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Role of Calcium Supplementation on Pregnancy Induced Hypertension Outcomes

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Abstract

Background: Pregnancy induced hypertension (PIH), is an important cause of both maternal and perinatal morbidity and mortality. Low dietary calcium (Ca) intake represents a factor associated with an increased incidence of hypertensive disease in general and in pregnant population in most low and middle income countries. Ca supplementation has the potential to reduce adverse gestational outcomes of PIH.

Aim: To assess the effects of low-dose Ca supplementation on PIH outcomes.

Method: A single- blind, randomized controlled trial was conducted in January through March, 2021. A total number of 66 pregnant women with PIH at their 20th week of gestation attended maternal care outpatient in Baghdad Medical City were assigned randomly in two groups those received Ca supplementation 500 mg/day vs none and follow up both groups till delivery for outcomes.

Results: A significant reduction in diastolic blood pressure mean (93.28 mmHg vs. 88.62 mmHg, P= 0.015) and almost significant reduction in systolic blood pressure mean (149.65 mmHg vs. 142.58 mmHg, P= 0.051) in the participants after receiving Ca supplements. Pre eclampcia (10.3% vs. 45.9%, P = 0.002), Low birth weight (6.9% vs. 40.5%, P = 0.002), Pre term delivery (10.3% vs. 43.2%, P=0.003), and admissions to neonatal intensive care unit (10.3% vs. 45.9%, P = 0.002) were significantly lower in the intervention group.

Conclusion: Ca supplementation of 500 mg daily started at 20th week of gestation associated with reduction of maternal blood pressure, pre-eclampcia, preterm delivery, low birth weight and admission to neonatal intensive care unit especially in a low dietary Ca intake mothers.

Keywords: Calcium supplementation; pre-eclampcia; preterm; low birth weight.

Introduction

Pregnancy induced hypertension (PIH), is a form of high blood pressure in pregnancy, characterized by systolic blood pressure (sBP) ≥140 mmHg or diastolic blood pressure (dBP) ≥90 mmHg,[1] an important cause of both maternal and perinatal morbidity and

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mortality,[2-3] complicated 6 to 10% of pregnancies,[4] responsible for approximately 14% of global maternal deaths.[5] Although overall maternal mortality has been decreased, the percentage of maternal deaths resulting from hypertension has remained stagnant.[6] Low dietary calcium (Ca) intake represents a factor associated with an increased incidence of hypertensive disease in general population,[7,8] and with hypertensive pregnancy disorders in most low and middle income countries (LMIC).[9,10] Ca supplementation has the potential to reduce adverse gestational outcomes, by decreasing the risk of developing hypertensive disorders during pregnancy, which have been associated with low birth weight (LBW), preterm delivery and maternal mortality.[11,12]

Pregnancy is a state of high Ca demand, as ~ 30g of it is transferred to the fetus during gestation.[13] Although intestinal Ca absorption normally increases during pregnancy and there is no need for additional intake to supply sufficient Ca to the fetus, but such increase in the absorption is directly related to maternal Ca intake.[14]

Recommended dietary allowance of Ca for pregnant women established by Food and Nutrition Board is 1300 – 1000 mg/day depending on age. Ca intake could be a useful indicator of status at the population level. Serum Ca concentrations are maintained within narrow limits in the body and thus have limited use for assessment of Ca nutritional status at both individual and population levels.[15]

Several Ca salt formulations are recently available in a variety of doses. Ca carbonate is cheaper, provides 40% elemental Ca, better absorbed, well tolerated especially when taken with a meal and the very cost-effective choice in most settings. The percentage absorbed influenced by Ca dose; as the Ca content of the dose increases, the fractional absorption of Ca decreases. Doses of ≤ 500 mg per administration are recommended for the best absorption.[15-16] This implies that the World Health Organization (WHO) recommendations of 1.5 to 2 gm will involve ≥ 3 pill-taking events daily. Moreover there is a concern that Ca might interfere with iron-folic acid (IFA) absorption and the mother should not take Ca tablets with them. [17] Research on other drugs and supplements has found that adherence decreases as the number of pill-taking events increases.[18] It is likely that the benefits of a feasible lower-dose regimen may be greater than a higher-dose regimen with low uptake and adherence.[19]

Aim of the study:

To assess the effects of low-dose Ca supplementation on both maternal and fetal outcomes of PIH.

Patients and method:

A single- blind, randomized controlled trial (RCT) was conducted from January through March, 2021. A total number of 66 pregnant women with PIH attended maternal care outpatient in Baghdad Medical City were involved and assigned randomly in two groups, 29 of them were received Ca carbonate supplements of 500 mg (elemental Ca) once daily from the start of their 20th week of gestation till delivery, and the other 37 were receive nothing, follow up both groups for the outcomes, compliance with Ca intake were assessed by counting the remaining tablets, Contact was maintained by telephone calls.

