WHO recommendation on

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

World Health Organization

human reproduction programme hrp
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Leanne Jones, Frances Kellie and Myfanwy Williams reviewed the scientific evidence, prepared the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables and drafted the narrative summary of evidence. Joshua Vogel, Abiodun Adanikin and Olufemi Oladapo revised the narrative summaries and double-checked the corresponding GRADE tables and prepared the evidence-to-decision (EtD) frameworks. Abiodun Adanikin, Fernando Althabe, Ana Pilar Betrán, Mercedes Bonet, Maurice Bucagu, Fran McConville, Olufemi Oladapo, Juan Pablo Peña-Rosas, Anayda Portela, Lisa Rogers, Özge Tuncalp and Joshua Vogel commented on a preliminary draft document before discussions and deliberations by the WHO Guideline Development Group members. The External Review Group peer reviewed the final document prior to executive clearance by WHO and publication.

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Acronyms and abbreviations

ANC	Antenatal care
BMGF	Bill & Melinda Gates Foundation
CI	Confidence interval
DOI	Declaration of Interest
EtD	Evidence-to-decision
FIGO	International Federation of Gynaecology and Obstetrics
FWC	Family, Women's and Children's Health (a WHO cluster)
GDG	Guideline Development Group
GRC	Guidelines 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 and Ageing
MCSP	Maternal and Child Survival Programme
MPH	Maternal and Perinatal Health (a unit in WHO's Department of Sexual and Reproductive Health and Research)
NFS	[WHO Department of] Nutrition and Food Safety
NICU	Neonatal intensive care unit
NNT	Number needed to treat
PICO	Population (P), intervention (I), comparison (C), outcome (O)
RCT	Randomized controlled trial
RR	Relative risk
SDG	Sustainable Development Goals
SoF	Summary of findings
SRH	[WHO Department of] Sexual and Reproductive Health and Research
UN	United Nations
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
WHO	World Health Organization

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. Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. Most of the 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 are necessary steps 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 2019, the Executive Guideline Steering Group (GSG) on WHO maternal and perinatal health recommendations prioritized the development of a new WHO recommendation on calcium supplementation before and/or early in pregnancy for preventing hypertensive disorders of pregnancy, in response to the publication of a multi-country trial evaluating the use of pre-pregnancy calcium supplementation.

Target audience

The primary audience of this recommendation includes health professionals who are responsible for developing national and local health protocols (particularly those related to pre-eclampsia and eclampsia, and nutrition for non-pregnant and pregnant women and adolescent girls), 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. It aims to help in increasing capacity in countries to respond to their needs on interventions before and/or early in pregnancy to prevent the risk of pre-eclampsia during pregnancy, and to prioritize essential actions in national health policies, strategies and plans.

Guideline development methods

The development 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 recommendation.

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 the evidence profiles for the prioritized question. WHO convened an online meeting on 31 July 2019 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.

Recommendation

The GDG reviewed the balance between the desirable and undesirable effects and the overall quality of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability,

feasibility and equity. The GDG issued a new recommendation on pre-pregnancy calcium supplementation, with remarks and implementation considerations. 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 pre-pregnancy calcium supplementation for the prevention of pre-eclampsia and its complications

Pre-pregnancy calcium supplementation for the prevention of pre-eclampsia and its complications is recommended only in the context of rigorous research.

(Recommendation in research context)

Justification

- Low-certainty evidence suggests that starting calcium supplementation before and/or early in pregnancy (compared to placebo or no treatment) may make little or no difference to women's risk of developing hypertensive disorders during pregnancy. The estimate of effect of this intervention on the outcome "pre-eclampsia and/or pregnancy loss and/or stillbirth at any gestational age" included the possibility of a risk reduction, but the 95% confidence interval touched the line of no effect. There is a possibility of clinical benefit for those women with greater than 80% compliance with calcium supplementation. However, this is uncertain and needs further research. The maternal adverse effects of the intervention are not known.

- The acceptability of calcium supplementation by women may vary – while women may value nutritional interventions that can lead to a healthy baby and a positive pregnancy experience, calcium tablets can be large, have a powdery texture and be unpalatable to consume. Feasibility may also be limited in settings where calcium is not always available due to logistical or staff constraints or cost. In addition, limited access to pre-conception healthcare services may be a barrier to the provision of calcium supplements prior to pregnancy. The cost-effectiveness of this intervention is not known.

