WHO recommendation

Calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications

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Acronyms and abbreviations

ANC	Antenatal care
BMGF	Bill & Melinda Gates Foundation
CI	Confidence interval
DOI	Declaration of Interest
FIGO	International Federation of Gynaecology and Obstetrics
FWC	Family, Women's and Children's Health (a WHO cluster)
GDG	Guideline Development Group
GRC	Guideline Review Committee
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (a WHO project)
GSG	Executive Guideline Steering Group
HELLP	Haemolysis, elevated liver enzymes, low platelets
ICM	International Confederation of Midwives
ICU	Intensive Care Unit
LMIC	Low and middle-income country
MAP	Mean Arterial Pressure
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health
MCSP	Maternal and Child Survival Programme
MPA	Maternal and Perinatal Health and Preventing Unsafe Abortion (a team in WHO's Department of Reproductive Health and Research)
MPH	Maternal and perinatal health
NHD	[WHO Department of] Nutrition for Health and Development
NICU	Neonatal Intensive Care Unit
NNT	Number needed to treat
PICO	Population (P), intervention (I), comparison (C), outcome (O)
RCT	Randomized Controlled Trial
RHR	[WHO Department of] Reproductive Health and Research
RR	Relative risk
SDG	Sustainable Development Goals
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization

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Executive Summary

Introduction

Hypertensive disorders of pregnancy are a significant 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 *(1)*. 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.

Improving care for women during pregnancy and around the time of childbirth to prevent and treat pre-eclampsia and eclampsia is a necessary step towards the achievement of the health targets of the Sustainable Development Goals (SDGs). Efforts to prevent and reduce morbidity and mortality due to these conditions can help address the profound inequities in maternal and perinatal health globally. To achieve this, healthcare providers, health managers, policy-makers and other stakeholders need up-to-date and evidence-informed recommendations to guide clinical policies and practices.

In 2017, the Executive Guideline Steering Group (GSG) on WHO maternal and perinatal health recommendations prioritized the updating of the existing *WHO recommendation on calcium supplementation during pregnancy* in response to new evidence available on the effects of this intervention. This recommendation is a revalidation of the previous recommendation on calcium supplementation issued in 2016 in the *WHO recommendations on antenatal care for a positive pregnancy experience (2)*.

Target audience

The primary audience of this recommendation includes healthcare professionals who are responsible for developing national and local healthcare protocols (particularly those related to pre-eclampsia and eclampsia) and those directly providing care to pregnant women and their newborns, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes, and relevant staff in ministries of health, in all settings.

Guideline development methods

The update of this recommendation was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendation was initially developed using this process, namely:

(i) identification of the priority question and critical outcomes;

(ii) retrieval of evidence;

(iii) assessment and synthesis of evidence;

(iv) formulation of the recommendation; and

(v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

The scientific evidence supporting the recommendation was synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. An updated systematic review was used to prepare evidence profiles for the prioritized question. WHO convened an online meeting on 2 May 2018 where the Guideline Development Group (GDG) members reviewed, deliberated and achieved consensus on the strength and direction of the recommendation presented herein. Through a structured process, the GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG revalidated the WHO recommendation on calcium supplementation during pregnancy published in 2016 with minor revisions to the remarks and implementation considerations.

The recommendation

To ensure that the recommendation is correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

Table 1: WHO recommendation on calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications

In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0g oral elemental calcium) is recommended for pregnant women to reduce the risk of pre-eclampsia. ***(Context-specific recommendation, moderate-certainty evidence)***
Remarks • This recommendation is consistent with the 2016 *WHO recommendations on antenatal care for a positive pregnancy experience (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 1.5-2.0g 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 micronutrients should preferably be administered several hours apart rather than concomitantly *(3)*. • As there is no clear evidence on the timing of initiation of calcium supplementation, stakeholders may wish to commence supplementation at the first antenatal care contact, in order to improve compliance to the regimen. • 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 healthcare professionals *(4)*. • 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. Barriers, enablers and pathways should be evaluated to inform integration of this recommendation into the antenatal care package.

1. Background

An estimated 303 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2015, around 99% of which occurred in low-resource settings *(5)*. Haemorrhage, hypertensive disorders and sepsis are responsible for more than half of all maternal deaths worldwide. Thus, improving the quality of maternal healthcare for women is a necessary step towards achievement of the health targets of the Sustainable Development Goals (SDGs) and the targets and indicators of WHO's Thirteenth General Programme of Work, particularly for achieving universal health coverage *(6)*. International human rights law includes fundamental commitments of WHO Member States to enable women and adolescent girls to survive pregnancy and childbirth, as part of their enjoyment of sexual and reproductive health and rights and living a life of dignity *(7)*. The World Health Organization (WHO) envisions a world where "every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and the postnatal period" *(8)*.

There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications *(9)*. Almost two-thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings *(10)*. To provide good-quality care, healthcare providers at all levels of maternal healthcare services (particularly in low- and middle-income countries) need to have access to appropriate medications and training in relevant procedures. Healthcare providers, health managers, policymakers and other stakeholders also need up-to-date, evidence-informed recommendations to guide clinical policies and practices, in order to optimize quality of care, and enable improved healthcare outcomes.

Hypertensive disorders of pregnancy are a significant 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 *(1)*. 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 would be avoidable through the provision of timely and effective care to women presenting with these complications. Efforts to prevent and reduce pre-eclampsia and eclampsia-associated morbidity and mortality could reduce the profound inequities in maternal health globally.

In 2011, WHO published 22 recommendations for the prevention and treatment of pre-eclampsia and eclampsia, including a recommendation on the use of calcium supplementation during pregnancy *(11)*. These recommendations were developed according to the WHO guideline development standards, including synthesis of available research evidence, use of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, and formulation of recommendations by a guideline panel composed of international experts. In 2016, the WHO guideline panel on antenatal care recommendations for a positive pregnancy experience reviewed updated evidence and revised the calcium supplementation recommendation *(2)*. This was consistent with the 2011 recommendation, however additional remarks and implementation considerations were added, particularly in how the recommendation related to the implementation of the WHO 2016 antenatal care package.

Rationale and objectives

WHO has established a novel process for prioritizing and updating maternal and perinatal health recommendations whereby an Executive Guideline Steering Group (GSG) oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating *(12)*. Recommendations were prioritized on the basis of changes or important new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes,

acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized the updating of the existing WHO recommendation on calcium supplementation during pregnancy in response to new, potentially important evidence.

The primary goal of this recommendation is to improve the quality of care and outcomes for pregnant women, particularly those related to pre-eclampsia, eclampsia and resulting complications. This recommendation provides a foundation for the sustainable implementation of calcium supplementation during pregnancy for prevention of pre-eclampsia and its complications globally.

Target audience

The primary audience includes healthcare professionals who are responsible for developing national and local health guidelines and protocols (particularly those related to pre-eclampsia and eclampsia) and those directly providing care to women during labour and childbirth, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes and relevant staff in ministries of health, in all settings.

This recommendation may be of interest to professional societies involved in the care of pregnant women, nongovernmental organizations concerned with promoting people-centred maternal care and implementers of maternal and child health and nutrition programmes.

Scope of the recommendation

Framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format, the questions for this recommendation were:

- In pregnant women (P), does calcium supplementation (I) compared to placebo or no calcium supplementation (C), improve maternal and perinatal outcomes (O), including the onset of pre-eclampsia?
    - o If so, in what populations of pregnant women or contexts is calcium supplementation most beneficial?
    - o If so, what dosing regimen of calcium supplementation is most beneficial?

