental calcium daily. They were instructed to take 2 tablets (600mg) in the morning and 2 tablets (600mg) in the evening in addition to all other standard treatment (haematinics). Those in the control group received all other standard treatment except calcium supplementation. Ingestion of the tablets was only to commence from after the 13th week of gestation and until delivery, diagnosis of preeclampsia and/or eclampsia, or suspicion of urolithiasis. Once preeclampsia or eclampsia occurred, the patient was treated as per the hospitals standard protocol. Other information obtained included gestational age which was calculated based on best available estimate; the women's recollection of the date of their last menstrual period or earliest ultrasound scan estimate where they were not sure of their last menstrual period, age, weight and blood pressure. Surveillance for hypertension and proteinuria was conducted using standardized measurements of blood pressure and urinary protein excretion at scheduled clinic visits, during the hospitalization for delivery, and reviews of the medical records until 24 hours postpartum. Blood pressure was recorded with a mercury sphygmomanometer with the subject seated for ≥5 minutes with the cuff at the level of the heart on the right arm. Diastolic blood pressure was determined by using the fifth Korotkoff sound unless a measurement was zero, in which case the fourth sound was used. Voided urine was collected for the measurement of protein by dipstick and proteinuria of 1+ (300 mg per liter) confirmed by testing a clean-catch, midstream sample. The women returned all unused tablets at every study visit and at the time of hospitalization for delivery. Compliance was then computed by dividing the number of used tablets by the total number of prescribed tablets. The primary outcome was the development of pregnancy induced hypertension /preeclampsia while secondary outcomes included preterm delivery (<37 weeks of gestation), Caesarean section, maternal admission to intensive care unit, severe preeclampsia, placental abruption, HELLP syndrome, death of mother, low birth weight, admission in the neonatal intensive care unit and perinatal death. The sample size of each arm of the study was calculated using the formula for randomized controlled trials. A study sample of 484 women was therefore estimated to have a 90% probability of detecting differences in the development of Pregnancy Induced hypertension /Preeclampsia at p=0.05. All women were initially included in the group to which they were assigned but those lost to follow up were however not included in the final analysis. Data was analyzed using Statistical Package for Social Science (SPSS version 20). Comparison of outcomes was performed in groups with risk ratio and at 95% CI. Tests of associations for categorical variables were done using Chi square or Fisher's exact test while student's t-test was used for continuous variables. Poisson's regression analysis was used to adjust for potential cofounders which included age and body weight.

Ethical Considerations

Ethical clearance for this study was obtained from the Research and Ethics Committee of the University of Abuja Teaching Hospital.

Results

Results

Data were unavailable for 9 women (3.7%) in the calcium group and 23 women (9.5%) in the control group. This was due to mid trimester miscarriages in 8 women (1.7%) and failure to deliver in the hospital facility with loss of contact in 23 women (5.0%) and death in one woman (0.4%) (Figure1).

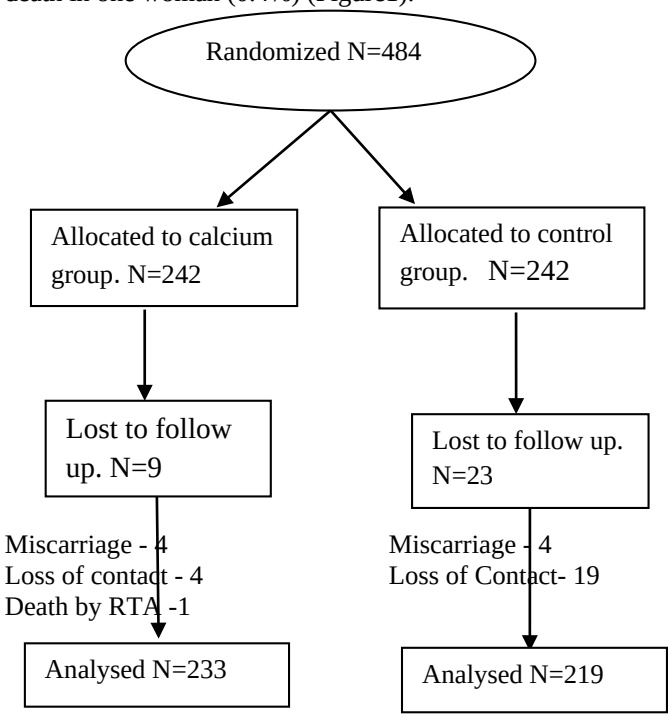

Figure 1: Trial Profile

Table 1: Characteristics of Women in the treatment and control groups at commencement of the study