Remarks

- The GDG noted that in 2018 WHO revalidated the recommendation that 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 *(1)*. However, there is insufficient evidence to determine with precision at what gestational age calcium supplementation should be commenced in order to confer this benefit. The 2018 recommendation specified that stakeholders may wish to commence calcium supplementation at the first antenatal care contact, in order to optimize compliance with this regimen. Evidence review on initiation of calcium supplementation before pregnancy and continuing through pregnancy, however, shows that it remains uncertain whether this will confer additional health benefits, and further research is required.

- Food fortification of staple foods with calcium may be an important public health intervention in settings where dietary calcium intake is low. Dietary counselling of all women who are considering pregnancy should promote adequate calcium intake through locally available, calcium-rich foods. Adequate calcium intake could be easily achieved by the incorporation of dairy products in the diet on a daily basis. However, dairy products are not part of all regular diets, or are not available in certain populations. Likewise, a high-salt diet decreases body-calcium retention compared to a diet that is low in salt. Caffeine and protein can also induce hypercalciuria, but to a much lesser extent. This has become more important in recent years due to the consumption of caffeine-containing beverages such as soda and energy drinks.

1. Background

An estimated 295 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2017, around 99% of which occurred in low-resource settings *(2)*. 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 *(3)*. International human rights law includes fundamental commitments of 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 *(4)*. 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" *(5)*.

There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications *(6)*. Almost two thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings *(7)*. To provide good-quality care, healthcare providers at all levels of maternal healthcare services, particularly in low and middle-income countries (LMICs) need to have access to appropriate medicines and health products, 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. Efforts to prevent and reduce morbidity and mortality in pregnancy and childbirth could reduce the profound inequities in maternal and perinatal health globally.

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 *(8)*. 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.

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 *(9)*. Recommendations were prioritized, based on 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 development of a new WHO recommendation on pre-pregnancy calcium supplementation for preventing hypertensive disorders of pregnancy, in response to the publication of a multi-country trial evaluating the use of this intervention *(10)*. The primary goal of this recommendation is to improve the quality of care and outcomes for pregnant women and women intending to become pregnant, particularly those related to prevention of pre-eclampsia, eclampsia and resulting complications.

Target audience

The primary audience includes health professionals who are responsible for developing national and local health guidelines and protocols (particularly those related to nutrition in pregnancy and 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 pre-conception and maternal care, and implementers of maternal and child health and nutrition programmes. It aims to help in increasing capacity in the countries to respond to their needs on interventions before and/or early in pregnancy to prevent the risk of pre-eclampsia during pregnancy, and to prioritize essential actions in national health policies, strategies and plans.

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 and women intending to become pregnant (P), does starting calcium supplementation before and/or early in pregnancy (I), compared to placebo or no calcium supplementation before and/or early in pregnancy (C), improve maternal and perinatal outcomes (O), including the onset of pre-eclampsia?
    - If yes, in what populations of women/pregnant women is pre-pregnancy calcium supplementation most beneficial?
    - What dosing regimen of calcium supplementation is most beneficial?

Persons affected by the recommendation

The population affected by this recommendation includes women (particularly those intending to become pregnant and those women at higher risk of gestational hypertensive disorders) in low, middle or high-income settings *(11)*.

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (12)*. 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, early/pre-pregnancy calcium supplementation was identified by the Executive GSG as a high priority for development of a recommendation, in response to new, potentially important evidence on this question *(10, 13)*. 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 (Executive GSG) for updating WHO maternal and perinatal health recommendations (2017–2019)

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 *(13)*.

WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research (SRH), the Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA), and the Department of Nutrition and Food Safety (NFS) managed the updating process. The Group drafted the key recommendation questions in PICO format, identified the systematic review team and guideline methodologists, 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 GDG 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

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 perceived or real conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health and nutrition during pregnancy.

From the MPH-GDG pool, 17 external experts and relevant stakeholders were invited to participate as members of the GDG for updating this recommendation. Those selected were a diverse group with expertise in research, guideline development methods, gender, equity and rights, clinical policy and programmes relating to pre-eclampsia and eclampsia prevention and treatment, as well as implementation of essential nutrition actions.