Persons affected by the recommendation

The population affected by this recommendation includes all pregnant women (particularly those at higher risk of gestational hypertensive disorders) in low-, middle- or high-income settings, and those living in areas where dietary intake of calcium is low *(13)*.

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (14)*. In summary, the process included:

(i) identification of the priority question and critical outcomes;

(ii) retrieval of evidence;

(iii) assessment and synthesis of evidence;

(iv) formulation of the recommendation; and

(v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2017, the WHO recommendation on calcium supplementation in pregnancy was identified by the Executive GSG as a high priority for updating in response to new, potentially important evidence on this question. Six main groups were involved in this process, with their specific roles described in the following sections.

Contributors to the guideline

Executive guideline steering group for updating WHO maternal and perinatal health recommendations (2017-2019) (Executive GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating *(12)*.

WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Reproductive Health and Research (RHR), the Department of Maternal, Newborn, Child and Adolescent Health (MCA), and the Department of Nutrition for Health and Development (NHD) managed the updating process. The Group drafted the key recommendation questions in PICO format, identified the systematic review team and guideline methodologist, as well as the guideline development and external review groups. In addition, the WHO Steering Group supervised the syntheses and retrieval of evidence, organized the Guideline Development Group meeting, drafted and finalized the guideline document, and managed the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

Guideline Development Group on Maternal and Perinatal Health

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool is a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-informed recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance and there were no significant conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health and nutrition during pregnancy.

From the MPH-GDG pool, 16 external experts and relevant stakeholders were invited to participate as members of the Guideline Development Group (GDG) for updating this recommendation. Those selected were a diverse group with expertise in research, guideline development methods, and clinical policy and programmes relating to pre-eclampsia and eclampsia prevention and treatment, as well as implementation of nutrition actions.

The 16 GDG members for this recommendation were also selected in a way that ensured geographic representation and gender balance and there were no important conflicts of interest. The Group appraised the evidence that was used to inform the recommendation, advised on the interpretation of this evidence, formulated the final recommendation based on the draft prepared by the Steering Group, and reviewed and reached unanimous consensus for the recommendation in the final document. The members of this Group are listed in Annex 1.

External Review Group

An external review group included eight technical experts with interest and expertise in the provision of evidence-based obstetric care. None of its members declared a conflict of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision- making processes had considered and incorporated contextual values and the preferences of potential users of the recommendations, healthcare professionals and policy makers. They did not change the recommendation that was formulated by the GDG. The members of the External Review Group are listed in Annex 1.

Systematic review team and guideline methodologists

A Cochrane systematic review on this question was updated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the updated protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Representatives of the Cochrane Pregnancy and Childbirth Group attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

External partners and observers

Representatives of the United States Agency for International Development (USAID), the Maternal and Child Survival Programme (MCSP)/Jhpiego, the Bill & Melinda Gates Foundation (BMGF), the International Confederation of Midwives (ICM), the International Federation of Gynaecology and Obstetrics (FIGO) and the Population Council participated in the GDG meeting as observers. These organizations, with a long history of collaboration with the relevant WHO Departments in guideline dissemination and implementation, are among the implementers of the recommendation. The list of observers who participated in the GDG meeting is included in Annex 1.

Identification of critical outcomes

The critical and important outcomes were aligned with the prioritized outcomes from the 2011 *WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (11)*. These outcomes were initially identified through a search of key sources of relevant, published, systematic reviews and a prioritization of outcomes by the 2011 GDG panel. All the outcomes were included in the scope of this document for evidence searching, retrieval, grading and formulation of the recommendation. The list of critical and important outcomes is provided in Annex 2.

Evidence identification and retrieval

A Cochrane systematic review was updated by the Cochrane Pregnancy and Childbirth Group *(15)*. This systematic review was the primary source of evidence for this recommendation.

Randomized controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were entered into Review Manager (RevMan) software. The RevMan file was retrieved from

the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). Then the RevMan file was exported to GRADE profiler software (GRADEpro) and GRADE criteria were used to critically appraise the retrieved scientific evidence. Finally, evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach *(16)*. Using this approach, the certainty of evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

Study design limitations: The risk of bias was first examined at the level of each individual study and then across the studies contributing to the outcome. For randomized trials, certainty was first rated as 'high' and then downgraded by one ('moderate') or two ('low') levels, depending on the minimum criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence, that is, whether there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision: This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias: The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

Certainty of evidence assessments are defined according to the GRADE approach:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Formulation of the recommendation

The WHO Steering Group used the evidence profiles to summarise the evidence on effects on the pre-specified outcomes. The evidence summary and corresponding GRADE tables, other related documents for assessment of values and preferences, resource requirements and cost-effectiveness, acceptability, feasibility and equity were provided in advance to meeting participants, who were invited to submit any their comments electronically in advance of the meeting.

The GDG members and other participants were then invited to attend an online GDG meeting (see Annex 1 for the list of participants) organized by the Steering Group on 2 May 2018. During the meeting, the GDG members reviewed and discussed the balance between the desirable and undesirable effects of the intervention and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity, before finalizing the recommendation and remarks.

Management of declaration of interests

The disclosure and appropriate management of relevant financial and non-financial conflicts of interest of guideline development group members and other external experts and contributors is a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings. All GDG members were therefore required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development process. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflict of interests as outlined in the WHO Handbook for Guideline Development to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting and no further actions were taken.

Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the Steering Group.

Decision-making process

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE evidence-to-decision framework to determine the direction and strength of the recommendation. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experience and opinions of members of the GDG and supported by evidence from a literature search where available. Evidence- to-decision tables were used to describe and synthesize these considerations.

Decisions were made based on consensus, defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendation.

Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, the evidence summary and other documents relevant to the GDG's deliberation. The draft documents were made available to the participants of the meeting two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members and the External Review Group for their final review and approval.

Peer review

Following review and approval by GDG members and the External Review Group, the final document was sent to eight external independent experts who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and improving language to address any lack of clarity.

3. Recommendation and supporting evidence

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The evidence-to-decision table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendation, is presented in the evidence-to-decision framework (Annex 4).

The following recommendation was adopted by the GDG. Evidence on the effectiveness of this intervention was derived from the updated Cochrane systematic review and was summarized in GRADE tables (Annex 5). The certainty of the supporting evidence was rated as 'moderate' for most of the critical outcomes.

To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional 'remarks' reflecting the summary of the discussion by the GDG are included under the recommendation.

4. Dissemination and implementation of the recommendation

The dissemination and implementation of this recommendation is to be considered by all actors involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase access and strengthen the capacity of health centres to provide high quality services to all women giving birth. It is therefore crucial that this recommendation is translated into antenatal care packages and programmes at country and health-facility levels (where appropriate).

Recommendation dissemination and evaluation

A shorter document containing the recommendation, remarks, implementation considerations and research priorities will be formulated for public dissemination. This document will have annexes (also made publicly available) containing all the information in this document, including methods, evidence-to-decision frameworks and GRADE tables.

Table 1: WHO recommendation on calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications

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

(Context-specific recommendation, moderate-certainty evidence)

Remarks

- This recommendation is consistent with the 2016 *WHO recommendations on antenatal care for a positive pregnancy experience (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 1.5–2.0g 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 micronutrients should preferably be administered several hours apart rather than concomitantly *(3)*.
- As there is no clear evidence on the timing of initiation of calcium supplementation, stakeholders may wish to commence supplementation at the first antenatal care contact, in order to improve compliance to the regimen.
- 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 healthcare professionals *(4)*.
- 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. Barriers, enablers and pathways should be evaluated to inform integration of this recommendation into the antenatal care package.

