Calcium supplementation to prevent pre-eclampsia — a systematic review

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Background. Calcium supplementation during pregnancy may prevent high blood pressure and preterm labour.

Objective. To assess the effects of calcium supplementation during pregnancy on hypertensive disorders of pregnancy and related maternal and child adverse outcomes.

Design. A systematic review of randomised trials that compared supplementation with at least 1 g calcium daily during pregnancy with placebo.

Search strategy. The Cochrane Pregnancy and Childbirth Group trials register (October 2001) and the Cochrane Controlled Trials Register (Issue 3, 2001) were searched and study authors were contacted.

Data collection and analysis. Eligibility and trial quality were assessed. Data were extracted and analysed.

Main results. There was a modest reduction in the risk of pre-eclampsia with calcium supplementation (relative risk (RR) 0.68, 95% confidence interval (CI): 0.57- 0.81). The effect was greatest for women at high risk of hypertension (RR 0.21, 95% CI: 0.11 - 0.39) and those with low baseline calcium intake (RR 0.32, 95% CI: 0.21 - 0.49). There was no overall effect on the risk of preterm delivery, although there was a reduction in risk among women at high risk of hypertension (RR 0.42, 95% CI: 0.23 - 0.78). There was no evidence of any effect of calcium supplementation on stillbirth or death before discharge from hospital. There were fewer babies with birthweight < 2 500 g (RR 0.83, 95% CI: 0.71 - 0.98). In one study, childhood systolic blood pressure > 95th percentile was reduced (RR 0.59, 95% CI: 0.39 - 0.91).

Conclusions. Calcium supplementation appears to be beneficial for women at high risk of gestational hypertension and in communities with low dietary calcium intake. These benefits were confined to several rather small trials, and were not found in the largest trial to date, conducted in a low-risk population. Further research is required.

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High blood pressure (BP) with or without proteinuria are major causes of maternal death and morbidity worldwide,[1,2] and of perinatal morbidity and mortality. Preterm birth, a common association with hypertensive disorders, is the leading cause of early neonatal death and infant mortality, particularly in low-income countries.[3] For these reasons, strategies to reduce the risk of hypertensive disorders of pregnancy have received considerable attention.[4-7]

During early pregnancy BP normally falls, climbing slowly in later pregnancy to reach pre-pregnancy levels at term.[8] These normal changes in BP make the diagnosis of hypertension during pregnancy difficult. A widely accepted definition for hypertension is a diastolic BP (DBP) equal to or greater than 90 mmHg before the onset of labour, or an increase in systolic BP (SBP) of 30 mmHg or more or DBP of 15 mmHg or more. Significant proteinuria is commonly defined as 2+ by dipstick testing, equal to or greater than 300 mg per 24 hours, or equal to or greater than 500 mg per litre. Hypertension and significant proteinuria occurring for the first time in the second half of pregnancy usually indicate the presence of pre-eclampsia.

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980.[9] This was based on the observation that Mayan Indians in Guatemala, who traditionally soak their corn in lime before cooking, had a high calcium intake and a low incidence of pre-eclampsia and eclampsia. A very low prevalence of pre-eclampsia had been reported from Ethiopia where the diet, among other features, contained high levels of calcium.[10] These observations were supported by other epidemiological and clinical studies, [11-14] and led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high BP and pre-eclampsia among women with low calcium intake.

Low calcium intake may cause high BP by stimulating either parathyroid hormone or renin release, thereby increasing intracellular calcium in vascular smooth muscle,[12] leading to vasoconstriction. A possible mode of action for calcium supplementation is that it reduces parathyroid release and

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intracellular calcium, and so reduces vascular smooth-muscle contractility. By a similar mechanism, calcium supplementation could also reduce uterine smooth-muscle contractility and prevent preterm labour and delivery.[15] Calcium might also have an indirect effect on smooth-muscle function by increasing magnesium levels.[16]

Calcium supplementation is attractive as a potential intervention to reduce the risk of women developing pre-eclampsia. It is relatively cheap and readily available. Also, it is likely to be safe for the woman and her child, although this safety would need to be clearly demonstrated in pregnant women before any attempt at widespread introduction into clinical practice.

