WHO recommendation on calcium supplementation during pregnancy

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Recommendation

In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of pre-eclampsia. (context-specific recommendation)

Publication history

First published: October 2011

Updated: November 2016

Assessed as up-to-date: November 2016

Remarks

- This recommendation is consistent with the 2011 WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (1) (strong recommendation, moderate-quality evidence) and supersedes the WHO recommendation found in the 2013 Guideline: calcium supplementation in pregnant women. (2)
- Dietary counselling of pregnant women should promote adequate calcium intake through locally available, calcium-rich foods.
- Dividing the dose of calcium may improve acceptability. The suggested scheme for calcium supplementation is 1.5–2 g daily, with the total dose divided into three doses, preferably taken at mealtimes.
- Negative interactions between iron and calcium supplements may occur. Therefore, the two nutrients should preferably be administered several hours apart rather than concomitantly. (2)
- As there is no clear evidence on the timing of initiation of calcium supplementation, stakeholders may wish to commence supplementation at the first ANC visit, given the possibility of compliance issues.
- To reach the most vulnerable populations and ensure a timely and continuous supply of supplements, stakeholders may wish to consider task shifting the provision of calcium supplementation in community settings with poor access to health-care professionals.
- The implementation and impact of this recommendation should be monitored at the health service, regional and country levels, based on clearly defined criteria and indicators associated with locally agreed targets. Successes and failures should be evaluated to inform integration of this recommendation into the ANC package.
Background

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths, whereas in Latin America and the Caribbean, they contribute to approximately 22% of all maternal deaths. (3)

Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. The majority of deaths due to pre-eclampsia and eclampsia are avoidable through the provision of timely and effective care to the women presenting with these complications.

There as an inverse relationship between calcium levels and risk of pre-eclampsia in pregnancy.(2) Increasing calcium intake in pregnancy (such as through oral supplementation) has been shown to reduce blood pressure directly.(4) This intervention has been trialled to assess potential benefits in reducing the risk of pre-eclampsia and related complications.

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(5, 6) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of pre-eclampsia eclampsia (2011).(1)

A Cochrane systematic review on the effects of calcium on maternal and perinatal outcomes other than hypertension was conducted.(7) The first version of this recommendation was also informed by a separate Cochrane review on the effects of calcium for preventing hypertensive disorders and related problems.(8)

In these reviews, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting on recommendations for prevention and treatment of pre-eclampsia or eclampsia in April 2011, where this recommendation was first developed. The recommendation was reviewed and updated at a GDG meeting on antenatal care recommendations in March 2016.

Both GDGs were comprised of a group of independent experts, who used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Recommendation question

For this recommendation, we aimed to answer the following questions:
In pregnant women, does calcium supplementation during pregnancy compared to placebo or no treatment, improve maternal and perinatal outcomes, particularly the onset of pre-eclampsia?

In what populations/contexts is calcium supplementation most beneficial?

**Evidence Summary**

Evidence on the effects of calcium supplements on outcomes other than hypertension/pre-eclampsia was derived from a Cochrane systematic review.(7) The review included data from 23 trials involving 18 587 pregnant women. The aim of the review was to determine the effect of calcium on maternal and perinatal outcomes other than hypertension. There is a separate Cochrane review on the latter,(8) which has been referenced to support existing WHO recommendations on calcium supplementation to prevent pre-eclampsia in populations with low dietary calcium intake.(1, 2)

In 14 trials, daily calcium doses ranged from 1000 mg to 2000 mg, and in the remainder it was less than 1000 mg. Eleven trials started calcium supplementation at or after 20 weeks of gestation, five trials started before 20 weeks, and the rest did not specify when supplementation was initiated. The primary outcome of 16 of the trials was pregnancy-induced hypertension. For outcomes other than hypertension, few trials contributed to each outcome; this is the evidence presented in this section.

**Maternal outcomes**

High-certainty evidence shows that calcium supplementation does not have important effects on maternal anaemia (1 trial, 1098 women; RR: 1.04, 95% CI: 0.90–1.22) or caesarean section rates (9 trials, 7440 women; RR: 0.99, 95% CI: 0.89–1.10). Moderate-certainty evidence indicates that calcium supplementation probably has little or no effect on maternal mortality (2 trials, 8974 women; RR: 0.29, 95% CI: 0.06–1.38) and probably makes little or no difference to the risk of urinary tract infections (3 trials, 1743 women; RR: 0.95, 95% CI: 0.69–1.30). Low-certainty evidence suggests that calcium supplementation may make little or no difference to maternal weight gain (3 trials; MD: –29.46 g per week, 95% CI: –119.80 to 60.89 g per week). Maternal satisfaction was not reported in any of the trials included in the Cochrane review.