The recommendation will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. This recommendation will also be available on the WHO website, the WHO Reproductive Health Library (www.who.int/rhl) and WHO e-Library of Evidence for Nutrition Actions (eLENA) (www.who.int/elena). Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO maternal and perinatal health staff.

The recommendation document will be translated into the six UN languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendation into any of these languages.

Implementation considerations

- The successful introduction of this recommendation into national programmes and healthcare 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 provider 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;

- Policymakers and other stakeholders should consider the level of dietary calcium intake amongst pregnant women;

- The WHO antenatal care guidelines outline the 2016 WHO antenatal care model, which includes timing, content and frequency of antenatal care contacts *(2)*. In that model, the need for and compliance with calcium supplementation should be considered at all antenatal care contacts.

- Healthcare providers should be trained in how to correctly advise women on calcium intake during pregnancy, and how to encourage compliance;

- Healthcare services implementing this recommendation should put in place measures to ensure adequate stocks of calcium supplements are consistently available wherever antenatal care is provided;

- The target group for this recommendation comprises populations with observed low dietary calcium intake, or those living in geographical areas where calcium-rich foods are not commonly available or consumed. Calcium intake at population level can be estimated through various means including dietary surveys using 24-hour recalls, food frequency questionnaires or food weighing, as well as through secondary data estimates derived from the Food and Agriculture Organization (FAO) food balance sheets or household consumption and expenditure surveys *(22)*;

- When determining dosage for individual women, healthcare providers should take into consideration a woman's calcium intake from other sources, such as medications (e.g. antacids).

5. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on this recommendation. The following questions were identified as those that demand urgent priority:

- What is the minimal dose and optimal commencement schedule for calcium supplementation to achieve a positive effect on pre-eclampsia and preterm birth?
- What are the biological mechanisms underlying the relationships among calcium supplementation, pre-eclampsia, haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome and preterm birth?
- What is the most effective, acceptable and feasible regimen of recommended supplements (iron, calcium and folic acid)?
- 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 are the effects, feasibility, acceptability and equity implications of healthy eating and exercise interventions in LMICs?

6. Applicability issues

Anticipated impact on the organization of care and resources

Implementing this evidence-based recommendation requires resources for sustainable procurement and stocks of calcium tablets. The GDG noted that updating training curricula and providing training on the recommendation would increase the recommendation's impact and facilitate its implementation. Standardization of care by including this recommendation into existing antenatal care packages can encourage healthcare provider behaviour change.

Monitoring and evaluating guideline implementation

Implementation should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of maternal and newborn care. For example, interrupted time series, clinical audits or criterion-based clinical audits can be used to obtain relevant data related to pre-eclampsia and eclampsia. Clearly defined review criteria and indicators are needed; these could be associated with locally agreed targets and aligned with the standards and indicators described in the WHO document *Standards for improving quality of maternal and newborn care in health facilities (23)*.

7. Updating the recommendation

The Executive GSG convenes regularly to review WHO's current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. Accordingly, this recommendation will be reviewed and prioritized by the Executive GSG. In the event that new evidence that could potentially impact the current evidence base is identified, the recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concerns about the validity of the recommendation should be promptly communicated to the guideline implementers, in addition to any plans to update the recommendation.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendation. Please email your suggestions to mpa-info@who.int.

References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2*(6)*: e323-33.
2. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016.
3. Guideline: Calcium supplementation in pregnant women. Geneva: World Health Organization; 2013.
4. WHO Recommendations: Optimizing Health Worker Roles to Improve Access to Key Maternal and Newborn Health Interventions Through Task Shifting. Geneva: World Health Organization; 2012.
5. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2015.
6. Thirteenth general programme of work, 2019–2023. Geneva: World Health Organization; 2018.
7. Office of the United Nations High Commissioner for Human Rights. Technical guidance on the application of a human rights-based approach to the implementation of policies and programmes to reduce preventable maternal morbidity and mortality. Human Rights Council, twentieth session. New York: United Nations General Assembly; 2012.
8. Tunçalp Ö, Were WM, MacLennan C, Oladapo OT, Gülmezoglu AM, Bahl R, et al. Quality of care for pregnant women and newborns - the WHO vision. BJOG. 2015; 122*(8)*:1045-9.
9. Campbell OM, Graham WJ, group LMSSs. Strategies for reducing maternal mortality: getting on with what works. Lancet. 2006 Oct; 368(9543): 1284-99.
10. Fisk NM, McKee M, Atun R. Relative and absolute addressability of global disease burden in maternal and perinatal health by investment in R&D. Trop Med Int Health. 2011; 16*(6)*: 662-8.
11. WHO recommendations for prevention and treatment pre- eclampsia and eclampsia. Geneva: World Health Organization; 2011.
12. Executive Guideline Steering Group for Updating WHO Maternal and Perinatal Health Recommendations (2017-2019). Geneva: World Health Organization; 2017 http://www.who.int/reproductivehealth/publications/updating-mnh-recommendations/en/, accessed 7 December 2018).
13. Cormick G, Betrán AP, Romero IB, Lombardo CF, Gülmezoglu AM, Ciapponi A, Belizán JM. Global inequities in dietary calcium intake during pregnancy: a systematic review and meta-analysis. BJOG. 2018; doi: 10.1111/1471-0528.15512.
14. WHO Handbook for Guideline Development (second edition). Geneva: World Health Organization; 2014.
15. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018; (10):CD001059.
16. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011; 64*(4)*:401-6.
17. Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M, Medley N. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. Cochrane Database Syst Rev. 2015; *(2)*: CD007079.
18. Downe S, Finlayson K, Tunçalp Ö, Metin Gülmezoglu A. What matters to women: a systematic scoping review to identify the processes and outcomes of antenatal care provision that are important to healthy pregnant women. BJOG. 2016; 123*(4)*: 529-39.

19. OneHealth Tool: intervention assumptions (draft January 2016). Geneva and Glastonbury (CT): United Nations InterAgency Working Group on Costing and the Futures Institute; 2016 (https://avenirhealth.org/Download/Spectrum/Manuals/Treatment%20Assumptions%202016%201%2010.pdf, accessed 8 November 2018).

20. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017.

21. State of inequality: Reproductive, maternal, newborn and child health. Geneva: World Health Organization; 2015.

22. World Health Organization, Food and Agricultural Organization of the United Nations. Guidelines on food fortification with micronutrients. Geneva: World Health Organization; 2006.

23. Standards for improving quality of maternal and newborn care in health facilities. Geneva: World Health Organization; 2016.

