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[Intervention Review]

Calcium supplementation commencing before or early in pregnancy, or food fortification with calcium, for preventing hypertensive disorders of pregnancy

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ABSTRACT

Background

Pre-eclampsia is considerably more prevalent in low- than high-income countries. One possible explanation for this discrepancy is dietary differences, particularly calcium deficiency. Calcium supplementation in the second half of pregnancy reduces the serious consequences of pre-eclampsia and is recommended by the World Health Organization (WHO) for women with low dietary calcium intake, but has limited effect on the overall risk of pre-eclampsia. It is important to establish whether calcium supplementation before and in early pregnancy has added benefit. Such evidence would be justification for population-level fortification of staple foods with calcium.

Objectives

To determine the effect of calcium supplementation or food fortification with calcium, commenced before or early in pregnancy and continued at least until mid-pregnancy, on pre-eclampsia and other hypertensive disorders, maternal morbidity and mortality, as well as fetal and neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Trials Register (10 August 2017), PubMed (29 June 2017), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (10 August 2017) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials of calcium supplementation or food fortification which include women of child bearing age not yet pregnant, or in early pregnancy. Cluster-RCTs, quasi-RCTs and trials published in abstract form only would have been eligible for inclusion in this review but none were identified. Cross-over designs are not appropriate for this intervention.

The scope of this review is to consider interventions including calcium supplementation with or without additional supplements or treatments, compared with placebo or no intervention.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

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Main results

This review is based on one RCT (involving 60 women) which looked at calcium plus additional supplements versus control. The women (who had low antioxidant status) were in the early stages of pregnancy. We did not identify any studies where supplementation commenced pre-pregnancy. Another RCT comparing calcium versus placebo is ongoing but not yet complete. We did not identify any studies looking at any of our other planned comparisons.

Calcium plus antioxidants and other supplements versus placebo

We included one small study (involving 60 women with low antioxidant levels) which was conducted in an academic hospital in Indonesia. The study was at low risk of bias for all domains with the exception of selective reporting, for which it was unclear. Women in the intervention group received calcium (800 mg) plus N-acetylcysteine (200 mg), Cu (2 mg), Zn (15 mg), Mn (0.5 mg) and selenium (100 mcg) and vitamins A (1000 IU), B6 (2.2 mg), B12 (2.2 mcg), C (200 mg), and E (400 IU) versus the placebo control group of women who received similar looking tablets containing iron and folic acid. Both groups received iron (30 mg) and folic acid (400 mcg). Tablets were taken twice daily from eight to 12 weeks of gestation and then throughout pregnancy.

The included study found that calcium supplementation plus antioxidants and other supplements may slightly reduce **pre-eclampsia (gestational hypertension and proteinuria)** (risk ratio (RR) 0.24, 95% confidence interval (CI) 0.06 to 1.01; *low-quality evidence*), but this is uncertain due to wide confidence intervals just crossing the line of no effect, and small sample size. It appears that **early pregnancy loss before 20 weeks' gestation** (RR 0.06, 95% CI 0.00 to 1.04; *moderate-quality evidence*) may be slightly reduced by calcium plus antioxidants and other supplements, but this outcome also has wide confidence intervals, which just cross the line of no effect. Very few events were reported under the composite outcome, **severe maternal morbidity and mortality index** and no clear difference was seen between groups (RR 0.36, 95% CI 0.04 to 3.23; *low-quality evidence*). However, the included study observed a reduction in the composite outcome **pre-eclampsia and/or pregnancy loss at any gestational age** (RR 0.13, 95% CI 0.03 to 0.50; *moderate-quality evidence*), and **pregnancy loss/stillbirth at any gestational age** (RR 0.06, 95% CI 0.00 to 0.92; *moderate-quality evidence*) in the calcium plus antioxidant/supplement group.