This hypothesis was tested in several randomised trials commencing in the late 1980s which suggested a promising beneficial effect for calcium supplementation. The first systematic reviews highlighted the need for larger trials to assess the effects on important clinical outcomes in addition to pre-eclampsia and preterm delivery, such as perinatal mortality.[4,17] A more recent systematic review[5] came to more enthusiastic conclusions, but this optimism was not confirmed by a large trial in the USA.[18]

Objective

The objective of this systematic review was to determine, from the best available evidence, the effect of calcium supplementation during pregnancy on the risk of high BP and related maternal and fetal/neonatal adverse outcomes.

Subgroup analyses were used to test whether these effects were influenced by a low/average or high risk of hypertensive disorders and by a low or adequate dietary calcium intake before trial entry.

Criteria for considering studies

The Cochrane Pregnancy and Childbirth Group's Specialised Register of Controlled Trials and the Cochrane Controlled Trials Register were searched to identify all published, unpublished and ongoing trials with random allocation to calcium supplementation during pregnancy versus placebo. The Group searches MEDLINE and the Cochrane Controlled Trials Register on a regular basis and reviews the contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service. Relevant conference proceedings are hand searched. There are no language limitations. Trials with no placebo and quasi-random trials were excluded. Trials included were those that demonstrated an intended supplementation of at least 1 g of calcium per day from, at the latest, 34 weeks of pregnancy compared with placebo treatment.

The participants were pregnant women, regardless of the risk of hypertensive disorders of pregnancy. Women being treated for hypertensive disorders of pregnancy were excluded.

Prespecified subgroups were compared as follows: (*i*) women at low or average risk of hypertensive disorders of pregnancy (unselected); (*ii*) women at above-average risk of hypertensive disorders of pregnancy (this included women selected by the trial authors on the basis of an increased risk of hypertensive disorders of pregnancy, e.g. teenagers, women with previous pre-eclampsia, those with an increased sensitivity to angiotensin II and with pre-existing hypertension); (*iii*) women or populations with a low baseline dietary calcium intake (as defined by trial authors, or if not defined, a mean intake of < 900 mg per day); and (*iv*) women or populations with adequate dietary calcium intake (as defined by trial authors, or if not defined, a mean intake equal to or greater than 900 mg per day).

The primary outcome measures were prespecified clinical measures as follows: For women: (*i*) high BP as defined by trial authors, with or without proteinuria (pre-eclampsia plus non-proteinuric hypertension); and (*ii*) high BP with significant proteinuria, as defined by trial authors (pre-eclampsia); and for children: (*i*) preterm delivery (delivery before 37 weeks of estimated gestation); (*ii*) birth weight < 2 500 g; (*iii*) admission to a neonatal intensive care unit (NICU); and (*iv*) stillbirth or death before discharge from hospital.

Eleven studies met the prestated criteria for inclusion.[14,15,18,19,20-26] All were well-designed, double-blind, placebo-controlled trials. The methodological quality appears sound but the possibility of reporting bias must be kept in mind for those outcomes with unreported data from some trials. In Lopez-Jaramillo *et al.*[22] a large discrepancy in numbers allocated to each group is not accounted for. In some trials individual denominators were not given for specific outcomes. Where it was clear that the outcomes were not measured in the entire group, the denominators were adjusted accordingly. When necessary, trial authors were contacted for additional information.

Methods

Data were extracted from the trial reports and checked.

Descriptive data included authors, year of publication, country, timespan of the trial, maternal age, parity, type of placebo, baseline dietary calcium intake, type, dose, onset and duration of calcium supplementation, compliance, co-interventions, trial quality assessments, and number randomised and analysed.

Categorical data were compared using relative risks (RRs) and 95% confidence intervals (CIs). Statistical heterogeneity between trials was tested using the chi-squared test with *N* (number of trials contributing data) minus 1 degree of freedom. In the absence of significant heterogeneity ($p > 0.10$) data were pooled using a fixed effects model. If heterogeneity was

present, a random effects model was used.

