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Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

Calcium supplementation reduces the risk of hypertension and pre-eclampsia during pregnancy. Since calcium inhibits absorption of iron, calcium supplementation should be separated in time during the day from the recommended daily iron+folic acid supplementation.

RHL Commentary by Palacios C and Pena-Rosas JP

1. INTRODUCTION

Hypertension complicates approximately 10% of all pregnancies worldwide, and pre-eclampsia and eclampsia are major causes of maternal and perinatal morbidity and mortality (1). Currently, pre-eclampsia and gestational hypertension are considered either separate diseases affecting the same organs or different levels of severity of the same underlying disorder (2). Based on available estimates and case-fatality rates, each year up to 40 000 women, mostly in developing countries, die of hypertensive disorders (3). Pre-eclampsia and eclampsia complicate 2–8% of pregnancies and, overall, 10–15% of direct maternal deaths are associated with these conditions (1).

A recent systematic review which sought to determine the distribution of causes of maternal deaths found a wide regional variation (4). Hypertensive disorders were reported as the cause of 16.1% of maternal deaths in developed countries, 9.1% in Africa, 9.1% in Asia, and 25.7% in Latin America and the Caribbean (4).

Observational studies have found an inverse association between maternal calcium intake and hypertension disorders of pregnancy (5). Clinical trials have also confirmed that calcium supplementation reduces blood pressure and hypertension-related disorders (6). However, the effects of this intervention on other maternal outcomes and on the mothers' offspring is less clear. The present RHL commentary relates to the review by Hofmeyr et al (7), which assessed the effects of supplementation with 1 g or more of calcium per day on hypertensive disorders and other maternal and child outcomes in non-hypertensive pregnant women at less than 34 weeks of gestation.

2. METHODS OF THE REVIEW

Only randomized controlled trials were included and women with hypertensive disorders were excluded from the review. The authors identified trials through the Cochrane Pregnancy and Childbirth Group Trials Register, the Cochrane Central Register of Controlled Trials and, when required, contacted study authors. The outcomes evaluated in women were high blood pressure with or without proteinuria, maternal death or serious morbidity, placental abruption, caesarean section, proteinuria, severe pre-eclampsia, eclampsia, admission of the woman to an intensive care unit, maternal death, and mother's hospital stay ≥ 7 days. The infant outcomes included preterm birth, low birth weight, newborn small for gestational age, admission of the newborn to a neonatal intensive care unit, newborn in intensive care unit ≥ 7 days, and stillbirth or death before discharge from the hospital. The primary outcomes were high blood pressure, pre-eclampsia, preterm birth, admission to neonatal intensive care unit, and stillbirth or neonatal death. Eligibility of trials for inclusion and trial quality were assessed by the authors.

Subgroup analyses were used to evaluate the outcomes by: (i) risk of hypertensive disorders [low- or average-risk (unselected) or high-risk (teenagers, history of pre-eclampsia, increased sensitivity to angiotensin II, or pre-existing hypertension)]; and (ii) baseline calcium intake in the women or in the study populations from which the women were recruited. Low dietary calcium intake was defined by individual authors as a mean population intake of < 900 mg/day. Adequate calcium intake was defined by individual authors as mean population intake of ≥ 900 mg a day. It is noteworthy that classification of dietary calcium intake was mostly based on surveys of populations or participating centres rather than of the women who were studied.

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3. RESULTS OF THE REVIEW

Twelve randomized controlled trials with 15 528 women were included in the review. Most studies assessed only nulliparous or primiparous women and women at low risk of hypertensive disorders.

Data from 11 trials involving 14 946 women suggest that women who had taken calcium supplementation (>1 g/day) during pregnancy were less likely to get high blood pressure (with or without proteinuria) compared with those who had taken a placebo [relative risk (RR) 0.70; 95% confidence interval (CI) 0.57–0.86]. The reduction in the RR appeared to be greatest for women at high risk of developing pre-eclampsia (RR 0.47; 95% CI 0.22–0.97) and for those with low baseline dietary calcium (RR 0.47; 95% CI 0.29–0.76). Similarly, data from 12 trials involving 15 206 women suggest that women who had taken calcium supplementation (>1 g/day) during pregnancy were half as likely to get pre-eclampsia than those who had taken a placebo (RR 0.48; 95% CI 0.33–0.69). This reduction was greatest for women considered at high risk of pre-eclampsia (RR 0.22; 95% CI 0.12–0.42) and in those with low baseline dietary calcium intake (RR 0.36; 95% CI 0.18–0.70). However, heterogeneity between the treatment effects was substantial (I^2 was greater than zero and either I^2 was greater than 30% or the P-value was < 0.10 in the Chi² test for heterogeneity). Therefore, the results should be interpreted with caution.

Data from four trials involving 9732 women suggest that women who had taken calcium supplementation (>1 g/day) during pregnancy were less likely to have a composite-outcome maternal death or serious morbidity compared with those who had taken a placebo (RR 0.80; 95% CI 0.65–0.97).