Other outcomes reported (**placental abruption, severe pre-eclampsia and preterm birth (less than 37 weeks' gestation)**) were too infrequent for meaningful analysis. No data were reported for the outcomes caesarean section, birthweight < 2500 g, Apgar score less than seven at five minutes, death or admission to neonatal intensive care unit (ICU), or pregnancy loss, stillbirth or neonatal death before discharge from hospital.

Authors' conclusions

The results of this review are based on one small study in which the calcium intervention group also received antioxidants and other supplements. Therefore, we are uncertain whether any of the effects observed in the study were due to calcium supplementation or not. The evidence in this review was graded low to moderate due to imprecision. There is insufficient evidence on the effectiveness or otherwise of pre- or early-pregnancy calcium supplementation, or food fortification for preventing hypertensive disorders of pregnancy.

Further research is needed to determine whether pre- or early-pregnancy supplementation, or food fortification with calcium is associated with a reduction in adverse pregnancy outcomes such as pre-eclampsia and pregnancy loss. Such studies should be adequately powered, limited to calcium supplementation, placebo-controlled, and include relevant outcomes such as those chosen for this review.

There is one ongoing study of calcium supplementation alone versus placebo and this may provide additional evidence in future updates.

PLAIN LANGUAGE SUMMARY

Extra calcium in food or tablets before pregnancy, or in early pregnancy, for preventing high blood pressure complications of pregnancy

What is the issue?

This review's aim is to find out whether calcium supplementation or food fortification with calcium taken before or early in pregnancy and continued at least until mid-pregnancy, will reduce the number of women developing pre-eclampsia, high blood pressure, other serious health problems and death, as well as fetal and neonatal outcomes.

Why is this important?

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Women can develop high blood pressure with protein in the urine after the 20th week of pregnancy, known as pre-eclampsia. Many women, particularly those in low-income countries, do not have enough calcium in their diets. Giving these women extra calcium during the second half of pregnancy has been shown to reduce their risk of serious consequences from developing high blood pressure and protein in the urine, such as convulsions (eclampsia), stroke, clotting disorders, fluid in the lungs, kidney failure and death. Taking extra calcium in the second half of pregnancy does not however appear to greatly reduce the number of women developing pre-eclampsia. It is important to know if taking extra calcium before pregnancy and in early pregnancy can reduce the number of women who develop blood pressure complications.

We searched for randomised controlled studies that looked at the effect of giving women extra calcium before or early in pregnancy on the number of women who developed pre-eclampsia.

What evidence did we find?

We searched the medical literature on 29 June 2017 and 10 August 2017 and found one randomised controlled study. Women with low antioxidant levels were given calcium, antioxidants and other supplements, starting within the first 12 weeks of pregnancy, or a dummy tablet. The tablets for both groups contained folic acid and iron supplements. Only 60 women took part in this study and the study was carried out in a hospital in Indonesia.

Women taking calcium plus antioxidants and other supplements were at reduced risk of experiencing pre-eclampsia, miscarriage or stillbirth when measured together compared with the women in the control group. For women taking the calcium supplement, miscarriage or stillbirth at any stage of pregnancy was also reduced (moderate-quality evidence). It is possible that pre-eclampsia alone (low-quality evidence), and early pregnancy losses before 20 weeks, might be reduced for women taking calcium plus antioxidants but we cannot be sure of this. Calcium supplementation did not make a clear difference to the number of women who developed severe pre-eclampsia or had a placental abruption - very few women developed these issues (low-quality evidence). Other outcomes were infrequent or not reported.

What does this mean?

The women who received calcium also received antioxidants and other supplements. This means that we cannot be certain that the reduction in pre-eclampsia and miscarriage or stillbirth, or any of the other results, were due to calcium or not. More research is needed to confirm this, and whether or not calcium reduces other outcomes such as preterm birth, caesarean section, low birthweight babies, and stillbirth or neonatal death before discharge from hospital. Only 60 women were involved in the included study so the quality of the evidence is not high, and future studies would need to be large enough to produce results that are more certain.

One trial of calcium supplementation given before pregnancy is currently underway but not yet complete.