Exclusion criteria:

Women weren't eligible for the trial if they were already taking Ca supplementation before 20th week of gestation; had chronic hypertension or other medical conditions; had a history or symptoms of urolithiasis, renal disease or parathyroid disease; and those with known hazardous condition (multifetal gestation or hydatidiform mole); were not on antihypertensive medication; were adequately intake of dietary Ca or were unwilling to enroll in the trial.

Ca supplementation was the primary exposure variable. Women were instructed to take one Ca tablet (500 mg) daily in the evening with dinner meal separately from IFA until pregnancy termination and were encouraged not to take any additional Ca supplements as analgesic or antiacid or pregnancy multivitamins that contain Ca.

The maternal outcomes assessed were blood pressure (BP), pre-eclampcia (PE), eclampsia (E) and admission to maternal intensive care unit (MICU). While **the neonatal outcomes** assessed were LBW, preterm delivery, admission to neonatal intensive care unit (NICU) and perinatal mortality. The outcomes variables validated through cross-checking with medical professionals and their documentation in patient's card.

Statistical analysis and data management:

IBM SPSS version 26 was used for this study statistical analysis. Participants' non-parametric data were presented as frequencies, percentages and

diagrams. Independent samples t test was used to compare BP mean change between the two study groups. Paired sample t test was used to compare BP mean before and after Ca supplement period for both study groups. Chi square test was used to assess the association between Ca supplement and maternal and fetal outcomes (significant P-value < 0.05).

Results

Ca supplementation: About 44% of participants received Ca supplement and 56% of them didn't (Figure 1). **Socio-demographic characteristics of participants:** There was no significant difference between the intervention vs none groups regarding age, parity, body mass index, socioeconomic status and educational level.

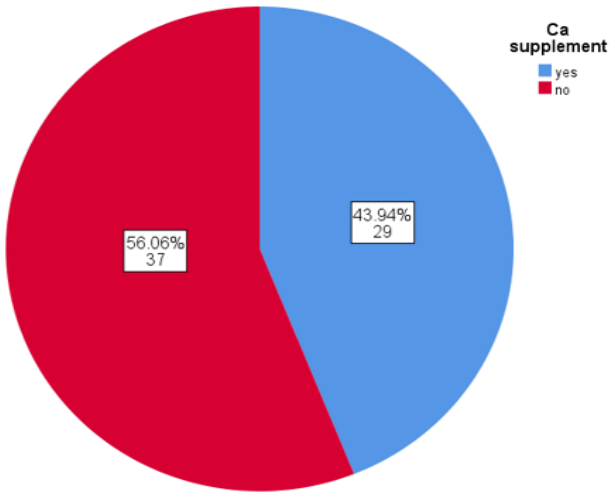

Figure 1: Distribution of study groups according to Ca supplement

Maternal BP: The dBP mean was significantly decreased and almost significant decrease in sBP mean in participants after receiving Ca supplementation (Table 1).

Table 1: Comparison of BP before and after Ca supplement

Diastolic BP (mmHg)	**Mean ±SD**		**Pre Ca**	**Post Ca**	**P value**
			Mean ±SD		
	Ca Supplement	Yes	93.28 ±4.28	88.62 ±8.75	0.015
		No	96.49 ±5.88	95.27 ±8.97	0.525
Systolic BP (mmHg)	Mean ±SD		Pre Ca	Post Ca	P value
			Mean ±SD		
	Ca Supplement	Yes	149.65±7.31	142.58±18.54	0.051
		No	153.64±14.27	154.45 ±14.32	0.808

Significant P-Value < 0.05

Maternal outcomes: PE was significantly lower in participants received Ca supplements (10.3% vs. 45.9%, *P = 0.002*). There was no **maternal death** in our study.