The 17 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 GDG 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 the GDG 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-informed obstetric and nutrition care, as well as gender, equity and rights. 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 names and affiliations of the external reviewers are provided here as an acknowledgement and by no means indicate their endorsement of the recommendations in this guideline. The acknowledgement of the

reviewers does not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. The members of the External Review Group are listed in Annex 1.

Evidence Synthesis Group

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 and methodologists 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 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 various WHO departments and programmes 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 (14)*. 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 in 2019 with the support of 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 5 (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 *(16)*. Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks *(17)*.

Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach (18). 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, the 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 recommendations

The WHO Steering Group supervised and finalized the preparation of summary of findings tables and narrative evidence summaries in collaboration with the Evidence Synthesis Group using the GRADE evidence-to-decision (EtD) framework. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For the priority questions, judgements were made on the impact of the intervention on each domain, in order to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and ESG created summary documents for each priority question covering evidence on each domain, as described below.

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: "What are the desirable and undesirable effects of the intervention?" and "What is the certainty of the evidence on effects?" Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement

that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the intervention. Where the intervention that showed evidence of potential harm was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result to a context-specific recommendation, with the context explicitly stated within the recommendation.

- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: "Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?" When the intervention resulted in benefit for outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the "effects" domain (see above), informed the "balance of effects" judgement.

- **Resources:** For this domain, the questions asked were: "What are the resources associated with the intervention?" and "Is the intervention cost-effective?" The resources required to implement pre-pregnancy calcium supplementation mainly include the costs of providing supplies, training, equipment and skilled human resources. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively.

- **Acceptability:** For this domain, the question was: "Is the intervention acceptable to women and healthcare providers?" Qualitative evidence from systematic reviews on women's and providers' views and experiences with routine antenatal care services *(19)* informed the judgements for this domain. The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.

- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of healthcare providers responsible for administering it. The question addressed was: "Is it feasible for the relevant stakeholders to implement the intervention?" Qualitative evidence from the systematic reviews on women's and providers' views and experiences with antenatal care services was used to inform judgements for this domain *(19)*. Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.

- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: "What is the anticipated impact of the intervention on equity?" The findings of a systematic review on inequities in calcium intake globally *(11)*, as well as the experiences and opinions of the GDG members, were used to inform judgements for this domain. The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences is described in the "additional considerations" subsections. Such considerations were derived from studies that might not have directly addressed the priority question, but which provided pertinent

information in the absence of direct evidence. These were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD frameworks, including evidence summaries, summary of findings (SoF) tables and other documents related to each recommendation, to GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meeting. During the GDG meeting (31 July 2019), which was conducted online under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD frameworks and any comments received through preliminary feedback, and formulated the recommendations. The purpose of the meeting was to reach consensus on each recommendation, including its direction and, in some instances, the specific context, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members. The GDG was asked to select one of the following categories for the recommendation:

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts ("context-specific recommendation"):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation, and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research ("research-context recommendation"):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties, related both to effectiveness of the intervention or option, and its acceptability and feasibility.

Management of declaration of interests

WHO has a robust process to protect the integrity of WHO in its normative work as well as to protect the integrity of individual experts the Organization collaborates with. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflict of interest. The disclosure and appropriate management of relevant financial and non-financial conflicts of interest of GDG 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 according to the *Guidelines for declarations of interest (WHO experts) (20).*

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 procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of

individuals were published online two weeks prior to the meeting. 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 during the GDG meeting

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 EtD 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. EtD 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, the final document was sent to eight external independent experts (External Review Group) 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 (EtD) 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 EtD 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 4). 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

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

Pre-pregnancy calcium supplementation for the prevention of pre-eclampsia and its complications is recommended only in the context of rigorous research.

(Recommendation in research context)

Justification

- Low-certainty evidence suggests that starting calcium supplementation before and/or early in pregnancy (compared to placebo or no treatment) may make little or no difference to women's risk of developing hypertensive disorders during pregnancy. The estimate of effect of this intervention on the outcome "pre-eclampsia and/or pregnancy loss and/or stillbirth at any gestational age" included the possibility of a risk reduction, but the 95% confidence interval touched the line of no effect. There is a possibility of clinical benefit for those women with greater than 80% compliance with calcium supplementation. However, this is uncertain and needs further research. The maternal adverse effects of the intervention are not known.