For continuous data, pooled estimates of effect size were calculated from a weighted average, with weight based on the inverse of the variance.[27]

Results

High BP with or without proteinuria

Overall there is less high BP with calcium supplementation (10 trials, 6 634 women, RR 0.81, 95% CI: 0.74 - 0.89), but there is variation in the magnitude of the effect across the subgroups. A funnel plot of RR against sample size showed asymmetry, with smaller effects in the larger trials of more than 1 000 subjects. The magnitude of the effect was considerably greater among women at high risk of developing hypertension (4 trials, 327 women, RR 0.45, 95% CI: 0.31 - 0.66), and those with low baseline dietary calcium (5 trials, 1 582 women; RR 0.49, 95% CI: 0.38-0.62).

Pre-eclampsia (Figs 1 and 2)

The results follow a similar pattern to those for gestational hypertension. The overall effect was a reduction in the risk of pre-eclampsia (11 trials, 6 894 women; RR 0.68, 95% CI: 0.57 - 0.81). The effect was smallest in the largest trial which studied low-risk women with an adequate baseline calcium diet, and where the placebo group received routine low-dose calcium supplementation.[18] The results are strongly influenced by the latter trial. The reduction is significant for women at low risk (6 trials, 6 307 women, RR 0.79, 95% CI: 0.65 - 0.94), but not those with adequate calcium intake (4 trials, 5 022 women: RR 0.82, 95% CI: 0.71 - 1.05). Pre-eclampsia was reduced by more than 50% in women at high risk of hypertension (5 trials, 587 women: RR 0.21, 95% CI: 0.11 - 0.39), and those with low baseline calcium intake (6 trials, 1 842 women; RR 0.32, 95% CI: 0.21 - 0.49).

Preterm delivery

There was no overall effect, but preterm delivery was reduced among women at high risk of developing hypertension (4 trials, 568 women, RR 0.42, 95% CI: 0.23 - 0.78).

Birth weight < 2 500 g

There were fewer babies with a birth weight of less than 2 500 g (7 trials, 6 491 women; RR 0.83, 95% CI: 0.71 - 0.98). The effect was greatest for women at high risk of hypertension (2 trials, 449 women, RR 0.45, 95% CI: 0.22 - 0.95), but this was a *post hoc* subgroup analysis.

Admission to NICU

This outcome was reported in only 3 trials and no effect was shown.

