Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials

Authors' objectives
To review the effect of calcium supplementation during pregnancy on blood-pressure, pre-eclampsia and adverse outcomes of pregnancy.

Searching
MEDLINE and EMBASE were searched from 1966 to 1994 using the Cochrane Collaboration strategy and the keywords 'calcium' and 'hypertension' or 'blood pressure'. Citation searches of frequently identified articles were performed on SciSearch. Authors of eligible trials were contacted to ensure accuracy, completeness of data, and to identify unpublished trials. Studies published in any language were considered. Full details are presented in the companion review (see Other Publications of Related Interest no.1).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Calcium supplementation.

Participants included in the review
Pregnant women (normotensive and hypertensive women, and women at risk of pre-eclampsia) were included.

Outcomes assessed in the review
Incidence of pre-eclampsia and hypertension (systolic and diastolic blood-pressure). For a subgroup of studies, outcomes included pre-term delivery, intra-uterine growth retardation and Caesarean section.

How were decisions on the relevance of primary studies made?
The titles and abstracts (if available) from the searches were printed in duplicate. Two reviewers independently examined the lists. Studies randomising pregnant women to treatment or control, measuring blood-pressure and following patients for more than 2 weeks, were included. Kappa scores for inter-rater reliability were calculated. Complete agreement was achieved (k=1.00).

Assessment of study quality
The criteria used to evaluate the validity of the study were: (1) concealment or possible concealment of the process of random allocation; (2) blinding of participants, caregivers and blood-pressure measurements to allocation to treatment or control; and (3) more than one measurement per observer of at least 1 minute apart, and technique of blood-pressure measurement including (4) use of random sphygmomanometer, (5) formal training of staff and (6) specification of measurement technique. Full details are presented in the companion review (see Other Publications of Related Interest no.1). Methodological quality was independently assessed by two reviewers according to the 6 quality criteria, and any disagreements were resolved by consensus. Kappa scores for inter-rater reliability were calculated. The K for the reviewers' agreement ranged between 0.86 and 1.0.

Data extraction
Data were abstracted in duplicate and differences were resolved by consensus. Primary authors of studies were contacted for additional information. Full details are presented in the companion review (see Other Publications of Related Interest no.1).
Methods of synthesis

How were the studies combined?
The data were summarised in fixed-effect and random-effects models, combined with summary tables of individual studies.

How were differences between studies investigated?
Tests for homogeneity were carried out using the Fleiss method for continuous data (see Other Publications of Related Interest no.2), and Breslow-Day method for binary data (see Other Publications of Related Interest no.3). In the absence of heterogeneity, the analysis was based on a fixed-effect model; where significant heterogeneity was present, a random-effects model was used. The exploratory variables to explain heterogeneity were: dose and duration of calcium supplementation, methodological quality, baseline calcium intake, parity, and maternal age and race.

Results of the review

Of the 17 studies identified, 14 randomised controlled trials were included (n=1,208 and n=1,231 for intervention and control groups, respectively).

The pooled estimate of all studies showed a reduction in systolic blood-pressure of -5.40 mmHg (95% confidence interval, CI: -7.81, -3.00, p<0.001) and in diastolic blood-pressure of -3.44 mmHg (95% CI: -5.20, -1.68, p<0.001). In the pooled analysis, there was evidence of heterogeneity for both systolic and diastolic blood-pressure (systolic blood-pressure, chi-squared=66.30, d.f.=11, p<0.001; diastolic blood-pressure, chi-squared=59.78, d.f.=11, p<0.001). For systolic blood-pressure, parity was the only variable to show a relationship with treatment effect. For diastolic blood-pressure, a number variables (parity and methodological quality) were related to treatment effect.

The odds ratio (OR) for pre-eclampsia in women with calcium supplementation, compared with placebo, was 0.38 (95% CI: 0.22, 0.65). There was no evidence of heterogeneity.

For pre-term delivery, intra-uterine growth retardation and Caesarean section, estimates were based on data from 5 studies, and the CIs were wide. The ORs were: for pre-term delivery, 0.69 (95% CI: 0.48, 1.01); for intra-uterine growth retardation, 0.77 (95% CI: 0.51, 1.16); and for Caesarean section, 0.80 (95% CI: 0.60, 1.07).

Six studies provided data on perinatal deaths, but deaths only occurred in 3 studies and the OR was 0.77 (95% CI: 0.31, 1.91).

Authors' conclusions

Calcium supplementation during pregnancy leads to an important reduction in systolic and diastolic blood-pressure, and pre-eclampsia. While pregnant women at risk should consider taking calcium, many more patient events are needed to confirm the impact of calcium on maternal and foetal morbidity.

CRD commentary

This is a well-conducted meta-analysis. The presentation is confusing due to the need to consult a companion review for more in-depth details of the search strategy and the quality assessment methods. However, the companion review does provide complete details of the search strategy. The summary tables provide extensive details on the primary studies. The analysis of the data is very thorough and every attempt has been made to explain differences in treatment effects.

The study includes 4 new studies completed since the publication of the last meta-analysis carried out in this area (see Other Publications of Related Interest no.4). In addition, this meta-analysis employs stricter inclusion criteria and quality assessments.

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**Record Status**
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