- The acceptability of calcium supplementation by women may vary – while women may value nutritional interventions that can lead to a healthy baby and a positive pregnancy experience, calcium tablets can be large, have a powdery texture and be unpalatable to consume. Feasibility may also be limited in settings where calcium is not always available due to logistical or staff constraints or cost. In addition, limited access to pre-conception healthcare services may be a barrier to the provision of calcium supplements prior to pregnancy. The cost-effectiveness of this intervention is not known.

Remarks

- The GDG noted that in 2018 WHO revalidated the recommendation that 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 (1). However, there is insufficient evidence to determine with precision at what gestational age calcium supplementation should be commenced in order to confer this benefit. The 2018 recommendation specified that stakeholders may wish to commence calcium supplementation at the first antenatal care contact, in order to optimize compliance with this regimen. Evidence review on initiation of calcium supplementation before pregnancy and continuing through pregnancy, however, shows that it remains uncertain whether this will confer additional health benefits, and further research is required.

- Food fortification of staple foods with calcium may be an important public health intervention in settings where dietary calcium intake is low. Dietary counselling of all women who are considering pregnancy should promote adequate calcium intake through locally available, calcium-rich foods. Adequate calcium intake could be easily achieved by the incorporation of dairy products in the diet on a daily basis. However, dairy products are not part of all regular diets, or are not available in certain populations. Likewise, a high-salt diet decreases body-calcium retention compared to a diet that is low in salt. Caffeine and protein can also induce hypercalciuria, but to a much lesser extent. This has become more important in recent years due to the consumption of caffeine-containing beverages such as soda and energy drinks.

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 at the international, national and local levels involved in the provision of care for women. As a recommendation for rigorous research, there is a need to further evaluate the benefits and harms of this intervention in a research context. However, it remains critical to ensure that the 2018 WHO recommendation on calcium supplementation during pregnancy (in populations with low dietary calcium intake) *(1)* is translated into antenatal care packages and programmes at country and health-facility levels (where appropriate).

Recommendation dissemination and evaluation

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 research considerations

- Pre-pregnancy calcium supplementation is recommended only in the context of rigorous research. This rating category indicates that there are important uncertainties about this intervention. The implementation can still be undertaken at a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related to effectiveness, as well as acceptability and feasibility.

- To assess effectiveness, rigorous research should – at least – compare women who are exposed to calcium supplementation prior to pregnancy with women who are not, and include a baseline assessment. These comparison groups should be as similar as possible to ensure that the effect of pre-pregnancy calcium supplementation is assessed, rather than the effect of other factors. Randomized trials are the most effective way to do this, but if these are not possible, then interrupted time series analyses or controlled before-and-after studies can be considered. Programmes that are evaluated without a comparison group or baseline assessment are at high risk of bias, and may not measure the true effect of this intervention.

- Relevant stakeholders (particularly those involved in programmes to improve calcium intake during pregnancy) should be informed that there is currently insufficient evidence to recommend in favour of or against the use of pre-pregnancy calcium supplementation for the prevention of pre-eclampsia and its complications.

- Women who opt to use calcium supplements before pregnancy for health benefits for themselves and/or their babies

should be well supported and informed of the uncertainties regarding the benefits and possible harms of this intervention.

- This recommendation should not detract from the importance of good nutrition for all women through all public health strategies. The implementation of the WHO recommendation on calcium supplementation during pregnancy (in populations with low dietary calcium intake) to reduce the risk of pre-eclampsia should also not be negatively affected. Specific guidance related to the implementation of calcium supplementation during pregnancy is available in the 2018 recommendation document *(1)*. The WHO antenatal care guidelines outline the 2016 WHO antenatal care model, which includes timing, content and frequency of antenatal care contacts *(21)*. In populations where calcium supplementation during pregnancy is implemented, the need for, and compliance with, calcium supplementation should be considered at all antenatal care contacts.