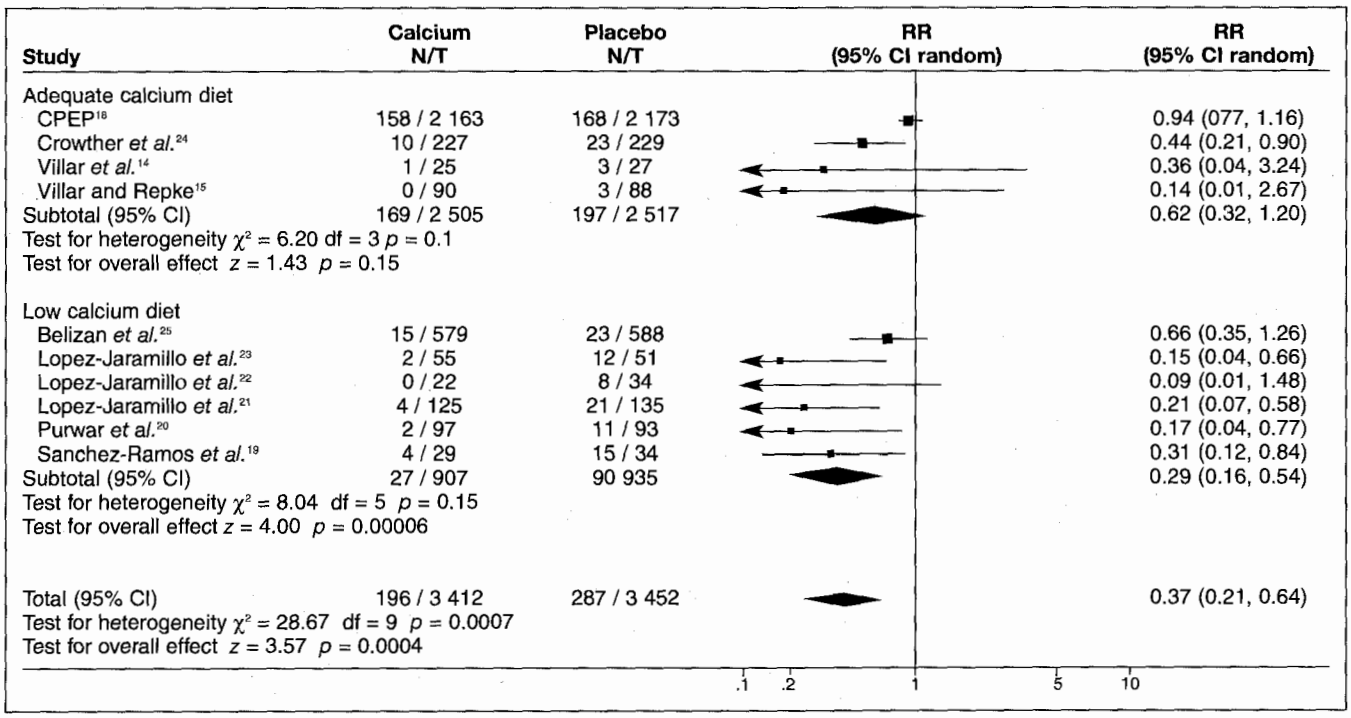

Fig. 1. Relative risk (RR) with 95% confidence intervals (CI), random effects model, of pre-eclampsia in women receiving calcium supplementation compared with placebo. Subgroup analysis by baseline dietary calcium intake. (N = number with pre-eclampsia, T = total number enrolled).