Characteristic	Calcium (n=242)	Control (n=242)	P value
Maternal age (years)*	27.6(4.4)	27.8 (4.3)	0.626
Weight at booking *	67.9(11.0%)	68.1(12.9%)	0.859
Blood pressure at entry* Systolic (mmHg) Diastolic (mmHg)	 109.2(9.5) 66.5 (7.3)	 109.0(11.5) 66.9(9.3)	 0.840 0.610

*Values as mean (SD) ** Values as number (%) of women;

Table 2. Effect of calcium supplementation on incidences and severity of pregnancy induced hypertension and preeclampsia in the intervention and control groups.

Hypertensive disease At any stage of pregnancy*	Calcium n=233	Control n=219	Relative risk	95%CI	P Value
PIH	18 (7.7)	30(13.7)	0.56	0.32-0.98	0.039
Mild	10(4.3)	24(11.0)	0.39	0.19-0.80	0.010
Severe	8 (3.4)	6 (2.7)	1.25	0.44-3.55	0.671
Preeclampsia	6 (2.6)	10 (4.6)	0.56	0.21-1.52	0.259
Mild	2 (0.9)	2 (0.9)	0.94	0.13-6.62	0.950
Severe	4 (1.7)	8 (3.7)	0.47	0.14-1.54	0.212
Overall incidence of PIH and PE	24(10.3)	40(18.3)	0.56	0.35-0.90	0.017

Values are as number (%) of women; PIH = pregnancy-induced hypertension; PE=preeclampsia CI = confidence interval

Table 3: Obstetric Outcomes

Outcome	Calcium n=233	Control n=219	Relative risk	95%CI	P Value
Gestational age at delivery <37 weeks >37 weeks	 12 (5.2) 221(94.8)	 18(8.2) 201(91.8)	 0.65 1.02	 0.32-1.31 0.89-1.17	 0.220 0.808
Mode of delivery Vaginal Instrumental vaginal delivery Caesarean section	 162(69.5) - 71(30.5)	 163(74.4) - 56 (25.6)	 0.91 1.15	 0.77-1.07 0.84-1.56	 0.254 0.385
Induction of labor Abruptio placentae	32 (13.7) 4 (1.7)	18 (8.2) - -	1.59 8.46	0.92-2.80 0.45-156.26	0.094 0.151

Values as number (%) of women;

Compliance with supplementation was 60.4%, with 44(18.8%) women stopping the trial medication during the antenatal period. The most frequent reason given was that of abnormal taste (12.9%) and side effects like nausea and vomiting (6.0%). For those that did not deliver in our facility, delivery information was obtained via phone interview and consequently, information on Apgar scoring in this group of patients was missed. Table 1 shows the baseline characteristics of the participants. The mean age of the study participants was 27.7± 4.4 years and there was no statistically significant difference between the mean ages of the two groups (27.6 vs. 27.8 years, P=0.626). Other baseline characteristics at the time of entry into the study, including the mean systolic and diastolic blood pressures did not show significant difference between the two groups. The overall incidence of pregnancy induced hypertension (PIH) was 10.6% with incidence rate of 7.7% and 13.7% in the intervention and control group respectively, RR=0.56(95% CI: 0.32-0.98). The overall incidence of pre-eclampsia was 3.5%, 2.6% in the intervention group and 4.6% in the control group, RR=0.56(95% CI: 0.21-1.52). The overall rate of hypertensive disorders of pregnancy was 14.2%; 10.3% in the intervention group and 18.3% in the control group, RR=0.56 (95% CI: 0.35-0.90), these are shown in table 2. After adjusting for maternal age and weight, there was still a significant difference in occurrence of PIH in the control group RR=0.67 (95% CI: 1.07-3.85), P=0.030, and the lack of significance in occurrence of preeclampsia among the two groups was maintained, RR=0.37(95% CI: 0.20-1.66), P=0.318. The mean pregnancy duration when hypertension was detected was similar in the two groups. It was 35.89±4.47 weeks in the intervention group and 35.78±2.59 weeks in the control group (P=0.91). Also, the mean duration of gestation at delivery was similar in the two groups (Calcium: 39.1±2.3 weeks Vs Control: 39.1±1.8weeks, P=1.000). Table 3 describes the obstetric performance of the participants and shows that even though the risk of preterm delivery was reduced by 35% in the calcium group, this was not statistically significant RR - 0.65 (95% CI: 0.32-1.31). Also, no significant difference was seen in rates of induction of labour and mode of delivery in both groups. Four cases of placental abruption were recorded in the intervention group and this also was not statistically significant RR - 8.462 (95% CI: 0.46-156.26). Two of the cases that had placental abruption were associated with severe preeclampsia while the other two had normal blood pressure. There was no record of other complications like HELLP syndrome, renal failure or maternal death. There were also no complaints of renal colic or haematuria in the treatment group. Amongst the participants who had calcium supplementation and developed preeclampsia, there was a statistically significant lower birth weight when compared with women in the same group who did not develop preeclampsia (Normal blood pressure: 3.24±0.33 Vs Preeclampsia: 2.77±0.45, P=0.033). This was however not so for those who developed PIH amongst the subpopulation of calcium supplement group. When the gestational ages at delivery was considered amongst women who developed either preeclampsia or PIH in the two groups, those with PIH in the intervention group had a statistically significant higher mean age at delivery than those in the control group (39.27±1.26 Vs38.25±1.44; P=0.017). (Table 4)