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:

- In pregnant women and non-pregnant women intending to become pregnant, does pre-pregnancy calcium provision or supplementation improve maternal and perinatal outcomes, including the onset of pre-eclampsia and its complications?
    - In what populations of women/pregnant women is pre-pregnancy calcium supplementation or provision most beneficial?
    - What dosing regimen (including dose, frequency and time of initiation) of calcium supplementation is most beneficial?
- What is the feasibility and acceptability of pre-pregnancy calcium supplementation to improve maternal and perinatal outcomes?

6. Applicability issues

Anticipated impact on the organization of care and resources

If a pre-pregnancy calcium supplementation programme targeting non-pregnant women and adolescent girls is implemented, resources are required for sustainable procurement and stocks of calcium tablets, as well as updated training curricula and provision of training to relevant health workers. The WHO model list of essential medicines (EML) *(22)* currently lists calcium tablets containing 500 mg (elemental calcium) in section 27 (Vitamins and minerals). Calcium is included in two different dosage forms – calcium tablets should be available in a 500 mg (elemental) dose. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford *(23)*.

Monitoring and evaluating guideline implementation

If a pre-pregnancy calcium supplementation programme targeting non-pregnant women and adolescent girls is implemented, it should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of primary healthcare, particularly women, 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 (24).

7. Updating the recommendation

The Executive GSG convenes annually 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. If 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 srhmph@who.int.

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Annex 2. Priority outcomes for decision-making

Key questions	Priority outcomes
In pregnant women and women intending to become pregnant (P), does starting calcium supplementation before and/or early in pregnancy (I), compared to placebo or no calcium supplementation before and/or early in pregnancy (C), improve maternal and perinatal outcomes (O), including the onset of pre-eclampsia? If yes, in what populations of women/ pregnant women is early calcium supplementation most beneficial? What dosing regimen of calcium supplementation is most beneficial?	**Maternal outcomes** • Maternal death • Eclampsia • Recurrent seizures • Pre-eclampsia • Severe maternal morbidity (including renal failure, liver failure, pulmonary oedema, cerebrovascular accident, HELLP syndrome, placental abruption, intensive care unit (ICU) admission) • Adverse effects of interventions • Maternal wellbeing • Maternal satisfaction **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
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	Grant support for a research study from the Government of Canada to former employer Nutrition International. As a WHO staff, coordinated the development of a guideline – *Calcium supplementation in pregnancy* – published by the WHO Department of Nutrition and Food Safety	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
Shireen MEHER	Content expert and end-user	Chief Investigator of a randomized control trial (RCT) evaluating calcium supplementation for prevention of pre-eclampsia in high-risk women (National Institute of Health Research (NIHR), United Kingdom of Great Britain and Northern Ireland).	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation
James NEILSON	Content expert and end-user	None declared	Not applicable
Hiromi OBARA	Content expert and implementer	None declared	Not applicable
Cristina PALACIOS	Content expert and end-user	Conducted a landscape review for WHO on the status of calcium fortification worldwide. Investigator on grant entitled – *Effect of Soluble Corn Fiber supplementation for 1 year on bone metabolism in adolescents* (National Institutes of Health)	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation

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
Kathleen RASMUSSEN	Content expert and end-user	None declared	Not applicable
Niveen Abu RMEILEH	Content expert and implementer	None declared	Not applicable
Eleni TSIGAS	Consumer representative	Pre-eclampsia Foundation received a 3-year grant from Merck for Mothers to organize a coalition of patient advocacy organizations Received travel expense reimbursement (US$ 1000) from Roche to visit corporate campus to learn more about state of pre-eclampsia biomarker research, and to share information about the Pre-eclampsia Foundation	The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation

Annex 4. Evidence-to-decision framework

1. BACKGROUND

- Calcium is an essential micronutrient that is absorbed via the intestine in activated form.
- Serum calcium levels are affected by the skeletal system (which serves as a calcium reservoir) and renal system (which filters ionized calcium through the glomeruli, though it is largely reabsorbed).
- Calcium intake is critical in pregnancy, particularly for fetal skeletal development. A lower incidence of pre-eclampsia has been reported in populations where local diets contain high levels of calcium *(25, 26)*.
- For pregnant women with low dietary calcium intake, WHO currently recommends calcium supplementation for the first antenatal care visit *(1)*.
- However, there are considerations that calcium supplementation before and/or early in pregnancy could have additional benefit of ensuring appropriate maternal calcium levels before the development of pre-eclampsia, which is often from 20 weeks' gestation.