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Annex 2. Priority outcomes for decision-making

Key questions	Priority outcomes
In pregnant women (P), does calcium supplementation (I) compared to placebo or no calcium supplementation (C), improve maternal and perinatal outcomes (O), including the onset of pre-eclampsia? If so, in what populations of pregnant women or contexts is calcium supplementation most beneficial? If so, what dosing regimen of calcium supplementation is most beneficial?	**Maternal outcomes** • Maternal death • Eclampsia • Pre-eclampsia • Recurrent seizures • Severe maternal morbidity • Maternal death or severe maternal morbidity • ICU admission • Adverse effects of interventions
	Fetal/neonatal outcomes • Perinatal death • Admission to neonatal intensive care unit (NICU)/ special nursery • Apgar scores

Annex 3. Summary and management of declared interests from GDG members

Name		Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Edgardo	**ABALOS**	Content expert and end-user	None declared	Not applicable
Ebun	**ADEJUYIGBE**	Content expert and end-user	None declared	Not applicable
Shabina	**ARIFF**	Content expert and end-user	None declared	Not applicable
Jemima	**DENNIS-ANTWI**	Content expert and end-user	None declared	Not applicable
Luz Maria	**DE-REGIL**	Content expert and end-user	Global Affairs Canada awarded a grant to Dr De-Regil's institution to implement nutrition interventions in low and middle-income countries. Some of the funded work included support for implementation research on calcium supplementation in pregnancy in Kenya and Ethiopia. The work was sub-granted to Cornell University, and Dr De-Regil was not part of the research team. As a former WHO staff member, she supported the development of a guideline on calcium supplementation in pregnancy (led by NHD).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation
Christine	**EAST**	Content expert and end-user	None declared	Not applicable
Lynn	**FREEDMAN**	Content expert and end-user	None declared	Not applicable
Pisake	**LUMBIGANON**	Content expert and end-user	None declared	Not applicable
Anita	**MAEPIOH**	Content expert and end-user	None declared	Not applicable
James	**NEILSON**	Content expert and end-user	None declared	Not applicable
Hiromi	**OBARA**	Content expert and implementer	None declared	Not applicable

Name		Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Rachel	**PLACHCINSKI**	Consumer representative	None declared	Not applicable
Zahida	**QURESHI**	Content expert and end-user	None declared	Not applicable
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Eleni	**TSIGAS**	Consumer representative	Ms Tsigas represents patient experiences around preeclampsia and other hypertensive disorders of pregnancy to organizations, committees, and other multidisciplinary bodies. She is also a voting member on the Council for Patient Safety in Women's Healthcare (USA).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation

Annex 4. Evidence-to-Decision framework

A) QUESTION

In pregnant women (P), does calcium supplementation (I) compared to placebo or no calcium supplementation (C), improve maternal and perinatal outcomes (O), including the onset of pre-eclampsia?

- If so, in what populations of pregnant women or contexts is calcium supplementation most beneficial?
- If so, what dosing regimen of calcium supplementation is most beneficial?

Problem: Preventing the onset of pre-eclampsia and its complications
Perspective: Clinical practice recommendation – population perspective
Population: All pregnant women, particularly those at higher risk of gestational hypertensive disorders
Intervention: Calcium supplementation
Comparison: No calcium supplementation or placebo
Outcomes: [1]

Maternal

- Pre-eclampsia
- Eclampsia
- Recurrent seizures
- Severe maternal morbidity
- ICU admission
- Maternal death or severe maternal morbidity
- Maternal death
- Adverse effects of interventions

Fetal/Neonatal

- Apgar scores
- Admission to neonatal intensive care unit (NICU)/ special nursery
- Perinatal death

[1] These outcomes reflect the prioritized outcomes used for this recommendation, in the WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (2011).

B) ASSESSMENT

1. EFFECTS OF INTERVENTIONS

Research evidence

Summary of the evidence

A Cochrane systematic review of 27 trials investigated the effects of routine (daily) calcium supplementation when used for preventing pre-eclampsia and related problems *(15)*. Evidence was presented in three comparisons: "high-dose" calcium supplementation (1 g or more/day) versus placebo or no treatment; "low-dose" calcium supplementation (less than 1 g/day) versus placebo or no treatment; high-dose versus low-dose calcium supplementation.

Since the WHO recommendation was first published in 2011, this review has been updated twice: once in June 2014 and once in March 2018. The most recent update of this review includes an analysis of two new comparisons: low-dose calcium supplementation versus placebo; and high-dose versus low-dose calcium supplementation. Overall, the updates have added 14 studies:

- 12 contributed data to low-dose calcium supplementation with or without co- interventions versus no calcium supplementation (2334 women)[2];
- one contributed data to high-dose versus low-dose calcium (272 women); and
- one was included under high-dose versus placebo but did not contribute any data (662 women).

High-dose calcium supplementation (1 g or more/day) versus placebo or no treatment

Fourteen randomized controlled trials (RCTs), 13 of which contributed data, involving a total of 15 730 women, investigated the effects of routine (daily) supplementation with at least 1 g of calcium when used for preventing pre-eclampsia and related problems. The studies were conducted in Argentina (1 study), Australia (1), Ecuador (3), Gambia (1 – did not contribute data), India (2), the Islamic Republic of Iran (1), USA (3), and two were conducted in multiple countries, including Argentina, Egypt, India, Peru, South Africa and Vietnam; and USA and Argentina. As many as 96.2% of the women recruited were at a low risk of developing pre-eclampsia. However, over 70% of women recruited had low baseline dietary calcium intake (less than 900 mg per day). Supplemental calcium dose used ranged between 1.5 g and 2.0 g per day in all trials.

Effects of interventions (by hypertension risk)

Pre-eclampsia: Moderate-certainty evidence suggests high-dose calcium supplementation probably reduces the risk of pre-eclampsia when compared to placebo in all women (13 studies, 15 730 women; 379/7851 vs 510/7879; risk ratio (RR) 0.45, 95% confidence interval (CI) 0.31 to 0.65) and those at low-risk of developing hypertensive disorders (eight studies, 15 143 women; 370/7570 vs 456/7573;

[2] Nine of these studies comparing low-dose calcium supplementation with placebos have not contributed data to the analysis, because the calcium supplementation regimens in these studies included a range of additional supplements as co-interventions.

RR 0.59, 95% CI 0.41 to 0.83). High-certainty evidence suggests high-dose calcium supplementation reduces pre-eclampsia in those at high risk of developing hypertensive disorders (five studies, 587 women; 9/281 vs 54/306; RR 0.22, 95% CI 0.12 to 0.42).

Perinatal death: High-certainty evidence suggests that high-dose calcium supplementation compared to placebo or no treatment has little or no effect on stillbirth or death before discharge from hospital in all infants (11 studies; 15 665 infants; 183/7821 vs 205/7844; RR 0.90, 95% CI 0.74 to 1.09). High-certainty evidence suggests high-dose calcium supplementation has little to no effect on this outcome for those born to women at low-risk of developing hypertension (eight studies; 15 153 infants; 183/7573 vs 204/7580; RR 0.9, 95% CI 0.74 to 1.09), and may have little to no effect for those born to women at high risk of developing hypertension (three studies; 512 infants; 0/248 vs 1/264; RR 0.39, 95% CI 0.02 to 9.2; *low-certainty evidence*).

Admission to neonatal intensive care unit: Evidence suggests that high-dose calcium supplementation compared to placebo or no treatment has little or no effect on admission to neonatal intensive care unit in all infants (four studies; 13 406 infants; 530/6689 vs 507/6717; RR 1.05, 95% CI 0.94 to1.18; *high-certainty evidence*); those born to women at low-risk of developing hypertension (three studies; 13 343 infants; 529/6660 vs 503/6683; RR 1.06, 95% CI 0.94 to 1.19; *high-certainty evidence*); and may have little or no effect on those born to women at high-risk of developing hypertension (one trial; 63 infants; 1/29 vs 4/34; RR 0.29, 95% CI 0.03 to 2.48; *low-certainty evidence*).

No data were reported for other prioritized outcomes.