Table 4: Comparison of characteristics of pre-eclampsia/PIH women with normotensive women in groups.

Variable	**Calcium group (n=233)**					**Control group (n=219)**				
	Normal	**Pre-eclampsia**	**P-value**	**PIH**	**P Value**	**Normal**	**Pre-eclampsia**	**P-value**	**PIH**	**P Value**
All deliveries										
No. of participants (%)	**209(89.7)**	**6(2.6)**	-	**18(7.7)**	-	**179(81.7)**	**10(4.6)**	-	**30(13.7)**	-
Gestational* age at delivery, wk	**39.08±2.32 24-42**	**36.67±1.37 35-38**	**0.012**	**39.27±1.26 38-42**	**0.146**	**39.35±1.48 34-42**	**35.2±2.62 32-39**	**0.0001**	**38.25±1.44 36-41**	**0.0002**
Birth* weight, kg	**3.24±0.53 1.3-4.6**	**2.77±0.45 2.3-3.3**	**0.033**	**3.37±0.55 2.3-4.5**	**0.321**	**3.15±0.37 2.1-4.5**	**2.5±0.98 1.6-4.1**	**0.0001**	**3.32±0.76 2.8-5.0**	**0.0545**

Risk reduction for admission into the SCBU was significantly lower in the intervention group compared to the controls, (0.9% in calcium group and 5.5% in control group, RR-0.164 (95% CI: 0.04-0.72) (Table 5)
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Table 5: Perinatal Outcomes

Outcome	Calcium n=233	Control n=219	Relative risk	95%CI	P Value
Birth weight(kg)*	3.2±0.6	3.1±0.5			0.055
<2.5kg**	12(5.2)	12(5.5)	0.94	0.43-2.06	0.882
≥2.5kg**	221(94.8)	207(94.5)	1.002	0.86-1.15	0.979
IUGR**	4(0.02)	1(0.005)	1.26	0.63-3.15	0.373
Apgar score <7 at 1min*$	18(9.9)	16(10.3)	0.968	0.51-1.84	0.920
Apgar score <7 at 5min*$	4(2.2)	4(2.6)	0.860	0.22-3.38	0.829
Admission into SCBU**	2(0.9)	12(5.5)	0.164	0.04-0.72	0.006
Still birth **	4((1.5)	8(3.7)	0.479	0.15-1.5	0.213
Early Neonatal deaths **	4(1.7)	6(2.7)	0.633	0.18-2.2	0.470

*Values as mean (SD); **Values as number (%); $total for calcium=182, total for control=156;
SCBU- Special Care Baby Unit

There were 22 perinatal deaths. Eight were in the intervention and 14 in the control group. Only 2 cases in each group were associated with a hypertensive disorder of pregnancy (severe preeclampsia). Two cases of still birth were due to intrauterine fetal death of unknown etiology prior to term and two others were due to placental abruption in normotensive women. The remaining 14 cases (10 Early Neonatal Death and 4 stillbirths) were due to severe birth asphyxia following complications of labour and these were seen mostly in those who delivered elsewhere.