**Side-effects**

Calcium supplementation makes little or no difference to the risk of “any side-effect”, a composite outcome including headache, vomiting, backache, swelling, vaginal and urinary complaints, dyspepsia and abdominal pain (1 trial, 8312 women; RR: 1.02, 95% CI: 0.93–1.12), and probably makes little or no difference to the risk of urinary stones (3 trials, 13 419 women; RR: 1.11, 95% CI: 0.48–2.54), renal colic (1 trial, 8312 women; RR: 1.67, 95% CI: 0.40–6.99) and impaired renal function (1 trial, 4589 women; RR: 0.91, 95% CI: 0.51–1.64), all assessed as moderate-certainty evidence. Low-certainty evidence suggests that it may have little or no effect on the risk of gallstones (1 trial, 518 women; RR: 1.35, 95% CI: 0.48–3.85).

**Fetal and neonatal outcomes**

Calcium supplementation probably has little or no effect on low-birth-weight babies (< 2500 g), as indicated by evidence that was of moderate certainty due to inconsistency (6 trials, 14 162 women; RR: 0.93, 95% CI: 0.81–1.07). Low-certainty evidence suggests that it may have little or no effect on preterm birth before 37 weeks of gestation (13 trials, 16 139 women; RR: 0.86, 95% CI: 0.70–1.05). However, when trials are stratified by dose (< 1000 mg vs ≥ 1000 mg), moderate-certainty evidence shows that high-dose calcium supplementation probably reduces preterm birth (12 trials, 15 479 women; RR: 0.81, 95% CI: 0.66–0.99).
Low-certainty evidence suggests that calcium supplementation may make little or no difference to perinatal mortality (8 trials, 15 785 women; RR: 0.87, 95% CI: 0.72–1.06), and moderate-certainty evidence shows that it probably has little or no effect on stillbirths or fetal deaths (6 trials, 15 269 women; RR: 0.91, 95% CI: 0.72–1.14).

Additional considerations

In the WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (2011), the recommendation on calcium states: “In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of pre-eclampsia in all women, but especially in those at high risk of developing pre-eclampsia (strong recommendation)”.(1) This recommendation is based on moderate-quality evidence showing a 64% risk reduction (CI: 35–80%) in pre-eclampsia among women or populations with low baseline dietary calcium intake.(1)

In considering the evidence from the review of “non-hypertensive” effects, the GDG agreed that the effect of calcium on preterm birth is probably not distinct from the effect on preventing pre-eclampsia, as preterm birth is frequently a consequence of pre-eclampsia.

Implementation considerations

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of oral calcium supplements in antenatal care settings), and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.
- The WHO antenatal care guidelines outline the 2016 WHO ANC model, which includes timing, content and frequency of antenatal care contacts. In that model, the need for and compliance with calcium supplementation should be considered at all antenatal care visits. The WHO antenatal care guidelines outline the 2016 WHO ANC model, which includes timing, content and frequency of antenatal care contacts. In that model, the need for and compliance with calcium supplementation should be considered at all antenatal care visits.

Research implications

The 2011 GDG identified that further research on the following questions related to calcium supplementation is a priority:

- It is unclear whether calcium supplementation corrects the pathological processes that underpin pre-eclampsia/eclampsia.
- Most calcium supplementation trials to date have used fairly high doses of daily calcium (1.5–2.0 g/day). While recommending those doses the guideline development group agreed that lower doses of calcium supplementation should be evaluated. This is important in view of the logistic and financial challenges of implementing large-scale calcium supplementation programmes.
• Calcium supplementation programme implementation should be monitored and evaluated carefully to assess their successes and failures in terms of integration of the programmes into the overall antenatal care package
• Evidence is weak on the effects of calcium supplementation in populations that are high risk of hypertensive disorders of pregnancy but have adequate intake of dietary calcium. It is unclear whether the observed effectiveness of calcium supplementation is the result of filling a dietary gap or whether calcium acts as a therapeutic agent.

Further research priorities were identified by the 2016 antenatal care GDG, related to calcium supplementation:

• What are the effects, feasibility, acceptability and equity implications of healthy eating and exercise interventions in LMICs?
• Can an intervention package with standardized guidance on nutrition be developed that is evidence-based, sustainable, reproducible, accessible and adaptable to different cultural settings?
• What is the most effective, acceptable and feasible regimen of recommended supplements (iron, calcium and folic acid)?
• What are the biological mechanisms underlying the relationships among calcium supplementation, preeclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) and preterm birth?
• What is the minimal dose and optimal commencement schedule for calcium supplementation to achieve a positive effect on pre-eclampsia and preterm birth?

Related links

WHO recommendations on antenatal care for a positive pregnancy experience (2016) full document and evidence tables (EB Table A3)

WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (2011) full document and evidence tables (EB Tables 6 and 7)

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors (third edition)

Supporting systematic review/s:


References


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