Effects of interventions (by baseline dietary calcium)

Pre-eclampsia: Moderate-certainty evidence suggests that high-dose calcium supplementation probably reduces pre-eclampsia in all women (13 studies, 15 730 women; 379/7851 vs 510/7879; RR 0.45, 95% CI 0.31 to 0.65) and those with a low calcium diet (eight studies, 10 678 women; 209/5331 vs 306/5347; RR 0.36, 95% CI 0.20 to 0.65); though in women with an adequate calcium diet high-dose calcium supplementation probably makes little or no difference to developing pre-eclampsia (four studies, 5022 women; 169/2505 vs 197/2517; RR 0.62, 95% CI 0.32 to 1.20).

Maternal death or serious morbidity: In women or populations with low calcium diets, high-certainty evidence suggests high-dose calcium supplementation slightly reduces the composite outcome of maternal death or serious morbidity compared with placebo (four studies, 9732 women; 167/4856 vs 209/4876; RR 0.80, 95% CI 0.66 to 0.98). All events under this outcome are taken from a large WHO RCT involving 8312 women. The events were recorded under the 'Severe maternal morbidity and mortality index' which includes at least one of the following outcomes: admission to intensive care or any special care unit, eclampsia, severe pre-eclampsia, placental abruption, haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, renal failure, or death. This outcome was not reported for women with an adequate calcium diet.

In addition, high-certainty evidence suggests that high-dose calcium supplementation increases the risk of developing HELLP syndrome in women who received calcium supplementation compared to placebos (two studies, 12 901 women; 16/6446 vs 6/6455; RR 2.67, 95% CI 1.05 to 6.82).

High-dose calcium supplementation made little or no difference to the two groups for other critical (and proxy) outcomes addressed by the review: eclampsia (three studies, 13 425 women; 21/6719 vs 29/6706; RR 0.73, 95% CI 0.41 to 1.27; *moderate-certainty evidence*); maternal intensive care unit admission (one trial, 8312 women; 116/4151 vs 138/4161; RR 0.84, 95% CI 0.66 to 1.07; *moderate-certainty evidence*); maternal death (one trial, 8312 women; 1/4151 vs 6/4161; RR 0.17, 95% CI 0.02 to 1.39; *moderate-certainty evidence*); stillbirth or death before discharge from hospital (11 trials, 15 665 women; 183/7821 vs 205/7844; RR 0.90, 95% CI 0.74 to 1.09; *high-certainty evidence*); and admission to neonatal intensive care unit (four studies, 13 406 women; 530/6689 vs 507/6717; RR 1.05, 95% CI 0.94 to 1.18; *high-certainty evidence*).

Low-dose calcium supplementation (less than 1 g/day) versus no calcium

Three studies with 820 women reported findings for women receiving supplementation with less than 1 g of calcium daily with no co-intervention compared with no calcium. The studies were conducted in the Philippines, Trinidad and Hong Kong.

The three studies involved women with varying degrees of hypertension risk: one study recruited primiparous women only and did not mention risk factors; another study included high-risk primiparous women only (using a cut-off of mean arterial pressure (MAP) <60mmHg in left-lateral position); the third study recruited both normotensive primiparous women, and multiparous women with a history of pre-eclampsia in a previous pregnancy. Baseline dietary calcium was not specified in any of the studies. There was insufficient data in the review to undertake a meaningful subgroup analysis under this comparison.

In two studies there were three groups and in the third study there were five groups: there were only data relevant from two arms of each trial and these were included in a pair-wise comparison for the review. The daily dose of calcium used in the studies was 600 mg in two studies and 360 mg in one study. Control groups were stated as not receiving calcium in two studies (no other details given) and in one study the control group was 80 mg of daily aspirin (80 mg aspirin was also given to calcium group). In two studies, supplementation started at 22 weeks' gestation and in one study it started at 20 weeks' gestation. Evidence for all outcomes was downgraded due to limitations in study design, imprecision or both.

Effects of interventions

Pre-eclampsia: Low-certainty evidence suggests that pre-eclampsia may be reduced for women receiving low-dose calcium compared with placebo or no calcium (three studies, 812 women; 24/440 vs 55/372; risk ratio (RR) 0.37, 95% confidence interval (CI) 0.23 to 0.60; *low-certainty evidence*). Similarly, low-certainty evidence suggests that **high blood pressure (with or without pre-eclampsia)** may be reduced for women receiving lower dose calcium (two studies, 390 women; 36/228 vs 37/162; RR 0.60, 95% CI 0.40 to 0.91).

Perinatal death: Evidence on this outcome is of very low certainty.

Neonatal intensive care unit admission: Low-certainty evidence suggests there may be a difference in NICU admission between groups with lower rates observed in the calcium supplementation group (one study, 422 infants; 8/212 vs 18/210; RR 0.44, 95% CI 0.20 to 0.99).

No data were reported for other prioritized outcomes.

High-dose compared with low-dose calcium supplementation

The same Cochrane review included evidence from a single study with 272 women conducted in India, comparing low-risk primiparous women receiving high-dose (2 g) versus low-dose (500 mg) daily calcium supplementation in pregnancy. Baseline dietary calcium was not specified.

Effects of interventions

Pre-eclampsia: Low-certainty evidence suggests pre-eclampsia may be reduced with a higher daily dose of calcium (one study, 262 women; 7/123 vs 19/139; RR 0.42, 95% CI 0.18 to 0.96).

Eclampsia: Evidence on this outcome is of very low certainty.

Stillbirth: Evidence on this outcome is of very low certainty.

No data were reported for other prioritized outcomes.

Desirable effects

How substantial are the desirable anticipated effects of **high-dose** calcium supplementation versus placebo or no treatment?

Judgement

☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☑ Large

How substantial are the desirable anticipated effects of **low-dose** calcium supplementation versus no treatment?

Judgement

☐ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☑ Large

How substantial are the desirable anticipated effects of **high-dose** versus **low-dose** calcium supplementation?

Judgement

☑ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☐ Large

Undesirable effects

How substantial are the undesirable anticipated effects of **high-dose** calcium supplementation versus placebo or no treatment?

Judgement

☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☑ Small	☐ Trivial

How substantial are the undesirable anticipated effects of **low-dose** calcium supplementation versus no treatment?

Judgement

☐ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☑ Trivial

How substantial are the undesirable anticipated effects of **high-dose** versus **low-dose** calcium supplementation versus no treatment?

Judgement

☑ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Certainty of the evidence

What is the overall certainty of the evidence of the effects of **high-dose** calcium supplementation versus placebo or no treatment?

☐ No included studies	☐ Very low	☐ Low	☑ Moderate	☐ High

What is the overall certainty of the evidence of the effects of **low-dose** calcium

☐ No included studies	☑ Very low	☐ Low	☐ Moderate	☐ High

What is the overall certainty of the evidence of the effects of **high-dose** versus **low-dose** calcium supplementation?

☐ No included studies	☑ Very low	☐ Low	☐ Moderate	☐ High

Additional considerations

Preterm birth was not a pre-specified outcome for this recommendation. However:

- Low-certainty evidence from the aforementioned Cochrane review suggests preterm birth (< 37 weeks' gestation) may be reduced with supplementation with lower dose calcium (one study, 422 women; 12/212 vs 30/210; RR 0.40, 95% CI 0.21 to 0.75) *(15)*.
- A separate Cochrane review has examined the effects of calcium supplementation in pregnancy (other than for preventing or treating hypertension) *(17)*. The review included data from 23 trials involving 18 587 pregnant women and informed the GDG panel for the WHO antenatal care recommendations *(2)*. No effects were identified for prioritized outcomes, however the antenatal care (ANC) recommendation (A3) states that "moderate-certainty evidence shows that high-dose calcium supplementation probably reduces preterm birth (12 trials, 15 379 women, RR 0.81 95% CI: 0.66 – 0.99)." However, 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.