Discussion

The study demonstrated that supplementation with 1.2g calcium given daily to primigravidae from 16 weeks gestation was associated with a reduced risk of pregnancy induced hypertension (PIH) by 44%. This result is comparable to findings from a meta-analysis of studies from only developing countries that showed calcium supplementation during pregnancy was associated with a significant reduction of 45% in risk of pregnancy induced hypertension [RR- 0.55; 95 % confidence interval (CI) 0.36-0.85][6]. This benefit however was seen in the development of preeclampsia.
The incidence of preeclampsia in this study was unaffected by the administration of calcium supplementation. This finding was not consistent with such outcome measure in two previous studies with similar methods[11,12]. An Australian study[11] administered 1.8g of calcium to 456 nulliparous women from 20 weeks while another study carried out in India[12] administered 2g of calcium to 552 primigravidae from 12-25 weeks. Even though these aforementioned trials were carried out in populations with high and low baseline calcium intakes respectively, they found that calcium supplementation significantly reduced the risk of pre-eclampsia. While the Indian study did not analyze for PIH, the Australian study reported that there was no effect on the incidence of PIH, contrary to our finding. The reduction in the risk of preeclampsia by calcium supplementation of at least 1g was further corroborated by findings from a systematic review in the Cochrane database[5] Among the women who developed PIH in this study, calcium supplementation was associated with improved duration of pregnancy as development of PIH was of late onset. A possible explanation for this pattern observed may be based on the hypothesis that early and late onset preeclampsia are two disease entities that might develop from divergent hemodynamics (low cardiac output(CO)-high total vascular resistance(TVR) for early, and high CO-low TVR for late PE)80. This could be linked to the mode of action of calcium supplementation which reduces smooth muscle contractility[13]. On the other hand, it could be that the finding is reflective of reports of some Nigerian studies which reported that late onset pregnancy induced hypertension accounts for most cases of hypertension in pregnancy and that early onset cases (presenting at or before 32 completed weeks of gestation) are relatively rare compared to Caucasian populations[14, 15].
It has also been suggested that calcium supplementation might also reduce the incidence of preterm deliveries, cesarean deliveries, births of infants small for their gestational ages, and perinatal deaths[16]. These beneficial consequences would be due in part to the prevention of preeclampsia and pregnancy induced

hypertension but could theoretically also result from direct effects of calcium on uterine smooth muscle to reduce contractility and prevent preterm labor[17]. In our study however, there were no differences seen in the rate of preterm delivery, low birth weight babies or perinatal death. Possible reasons for this outcome may have been the fact that the sample size was not large enough to produce effects with a low incidence rates but this may not hold true as similar results were obtained in the large trials carried out by WHO[18] and Belizan[19]. Paradoxically, positive results were obtained in the studies in India[12] and Austrailia[11]. These studies recruited 552 and 456 women respectively and found a significant risk reduction in preterm delivery by as much as 44.9% and 56% respectively. The low rates of adverse perinatal outcome which was not influenced by calcium supplementation may also be partly explained by the fact that late-onset PE (after 34 weeks) is mostly associated with normal or slight increased uterine resistance index, a low rate of fetal involvement, and more favorable perinatal outcomes[20].

The "non blinded" nature of the study due to the unavailability of placebo tablets is a possible limitation as this could have introduced some element of bias in favour of the intervention group. This was however overcome by ensuring uniformity in baseline characteristics which was achieved by recruitment of healthy nulliparous women prior to 16weeks gestation. This methodology was characteristic of various trial[11,12,18,19].

Regarding the implications for current pregnancy care, the findings of this study, together with the recommendation by WHO provide support for a policy of offering calcium supplementation to all nulliparous women during pregnancy. From the updated systematic review data using the baseline risk of hypertension and preeclampsia, the number of women needed to treat to prevent 1 woman from experiencing hypertension is 24 (95% CI 16-46) and to prevent preeclampsia 42 (95% CI 30-71) 5. This is similar to 16 and 50 obtained from this study respectively.

Conclusion

In conclusion, daily supplementation with 1.2 grams of calcium during pregnancy significantly reduced the risk of pregnancy induced hypertension in nulliparous women living in our environment. The treatment did not result in significantly improved obstetric and neonatal outcomes. Further large, well designed, and appropriately funded trials are needed to clarify the impact of calcium supplementation on major maternal and fetal morbidity and mortality, especially in developing countries.

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