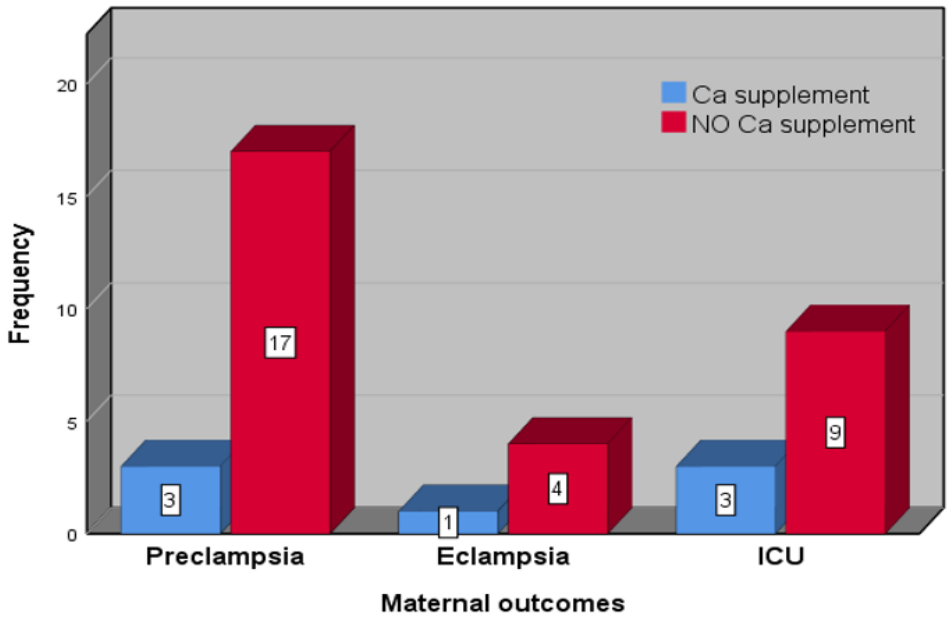

Figure 2: Distributions of study groups according to maternal outcomes

Fetal outcomes: LBW, Preterm delivery and admission to NICU were significantly lower in participants received Ca supplements (6.9% vs. 40.5%, *P =0.002)*, (10.3% vs. 43.2%, *P = 0.003*) and (10.3% vs. 45.9%, *P = 0.002*) respectively.

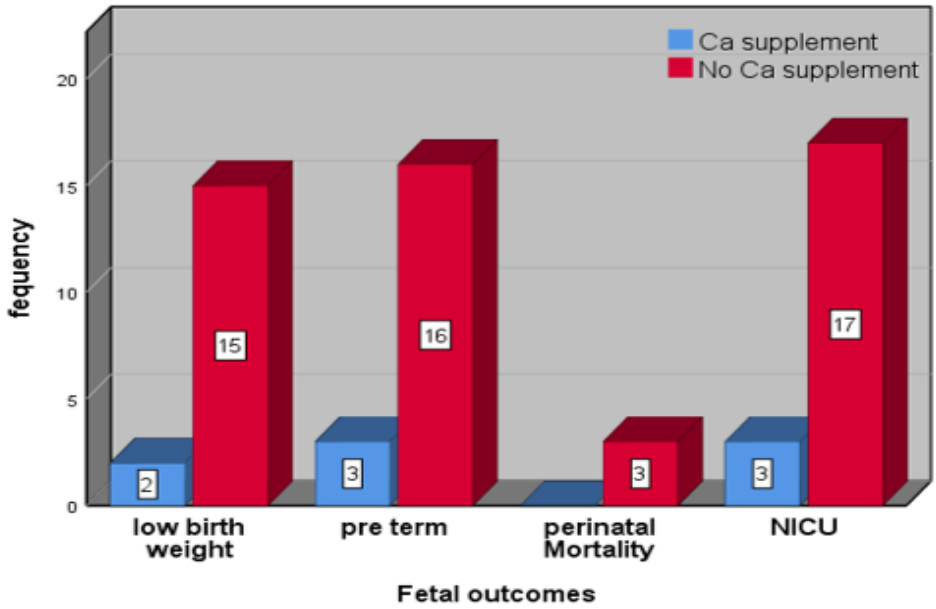

Figure 3: Distributions of study groups according to fetal outcomes.

Discussion

Daily supplementation of 1.5 to 2 gm of Ca during pregnancy reduces PIH outcomes. However, the efficacy of low-dose Ca supplementation on PIH is limited. We try to illustrate the effectiveness of use of low dose Ca supplement on both maternal and fetal outcomes.

In our study, there was significant decrease in dBP mean and almost significant decrease in sBP mean in participants after receiving Ca supplements. While there was non-significant decrease in dBP mean and non-significant increase in sBP mean in participants didn't receive Ca supplements. In Kumar et al. study the mean sBP and dBP were different significantly in the Ca and placebo group

(P = 0.007 and P = 0.02).[20] And WHO found that fewer women on Ca supplementation had high BP compared with those receiving placebo.[21] Fouzia et al. presented an absolute change in mean sBP and dBP from baseline to the last follow up visit, they observed a slower increase over time among those who consumed 500 mg/day Ca tablets, the slowness more obviously for those received Ca supplement for > 6 months during pregnancy than those consumed it for < 6 months.[22] On the other hand Goldberg et al. reported that no significant reduction in sBP (P = 0.3) or dBP (P = 0.8) between Ca compared with placebo after 1.5gm/day of Ca supplementation.[23]