There was no evidence of a significant difference between women receiving calcium supplementation (>1 g/day) and women receiving a placebo with regard to the following outcomes: placental abruption, caesarean section, proteinuria, severe pre-eclampsia, eclampsia, admission of the woman to an intensive care unit, maternal death, mother's hospital stay ≥ 7 days, preterm birth, low birth weight, small for gestational age newborn, admission to neonatal intensive care unit, newborn in intensive care unit ≥ 7 days, and stillbirth or death before discharge from hospital.

Heterogeneity in the outcome classification systems needs to be considered in interpreting these results. This includes, but is not limited to, the lack of standardization in the relationship between the different components of definitions of outcomes and the risk of short- and long-term adverse outcomes, the effect of training of individual health-care workers on the accuracy of blood pressure measurements in pregnant women, the different instruments used for measuring blood pressure, the different blood pressure measurements and proteinuria tests used in diagnosis and screening, and validity of the baseline calcium intake in the populations (3). Moreover, the tests and measurements taken in the process of conduct of research may not be feasible in routine practice in under-resourced settings, thus these results require operational research for implementation in real-life situations. In the present review, authors associated the heterogeneity with the study size, as small studies had most positive results. These studies included high risk women; therefore, the heterogeneity may be explained by calcium having a greater effect on high risk women.

Although the review authors used a careful and detailed methodology, they did not take into account the physiological processes taking place; the trials included in the review did not adjust for gestational age at the start of supplementation—some trials started supplementation before week 20 and others not until week 27—highlighting the need for a subgroup analysis for the different outcomes by time of exposure to the calcium supplement.

4. DISCUSSION

4.1 APPLICABILITY OF THE RESULTS

This review authors conclude that calcium supplementation reduces the risk of hypertension and pre-eclampsia during pregnancy. However, to determine whether this finding is applicable this to low- to middle-income countries several factors need to be considered. One issue is the bioavailability of calcium from supplements, which depends on whether the supplements are consumed with food, whether the supplement are soluble and size of the dose. Calcium citrate malate has shown to have greater bioavailability compared to other forms and can be consumed on an empty stomach and still be sufficiently absorbed. However, this seems not to be the case with other compounds (8). Doses >500 mg/day are less efficiently absorbed compared to lower doses (8). Calcium also interacts with iron, zinc, magnesium and phosphorus, all of which are important micronutrients needed during pregnancy (9). Calcium inhibits iron absorption in a dose-dependent and dose-saturable fashion, which suggests that calcium supplementation should be separated in time during the day from the recommended daily iron+folic acid supplementation, when used. Calcium concentration in multiple vitamin and mineral supplements for pregnancy is much lower than the amounts used in the trials in this review for the purposes of reducing the risk of hypertensive disorders. In fact, the WHO/UNICEF/UNU multiple micronutrient supplement does not contain calcium.

Studies have not reported adverse effects of calcium supplementation, and this intervention is considered relatively safe. Women with low habitual calcium intake appeared to benefit more from the supplementation. Thus, the findings of this review are applicable to under-resourced settings.

4.2 IMPLEMENTATION OF THE INTERVENTION

The provision of calcium supplementation to all pregnant women can pose major challenges, especially in under-resourced settings (3), as programme managers and policy-makers will have to plan for procurement of the preparation, storage, distribution, quality-control, and compliance assurance with daily supplements for large numbers of pregnant women. Cultural, financial, and educational barriers to changing policy and practice from iron+folic acid supplementation schemes will also need to be evaluated prior to the implementation of this intervention. Failures in implementation of this intervention have been attributed in many instances to inadequate infrastructure and poor compliance, particularly in developing countries (10). Updating current guidelines would require not only assessment of the evidence, but also contextualization of the recommendation, both in terms of feasibility and cost-effectiveness. It has been proposed recently that pregnancy-induced hypertension is the result of altered implantation (11). If this is true, then calcium supplementation would need to start peri-conceptionally, or at least during the first trimester.

Increasing dietary calcium intake may seem to be an easier intervention than calcium supplementation, although availability of dairy products in many countries may not be sufficient to fulfil the need. Alternatively, targeted food fortification with calcium may be a feasible intervention, especially for high-risk women, who may not be targeted for individual calcium supplementation because they do not come for antenatal care services. However, the effects of these interventions have not been evaluated.

4.3 IMPLICATIONS FOR RESEARCH

The effects of calcium supplementation on iron, magnesium, and zinc nutrition should be studied further. Also, operational research to guide the delivery platforms, regimens and programmatic aspect of the intervention need to be prioritized. Further, in view of the differences in calcium intake from animal and vegetable sources, and from supplements or fortified foods, a more specific characterization of pregnant women's calcium intake may be useful to identify priority groups in different settings. Future research should compare countries with calcium intake from dairy products with those where calcium is mostly taken in from vegetarian sources (Northern Europe and Central America could be good models). Given the large variations in calcium recommendations in different countries an internationally accepted value would be needed to calculate adequacy uniformly.

Lastly, more research is needed to understand better the changes in blood pressure throughout pregnancy, with longitudinal studies starting before pregnancy occurs. Studies should follow childhood hypertension in order to study whether fetal exposure to maternal hypertension or to calcium supplementation have long-term effects and whether those effects can be overcome with this intervention.

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