Values

Is there important uncertainty about, or variability in, how much women value the main outcomes associated with calcium supplementation?

Research evidence

Evidence from a qualitative systematic review of what women want from antenatal care showed that women from high-, middle- and low-resource settings valued having a positive pregnancy experience, the components of which included the provision of effective clinical practices (interventions and tests, including nutritional supplements), relevant and timely information (including dietary and nutritional advice) and psychosocial and emotional support, by knowledgeable, supportive and respectful healthcare practitioners, to optimize maternal and newborn health (*high confidence in the evidence*) *(18)*.

Additional considerations

Pre-eclampsia can increase the risk of adverse outcomes to mother and baby, as well as increase the use of additional interventions and hospital admission. Considering these risks, the GDG considers it unlikely that there would be important variability in how women value this outcome.

Judgement

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☑ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects **favour high-dose calcium supplementation** or the comparison?

Judgement

☐ Don't know	☐ Varies	☐ Favours the comparison	☐ Probably favours the comparison	☐ Does not favour the intervention or the comparison	☑ Probably favours the intervention	☐ Favours the intervention

Does the balance between desirable and undesirable effects **favour low-dose calcium supplementation** or the comparison?

Judgement

☐ Don't know	☐ Varies	☐ Favours the comparison	☐ Probably favours the comparison	☐ Does not favour the intervention or the comparison	☑ Probably favours the intervention	☐ Favours the intervention

Does the balance between desirable and undesirable effects **favour high-dose** or **low-dose calcium supplementation**?

Judgement

☑ Don't know	☐ Varies	☐ Favours the comparison	☐ Probably favours the comparison	☐ Does not favour the intervention or the comparison	☐ Probably favours the intervention	☐ Favours the intervention

2. RESOURCES

How large are the resource requirements (costs) of calcium supplementation?

Research evidence

The Cochrane review did not include studies or collate data related to cost-effectiveness of calcium supplementation in pregnancy. No cost-effectiveness studies were identified.

The following assumptions are taken from the WHO OneHealth tool:*(19)*

- Using the MSH International drug price calculator, the unitary cost of 600 mg calcium is 0.0213 USD/tablet
- Thus, 3 x 600 mg tablets per day for 20 weeks is estimated to cost US$ 8.95

Main resource requirements

Resource	Description
Staff training	Training in advising women on appropriate use of calcium supplementation and encouraging compliance
Supplies	Sufficient tablets for daily calcium supplementation during pregnancy (e.g. 420 x 600 mg tablets for 20 weeks). Calcium may be available in different formulations in different settings (e.g. 500 mg, 600 mg and 1 g tablets).
Equipment	-
Infrastructure	-
Staff time	As part of routine antenatal care services

Additional considerations

The cost of calcium is relatively high compared with other supplements such as iron and folate. The weight and volume of the supplement may have cost and logistics implications with respect to storage and transport for health services. Calcium supplements may be available in other doses (e.g.: 500 mg tablets) *(20)*.

Resources required

Judgement

☐ Don't know	☐ Varies	☐ Large costs	☑ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement

☑ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Cost-effectiveness

Judgement

☑ Don't know	☐ Varies	☐ Favours the comparison	☐ Probably favours the comparison	☐ Does not favour either the intervention or the comparison	☐ Probably favours the intervention	☐ Favours the intervention

3. EQUITY

What would be the impact of calcium supplementation on health equity?

Research evidence

A systematic review assessed global inequities in calcium intake during pregnancy, updating a 2005 systematic review on calcium intake by pregnant women worldwide *(13)*. The review included 105 studies of calcium intake during pregnancy. The weighed arithmetic mean was 948.3 mg/day (95% CI 872.1–1024.4 mg/day) for high income countries and 647.6 mg/day (95% CI 568.7–726.5 mg/day) for LMICs. Considering an estimated average calcium requirement of 800 mg/day, 14 (25.9%) studies from high-income countries report calcium intakes below this value, whereas 39 (76.5%) from LMICs did so.

In LMICs, women who are poor, least educated, and residing in rural areas have lower health intervention coverage and worse health outcomes than the more advantaged women. In the 2015 WHO State of Inequalities Report, antenatal care (ANC) coverage of at least four visits differed by at least 25% between the most and least educated, and the richest and poorest in half the LMICs studied *(21)*. Inequalities in ANC coverage of at least one visit were also demonstrated, though to a lesser extent. It is therefore likely that adverse consequences of calcium deficiency in pregnancy are worse in women living in disadvantaged circumstances. Effective, equitable implementation of this recommendation could potentially reduce health inequities.

Additional considerations

None

Judgement

Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased
☐	☐	☐	☐	☐	☑	☐

4. ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

Research evidence

A systematic review of qualitative research exploring women's views and experiences of antenatal care suggests that they tend to view antenatal care as a source of knowledge and information and generally appreciate any advice (including dietary or nutritional) that may lead to a healthy baby and a positive pregnancy experience (*high confidence in the evidence*) *(2)*.

However, calcium carbonate tablets might be unpalatable to many women, as they can be large and have a powdery texture *(15)*. In addition, this intervention usually involves taking three tablets a day, which significantly increases the number of tablets a woman is required to take on a daily basis (in addition to other supplements such as iron and folic acid). These factors could have implications for both acceptability and compliance, which needs to be assessed in a programmatic context.

Additional considerations

None

Judgement

Don't know	Varies	No	Probably No	Probably Yes	Yes
☐	☑	☐	☐	☐	☐

5. FEASIBILITY

Is the intervention feasible to implement?

Research evidence

Where there are likely to be additional costs associated with supplementation (*high confidence in the evidence*) or where the recommended interventions are unavailable because of resource constraints (*low confidence in the evidence*) women may be less likely to engage with services *(2)*.

In addition to the cost, providing calcium supplements may be associated with logistical issues (e.g. supplements are bulky and require adequate transport and storage to maintain stock in medical facilities) and other challenges (e.g. forecasting). Also, multiple pills are needed to reach the recommended dosage, therefore the feasibility of women using this intervention may be affected.

Qualitative evidence on healthcare providers' views suggests that resource constraints (lack of supplement availability, and lack of trained staff) may limit implementation (*high confidence in the evidence*) *(2)*.

Additional considerations

None.