PE was significantly lower in participants received Ca supplements. This is consistent with Imdad et al.[24] and Hofmeyr et al.[25] Pooled analysis where they show that Ca supplementation during pregnancy was associated with a significant reduction in the risk of pre-eclampsia. Although, imdad et al. showed that the effect was more statistically significant with 2 gm/day compared with < 2 gm/day.[24] While Hofmeyr et al. found a reduction in the risk of PE in both high and low dose of calcium supplementation.[25] WHO found that for all women, irrespective of the baseline risk of developing hypertension and Ca intake status, Ca supplementation more than halved the risk of PE when compared with a placebo.[4,21] Sun et al. found that Ca supplementation reduced incidence of PE and their sub-groups analysis showed that high, moderate and low-doses of Ca supplementation could reduce the risk.[26] While Wanchu et al. said that Ca supplementation didn't lower the incidence of PE, it did reduce its severity.[27] On the other hand, Trumbo et al. concluded that the relationship between Ca and risk of PIH and PE was highly unlikely.[28]

In present study there was no effect of Ca supplementation on incidence of E, similar to that founded by WHO[21] and Imdad et al.[24]

Also we found that Ca supplementation not affects MICU admission consistent with WHO[21] and Villar et al.[29] finding.

There was no maternal mortality in our study. Although Imdad et al.[24] and Villar et al.[29] reported that Ca supplemented women had a statistically significant lower risk for maternal mortality. While WHO found that Ca supplementation had no effect on risk of maternal death.[21]

About fetal outcomes; LBW was significantly lower in participants received Ca supplements. Similarly Imdad et al. showed a reduction of LBW by 15% and there was an extra gain of 85 gm following Ca supplementation; however the results were statistically non-significant.[24] Also Niromanesh et al. stated that infants born to the Ca group, on average, were 552 g heavier than infants born to the placebo group but the dose of Ca used was 2 gm/day.[30] On the other hand Pranom Buppasiri et al.[31] and WHO[21] found that there was no significant difference in LBW between two groups. However, Pranom Buppasiri et al found that compared to the control group, women in the Ca supplementation group gave birth to slightly heavier birth weight infants.

The preterm delivery was significantly lower in participant received Ca supplements. This is go with what Kumar et al.[20] found in their study, that the risk of preterm delivery was less in the Ca (7.0%) than in the placebo (12.7%) group. Imdad et al.[24] showed a significant reduction of 24% in the intervention group compared with the control group. While Hofmeyr et al.[25] found that the average risk was reduced in high dose of Ca supplements (≥ 1gm/day) but not in low dose (< 1 gm/day). WHO stated that there was no effect of Ca supplementation on preterm birth although a subgroup analysis by supplemental dose suggested that among pregnant women consuming ≥ 1.5 gm/day of Ca fewer babies were born before 37 weeks' gestation than among those receiving < 1.5 gm/day.[21]

We found that admission to NICU was significantly lower in participant received Ca supplements. This is consistent with Hofmeyr et al.[25] who noticed that supplementation with low dose of Ca reduced the risk of admission to NICU, while not affected by high dose supplementation. This finding is inconsistent with what WHO found.[21]

About the neonatal mortality, reduction in Ca supplemented group weren't statistically significant which is consistent with WHO[21] and Kumar et al.[20] who stated that there were no significant differences between two groups in risk of having a stillbirth or neonatal death before hospital discharge. Whereas Viller et al. found that the neonatal mortality rate was lower in the Ca group, but they use higher dose of Ca supplements (1.5 gm/day) than in our study.[29] Analysis in Mehnaz et al. has shown that Ca supplementation during pregnancy reduced stillbirths by 19 %; however results weren't statistically significant.[32]

Conclusion

The dilemma facing health policy-makers is often whether supplementation with a lower-dose would be better than no supplementation at all especially in LMIC. The findings of this trial are a step toward addressing this issue. Our trial demonstrated that maternal BP, pre eclampcia, LBW, preterm delivery and admission to NICU were significantly lower in participants received Ca carbonate supplements of 500 mg/day at 20th week of gestation. Other maternal and fetal adverse outcomes may be reduced when higher dose or earlier than 20th week are implemented and this should be considered when making decisions about the use of Ca supplementation during pregnancy, particularly for those with very low dietary Ca intake or high risk pregnancies. Further larger well designed RCTs are still required to clarify issues related to dose, timing, barrier, acceptability, adherence, feasibility, side effects and cost-effectiveness of full-scale implementation is urgently needed. Pending such results, in settings of low dietary Ca intake where high-dose supplementation is not feasible, the option of lower-dose supplements might be considered rather than no supplementation.

Conflict of interest: None.

Source of funding: None.

Ethical Considerations: Permission to conduct the study was obtained from health authorities. Oral consent was obtained from participants. Entering and leaving the study was completely voluntary and free of charge.

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