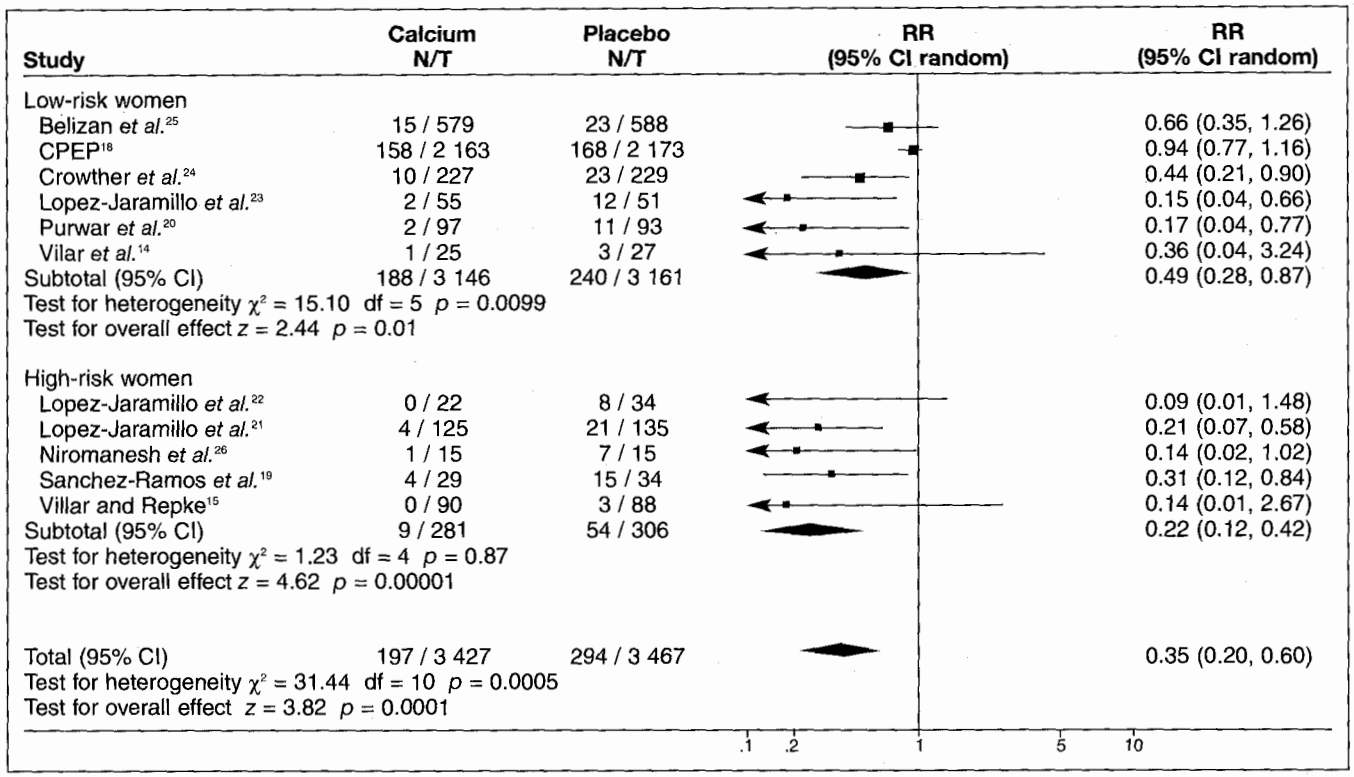

Fig. 2. Relative risk (RR) with 95% confidence intervals (CI), random effects model, of pre-eclampsia in women receiving calcium supplementation compared with placebo. Subgroup analysis by risk of developing pre-eclampsia (N = number with pre-eclampsia, T = total number enrolled).

Stillbirth, or death before discharge from hospital

No effect on this outcome was shown.

Childhood hypertension

In 1 study, childhood SBP > 95th percentile was reduced in the offspring of women who received calcium supplementation (RR 0.59, 95% CI: 0.39 - 0.91).

Discussion

Calcium supplementation was associated with: (*i*) reduced hypertension in all subgroups (although the effect was modest for those at low risk); (*ii*) reduced pre-eclampsia, particularly for those at high risk and with a low baseline dietary calcium intake (for those with adequate calcium intake the difference was not statistically significant); (*iii*) reduced low birth weight (for women at high risk of hypertension); (*iv*) reduced preterm delivery; and (*v*) reduced childhood hypertension.

No side-effects of calcium supplementation have been recorded in the trials reviewed. There is little information about the long-term follow-up of children within these trials (with the exception of BP assessment in 1 trial), and there is no information about any possible changes in the use of health care resources associated with calcium supplementation. Reduction in the risk of hypertension and pre-eclampsia may be regarded as a meaningful outcome in itself. Women may be distressed by these diagnoses and are commonly subjected to more interventions and hospitalisation (although the latter was not measured in the studies reviewed). There were, however, no documented differences in more substantive outcomes.

The heterogeneity of results is difficult to ascribe to a particular feature of the trials, as there is overlap between the classification of trials according to sample size, risk of hypertension and baseline dietary calcium intake. Most of the included trials employed sound methodology, being double-blind and placebo-controlled. The potential for being misled by bias was therefore small.

Conclusions

Implications for practice

The lack of convincing evidence of effectiveness from the largest trial to date[18] may discourage the use of calcium supplementation. It should be borne in mind that the latter trial included women with a low risk of hypertension, an adequate dietary calcium intake and, in addition, all women in both

groups received low-dose calcium supplementation as part of their routine prenatal supplementation. Data from that trial are not necessarily applicable to the care of women at greater risk and with low dietary calcium intake.

The data included in this review support calcium supplementation for women at high risk of gestational hypertension, and in communities with a low dietary calcium intake, provided that the reduction in the diagnosis of hypertension or pre-eclampsia is regarded as important. Whether lower dosages of calcium than used in the trials reviewed may have similar effects cannot be determined from this review. These benefits were confined to several rather small trials, and were not found in the largest trial conducted to date, in a low-risk population.

Implications for research

There is a need for a large confirmatory trial conducted in a high-risk population. Such a trial is currently being undertaken in several countries with demonstrated low calcium-intake populations, including South Africa, by the World Health Organisation, Reproductive Health and Research Department. In preparation for the trial, dietary surveys have been conducted at all potential sites. Nulliparous women attending the East London Hospital Complex and Coronation Hospital, Johannesburg, had median calcium intake below 50% of the recommended daily allowance (Merialdi M — unpublished data). The results of the trial will therefore be relevant to the many South African women with inadequate dietary calcium intake.

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