Judgement

☐	☑	☐	☐	☐	☐
Don't know	Varies	No	Probably No	Probably Yes	Yes

C) SUMMARY OF JUDGEMENTS – high-dose calcium supplementation versus placebo or no treatment

Desirable effects	– Don't know	– Varies		– Trivial	– Small	– Moderate	✔ **Large**
Undesirable effects	Don't know	– Varies		– Large	– Moderate	✔ **Small**	– Trivial
Certainty of the evidence	– No included studies			– Very low	– Low	✔ **Moderate**	– High
Values				– Important uncertainty or variability	– Possibly important uncertainty or variability	✔ **Probably no important uncertainty or variability**	– No important uncertainty or variability
Balance of effects	– Don't know	– Varies	– Favours the comparison	– Probably favours the comparison	– Does not favour either the intervention or the comparison	✔ **Probably favours the intervention**	– Favours the intervention
Resources required	– Don't know	– Varies	– Large costs	✔ **Moderate costs**	– Negligible costs or savings	– Moderate savings	– Large savings
Certainty of evidence of required resources	✔ **No included studies**			– Very low	– Low	– Moderate	– High
Cost-effectiveness	✔ **Don't know**	– Varies	– Favours the comparison	– Probably favours the comparison	Does not favour either the intervention or the comparison	– Probably favours the intervention	– Favours the intervention
Equity	– Don't know	– Varies	– Reduced	– Probably reduced	– Probably no impact	✔ **Probably increased**	– Increased
Acceptability	– Don't know	✔ **Varies**		– No	– Probably No	– Probably Yes	– Yes
Feasibility	– Don't know	✔ **Varies**		– No	– Probably No	– Probably Yes	– Yes

SUMMARY OF JUDGEMENTS – low-dose calcium supplementation versus placebo or no treatment

Desirable effects	– Don't know	– Varies		– Trivial	– Small	– Moderate	✔ **Large**
Undesirable effects	Don't know	– Varies		– Large	– Moderate	– Small	✔ **Trivial**
Certainty of the evidence	– No included studies			✔ **Very low**	– Low	– Moderate	– High
Values				– Important uncertainty or variability	– Possibly important uncertainty or variability	✔ **Probably no important uncertainty or variability**	– No important uncertainty or variability
Balance of effects	– Don't know	– Varies	– Favours the comparison	– Probably favours the comparison	– Does not favour either the intervention or the comparison	✔ **Probably favours the intervention**	– Favours the intervention
Resources required	– Don't know	– Varies	– Large costs	✔ **Moderate costs**	– Negligible costs or savings	– Moderate savings	– Large savings
Certainty of evidence of required resources	✔ **No included studies**			– Very low	– Low	– Moderate	– High
Cost-effectiveness	✔ **Don't know**	– Varies	– Favours the comparison	– Probably favours the comparison	Does not favour either the intervention or the comparison	– Probably favours the intervention	– Favours the intervention
Equity	– Don't know	– Varies	– Reduced	– Probably reduced	– Probably no impact	✔ **Probably increased**	– Increased
Acceptability	– Don't know	✔ **Varies**		– No	– Probably No	– Probably Yes	– Yes
Feasibility	– Don't know	✔ **Varies**		– No	– Probably No	– Probably Yes	– Yes

SUMMARY OF JUDGEMENTS – high-dose versus low-dose calcium supplementation

Desirable effects	✓ **Don't know**	– Varies		– Trivial	– Small	– Moderate	– Large
Undesirable effects	✓ **Don't know**	– Varies		– Large	– Moderate	– Small	– Trivial
Certainty of the evidence	– No included studies			✓ **Very low**	– Low	– Moderate	– High
Values				– Important uncertainty or variability	– Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	– No important uncertainty or variability
Balance of effects	✓ **Don't know**	– Varies	– Favours the comparison	– Probably favours the comparison	– Does not favour either the intervention or the comparison	– Probably favours the intervention	– Favours the intervention
Resources required	– Don't know	– Varies	– Large costs	✓ **Moderate costs**	– Negligible costs or savings	– Moderate savings	– Large savings
Certainty of evidence of required resources	✓ **No included studies**			– Very low	– Low	– Moderate	– High
Cost-effectiveness	✓ **Don't know**	– Varies	– Favours the comparison	– Probably favours the comparison	Does not favour either the intervention or the comparison	– Probably favours the intervention	– Favours the intervention
Equity	– Don't know	– Varies	– Reduced	– Probably reduced	– Probably no impact	✓ **Probably increased**	– Increased
Acceptability	– Don't know	✓ **Varies**		– No	– Probably No	– Probably Yes	– Yes
Feasibility	– Don't know	✓ **Varies**		– No	– Probably No	– Probably Yes	– Yes

Annex 5. GRADE Tables

Question: High-dose calcium supplementation (>1 g/day) with or without co-supplements compared to placebo for preventing hypertensive disorders and related problems

Setting: Fourteen studies with 15,730 women conducted in Argentina (1), Australia (1), Ecuador (3), Gambia (1 – did not contribute data), India (2), Iran (1), USA (3), and multiple countries (Argentina, Egypt, India, Peru, South Africa and Vietnam; and Argentina and USA) (2).

High-dose calcium supplementation in pregnancy versus placebo/no treatment overall, and by baseline risk of hypertension diseases

Certainty assessment							Summary of findings					Importance
							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine calcium supplementation	No calcium supplementation	Relative (95% CI)	Absolute		
Pre-eclampsia (all women)												
13	randomized trials	no serious limitations	serious [a]	no serious indirectness	no serious imprecision	none	379/7851 (4.8%)	510/7879 (6.5%)	**RR 0.45** (0.31 to 0.65)	**36 fewer per 1000** (from 23 fewer to 45 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Pre-eclampsia (women at low-risk of pre-eclampsia)												
8	randomized trials	no serious limitations	serious [a]	no serious indirectness	no serious imprecision	none	370/7570 (4.9%)	456/7573 (6%)	**RR 0.59** (0.41 to 0.83)	**25 fewer per 1000** (from 10 fewer to 36 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Pre-eclampsia (women at high-risk of pre-eclampsia)												
5	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/281 (3.2%)	54/306 (17.6%)	**RR 0.22** (0.12 to 0.42)	**138 fewer per 1000** (from 102 fewer to 155 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Perinatal death (stillbirth or death before discharge from hospital) (all women)												
11	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision [b]	none	183/7821 (2.3%)	205/7844 (2.6%)	**RR 0.9** (0.74 to 1.09)	**3 fewer per 1000** (from 7 fewer to 2 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							Summary of findings					Importance
							№ of patients		Effect		Certainty	
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Routine calcium supplementation**	**No calcium supplementation**	**Relative (95% CI)**	**Absolute**		
Stillbirth or death before discharge from hospital (women at low-risk of pre-eclampsia)												
8	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision [b]	none	183/7573 (2.4%)	204/7580 (2.7%)	**RR 0.9** (0.74 to 1.09)	**3 fewer per 1000** (from 7 fewer to 2 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Stillbirth or death before discharge from hospital (women with high risk of pre-eclampsia)												
3	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious [c]	none	0/248 (0%)	1/264 (0.4%)	**RR 0.39** (0.02 to 9.2)	**2 fewer per 1000** (from 4 fewer to 31 more)	⨁⨁◯◯ LOW	CRITICAL
Admission to neonatal intensive care unit (all women)												
4	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	530/6689 (7.9%)	507/6717 (7.5%)	**RR 1.05** (0.94 to 1.18)	**4 more per 1000** (from 5 fewer to 14 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Admission to neonatal intensive care unit (women at low-risk pre-eclampsia)												
3	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	529/6660 (7.9%)	503/6683 (7.5%)	**RR 1.06** (0.94 to 1.19)	**5 more per 1000** (from 5 fewer to 14 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							Summary of findings					Importance
							№ of patients		Effect		Certainty	
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Routine calcium supplementation**	**No calcium supplementation**	**Relative (95% CI)**	**Absolute**		
Admission to neonatal intensive care unit (women at high-risk of pre-eclampsia)												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[c]	none	1/29 (3.4%)	4/34 (11.8%)	**RR 0.29** (0.03 to 2.48)	**84 fewer per 1000** (from 114 fewer to 174 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Serious heterogeneity (I squared=70%) possibly due to variation in baseline dietary intake of calcium.
b. The confidence interval includes results from appreciable benefit to negligible harm. However, downgrading was not performed considering the very large sample size.
c. Very small sample size and few events

