

Role of calcium supplementation during pregnancy in reducing risk of developing gestational hypertensive disorders: a meta-analysis of studies from developing countries.

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Introduction

The Lives Saved Tool (LiST) is a computer-based software application freely available on the Internet, which allows users to estimate the impact of proven maternal, newborn and child health intervention packages and coverage levels on mortality and other selected health outcomes (for more information on LiST see: <http://www.jhsph.edu/dept/ih/IIP/list/>). The Child Health Epidemiology Reference Group (CHERG) of the World Health Organization and UNICEF sponsors systematic reviews and meta-analyses to provide the information needed to develop these estimates of program impact. As part of this process, the open access journal BioMedCentral Public Health published a special supplement in April, 2011, which included 35 new articles on the effectiveness of a broad range of interventions, including nine reviews of nutrition interventions, such as different forms of maternal nutritional supplementation during pregnancy.

We have selected for presentation in this month's NNA a systematic review of the effects of maternal calcium supplementation during pregnancy on maternal hypertension, pre-eclampsia, and newborn outcomes because this is a topic that has received relatively little attention, especially in sub-Saharan Africa; and, to our knowledge, there are no large scale programs currently addressing this issue.

Methods

The authors conducted a comprehensive search of several computerized bibliographic data bases to identify all randomized controlled trials in which pregnant women in lower income countries (Gross National Income per capita <US\$11,905) were assigned to receive calcium supplements before 32 weeks of pregnancy, as compared to either placebo supplementation or no intervention. The dose of calcium supplements in the different studies ranged from 0.5-2.0 g/day (with 8 of 10 studies providing 2.0 g/d).

Study outcomes included gestational hypertension (defined as diastolic blood pressure (BP) >90 mmHg or an increase in systolic BP >30 mmHg during pregnancy); pre-eclampsia (gestational hypertension plus proteinuria); severe pre-eclampsia (diastolic BP >110 and/or systolic BP >160 mmHg on more than two occasions plus proteinuria); eclampsia (convulsions and/or unexplained coma in women with signs of pre-eclampsia); and maternal mortality. Neonatal outcomes, such as neonatal mortality, preterm births, and low birth weight, were also examined.

Results and conclusions

A total of 10 studies were identified that fulfilled the authors' inclusion criteria. Together these studies enrolled more than 11,000 women. However, only one of these studies (a multi-center study of 8312 women carried out in Argentina, Egypt, India, Peru, South Africa, and Vietnam) included a site in sub-Saharan Africa (Villar, 2006). Average baseline calcium intakes were reported to be low (<900 mg/d) in all of the study populations.

All ten of the trials, provided information on the effects of maternal calcium supplementation on the risk of pre-eclampsia. Calcium supplementation reduced pre-eclampsia by 59% (RR 0.41; 95% CI 0.24-0.69). The three trials that also reported results for severe pre-eclampsia found a 30% reduction in relative risk. Only one study provided information on eclampsia (Villar, 2006). This large, multi-center study found 17 cases of eclampsia in the calcium-supplemented group and 25 cases in the control group (RR 0.68; 95% CI 0.48-0.97). Results for maternal all-cause mortality also were available just from the aforementioned multi-center trial, which reported one death in the intervention group and six deaths in the control group (RR 0.17; 95% CI 0.03-0.76). Because of the small number of deaths, this study also reported on severe morbidities related to maternal hypertensive disorders that could lead to maternal death; and they found that calcium supplementation during pregnancy reduced severe morbidities by 20% compared to the control groups (RR 0.80; 95% CI 0.70-0.91).

The multi-center trial was the only study that reported information on neonatal mortality. This study found a significant 30% reduction in neonatal deaths (RR 0.70; 95% CI 0.56-0.88). Five trials that reported on preterm births found a significant 12% reduction in prematurity among the calcium-supplemented mothers (RR 0.88; 95% CI 0.78-0.99). The results for risk of low birth weight, which were available from three trials, were not statistically significant (RR 0.81; 95% CI 0.81-1.12).

Program and Policy Implications

The results of this analysis are consistent with those of two previously published reviews, one by Hofmeyr *et al* (2006), which included studies from both lower income and more affluent countries, and another by Trumbo *et al* (2007), which included only studies from the USA and populations with adequate baseline calcium intakes. Hofmeyr *et al* found that calcium supplementation during pregnancy significantly reduced gestational hypertension by 43% and pre-eclampsia by 52%. By contrast, Trumbo *et al* did not detect any impact of calcium supplementation in settings where baseline calcium intakes were reportedly adequate.

The physiological mechanism for the reported effects of calcium supplementation during pregnancy is uncertain. However, it is believed that low calcium intakes may cause an increase in blood pressure by stimulating secretion of parathyroid hormone and/or renin, leading to increased intra-cellular calcium concentration in vascular smooth muscle and secondary vasoconstriction; calcium supplementation is thought to reverse this effect. A similar mechanism has been proposed with regard to uterine smooth muscle contractility and risk of premature labor and birth asphyxia.

The authors conclude that there is now sufficient evidence of a beneficial effect of maternal calcium supplementation during pregnancy on reducing gestational hypertensive disorders and premature births in populations with low baseline calcium intake such that future research should focus on issues of program implementation and optimal dosage regimens, including both food sources of calcium as well as supplements.

NNA Editors' comments*

These studies provide sufficiently convincing evidence on the potential value of maternal calcium supplementation during pregnancy to warrant the development of programmatic interventions to increase calcium intakes in populations with low baseline calcium consumption. However, caution is warranted for two reasons. Firstly, only one of the reported trials was conducted in sub-Saharan Africa, so more information from this continent would be desirable to confirm these results. Secondly, the available studies have not explored for possible adverse effects of calcium supplementation on absorption and utilization of other minerals, such as iron and zinc. Thus, future interventions should monitor the impact of calcium supplementation on other minerals to confirm that it is not associated with any harmful effects on these other nutrients.

* These comments have been added by the editorial team and are not part of the cited publication.

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