High-dose calcium supplementation in pregnancy versus placebo/no treatment overall, and by baseline dietary calcium

Certainty assessment							Summary of findings					
							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine calcium supplementation	No calcium supplementation	Relative (95% CI)	Absolute		
Pre-eclampsia												
13	randomized trials	no serious limitations	serious[a]	no serious indirectness	no serious imprecision	none[b]	379/7851 (4.8%)	510/7879 (6.5%)	**RR 0.45** (0.31 to 0.65)	**36 fewer per 1000** (from 23 fewer to 45 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Pre-eclampsia - Adequate calcium diet												
4	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[c]	none	169/2505 (6.7%)	197/2517 (7.8%)	**RR 0.62** (0.32 to 1.2)	**30 fewer per 1000** (from 53 fewer to 16 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Pre-eclampsia - Low calcium diet												
8	randomized trials	no serious limitations	serious[d]	no serious indirectness	no serious imprecision	none	209/5331 (3.9%)	306/5347 (5.7%)	**RR 0.36** (0.2 to 0.65)	**37 fewer per 1000** (from 20 fewer to 46 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Pre-eclampsia - Dietary calcium not specified												
1	randomized trials	no serious limitations	serious[e]	no serious indirectness	very serious[f]	none	1/15 (6.7%)	7/15 (46.7%)	**RR 0.14** (0.02 to 1.02)	**401 fewer per 1000** (from 457 fewer to 9 more)	⨁◯◯◯ VERY LOW	CRITICAL
Eclampsia												
3	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[c]	none	21/6719 (0.3%)	29/6706 (0.4%)	**RR 0.73** (0.41 to 1.27)	**1 fewer per 1000** (from 3 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							Summary of findings					Importance
							№ of patients		Effect		Certainty	
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Routine calcium supplementation**	**No calcium supplementation**	**Relative (95% CI)**	**Absolute**		
Maternal death/serious morbidity												
4	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	167/4856 (3.4%)	209/4876 (4.3%)	**RR 0.8** (0.66 to 0.98)	**9 fewer per 1000** (from 1 fewer to 15 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
HELLP syndrome												
2	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/6446 (0.2%)	6/6455 (0.1%)	**RR 2.67** (1.05 to 6.82)	**2 more per 1000** (from 0 more to 5 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Intensive care unit admission												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[c]	none	116/4151 (2.8%)	138/4161 (3.3%)	**RR 0.84** (0.66 to 1.07)	**5 fewer per 1000** (from 11 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Maternal death												
1	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[c]	none	1/4151 (0%)	6/4161 (0.1%)	**RR 0.17** (0.02 to 1.39)	**1 fewer per 1000** (from 1 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Stillbirth or death before discharge from hospital												
11	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision[g]	None	183/7821 (2.3%)	205/7844 (2.6%)	**RR 0.9** (0.74 to 1.09)	**3 fewer per 1000** (from 7 fewer to 2 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Certainty assessment							Summary of findings					Importance
							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine calcium supplementation	No calcium supplementation	Relative (95% CI)	Absolute		
Admission to neonatal intensive care unit												
4	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	None	530/6689 (7.9%)	507/6717 (7.5%)	**RR 1.05** (0.94 to 1.18)	**4 more per 1000** (from 5 fewer to 14 more)	⨁⨁⨁⨁ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Serious heterogeneity (I2=76%) due to variation in baseline risks of developing pre-eclampsia. All 3 studies that account for the inconsistency were conducted in women at low risk of developing pre-eclampsia.
b. No downgrading in spite of the evident asymmetry in the funnel plot because the studies are already downgraded for significant heterogeneity.
c. Wide confidence interval
d. Serious heterogeneity (I squared=76%) due to variation in baseline risks of developing pre-eclampsia. All studies showing no effect of intervention involved women at low risk of developing pre-eclampsia.
e. The only study was at moderate risk of bias
f. Very small sample size and few events; wide confidence interval
g. The confidence interval includes results from appreciable benefit to negligible harm. However, downgrading was not performed considering the very large sample size

Question: Low-dose calcium supplementation (< 1 g/day) with or without co-supplements compared to placebo for preventing hypertensive disorders and related problems

Setting: Three studies with 820 women conducted in the Philippines, Trinidad and Hong Kong.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low-dose calcium supplementation (< 1 g/day) with or without co-supplements**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pre-eclampsia												
3	randomized trials	very serious [a]	not serious	not serious	not serious	none	24/440 (5.5%)	55/372 (14.8%)	**RR 0.37** (0.23 to 0.60)	**93 fewer per 1,000** (from 59 fewer to 114 fewer)	⨁⨁◯◯ LOW	CRITICAL
High blood pressure (with or without pre-eclampsia)												
2	randomized trials	very serious [b]	not serious	not serious	not serious	none	36/228 (15.8%)	37/162 (22.8%)	**RR 0.60** (0.40 to 0.91)	**91 fewer per 1,000** (from 21 fewer to 137 fewer)	⨁⨁◯◯ LOW	CRITICAL
Perinatal death (Stillbirth or death before discharge)												
1	randomized trials	serious [d]	not serious	not serious	very serious [e]	none	1/84 (1.2%)	1/87 (1.1%)	**RR 1.04** (0.07 to 16.29)	**0 fewer per 1,000** (from 11 fewer to 176 more)	⨁◯◯◯ VERY LOW	CRITICAL
Neonatal intensive care unit admission												
1	randomized trials	very serious [b]	not serious	not serious	not serious [f]	none	8/212 (3.8%)	18/210 (8.6%)	**RR 0.44** (0.20 to 0.99)	**48 fewer per 1,000** (from 1 fewer to 69 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Studies contributing data had serious or very serious design limitations (-2)
b. All or more than 40% of the data were from a study with very serious design limitations (-2)
c. Small sample size and wide 95% CI crossing the line of no effect (-2)
d. Study contributing data had design limitations (-1)
e. Low event rate and wide 95% CI crossing the line of no effect (-2)
f. Not downgraded for imprecision although the total number of events was fairly low (0)

Question: High dose compared to low dose calcium supplements for preventing hypertensive disorders and related problems

Setting: Single study with 272 women conducted in India

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low-dose calcium supplementation (< 1 g/day) with or without co-supplements**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pre-eclampsia												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	7/123 (5.7%)	19/139 (13.7%)	**RR 0.42** (0.18 to 0.96)	**79 fewer per 1,000** (from 5 fewer to 112 fewer)	⨁⨁◯◯ LOW	CRITICAL
Eclampsia												
1	randomized trials	serious [a]	not serious	not serious	very serious [c]	none	2/123 (1.6%)	7/139 (5.0%)	**RR 0.32** (0.07 to 1.53)	**34 fewer per 1,000** (from 27 more to 47 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Stillbirth												
1	randomized trials	serious [a]	not serious	not serious	very serious [d]	none	3/123 (2.4%)	7/139 (5.0%)	**RR 0.48** (0.13 to 1.83)	**26 fewer per 1,000** (from 42 more to 44 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Single study with design limitations (-1)
b. Estimate based on study with small sample size (-1)
c. Wide 95% CI crossing the line of no effect and small sample size (-2)
d. Wide 95% CI crossing the line of no effect, small sample size and low event rate (-2)

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