2. QUESTION

Following are the questions of interest in PICO (population, intervention, comparator, outcome) format:

In pregnant women and women intending to become pregnant (P), does starting calcium supplementation before and/or early in pregnancy (I), compared to placebo or no calcium supplementation before and/or early in pregnancy (C), improve maternal and perinatal outcomes (O), including the onset of pre-eclampsia?

- If yes, in what populations of women/pregnant women is early calcium supplementation most beneficial?
- What dosing regimen of calcium supplementation is most beneficial?

Problem: Hypertensive disorders in pregnancy and their complications
Perspective: Clinical practice recommendation – population perspective
Population (P): Pregnant women or women intending to become pregnant, particularly those at higher risk of hypertensive disorders of pregnancy
Intervention (I): Starting calcium supplementation before and/or early in pregnancy
Comparison (C): No calcium supplementation or placebo
Setting: Community and hospital settings

Subgroups:

- Risk of pre-eclampsia (high, low, mixed/unclear)
- Dietary intake of calcium (low, adequate, mixed/unclear)
- Calcium supplementation regimen (≥1 g daily, <1 g daily)
- Timing of commencement of calcium supplementation (prenatally, first trimester)

Priority outcomes (O):[1]

Maternal outcomes

- Maternal death
- Eclampsia
- Recurrent seizures
- Pre-eclampsia
- Severe maternal morbidity (including renal failure, liver failure, pulmonary oedema, cerebrovascular accident, HELLP syndrome, placental abruption, intensive care unit (ICU) admission)
- Adverse effects of interventions
- Maternal wellbeing
- Maternal satisfaction

Fetal/neonatal outcomes

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

3. ASSESSMENT

3.1 EFFECTS OF INTERVENTIONS

What is the effect of calcium supplementation on the priority outcomes when used before or early in pregnancy for preventing hypertensive disorders of pregnancy?

Research evidence

Summary of the evidence

Source and characteristics of studies

Evidence on the efficacy of calcium supplementation starting before and/or early in pregnancy for preventing hypertensive disorders of pregnancy and its complications was derived from a Cochrane systematic review of trials, comparing calcium supplementation before or early in pregnancy with no calcium supplementation before or early in pregnancy *(27)*. The review found only one randomized trial involving 1355 eligible women *(10, 27)*.

Pre-pregnancy or early calcium supplementation versus placebo

The only included study conducted in Argentina, South Africa and Zimbabwe recruited total of 1355 parous women from nine study sites *(10, 28)*. The eligible participants were women whose most recent pregnancy had been complicated by pre-eclampsia or eclampsia, and who were

[1] These outcomes reflect the prioritized outcomes used in the development of the *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia* (2011). The outcomes "pre-eclampsia", "maternal wellbeing", and "maternal satisfaction" are added as priority outcomes in this update.

intending to become pregnant. The intervention was one chewable tablet of 500 mg elemental calcium (as calcium carbonate) daily, from pre-pregnancy randomization until 20 weeks' gestation; the control group received a tablet that was indistinguishable from the intervention in appearance and taste. Participants were asked to chew their tablet in the evening, at a different time from any other food or iron supplements. Later, from 20 weeks' gestation, all participants (both intervention and control groups) received 1.5 g calcium daily for the remainder of pregnancy.

Of the 1355 women randomized pre-pregnancy for the study, 651 women were known to become pregnant, and a total of 579 women were successfully followed-up beyond 20 weeks' gestation.

Effects of pre-pregnancy or early calcium supplementation on maternal and perinatal outcomes

Maternal outcomes

Maternal death: It is unclear whether calcium supplementation that starts before and early in pregnancy has an effect on the risk of maternal death, because the evidence was very low-certainty.

Eclampsia: It is unclear whether starting calcium supplementation before and early in pregnancy has an effect on the risk of eclampsia, because the evidence was very low-certainty.

Pre-eclampsia: Low-certainty evidence suggests that starting calcium supplementation before and early in pregnancy may make little or no difference to women's risk of developing **severe gestational hypertension** (1 study, 579 women; 93/296 vs 94/283; RR 0.95, 95% CI 0.75 to 1.20) or **pre-eclampsia** (1 study, 579 women; 69/296 vs 82/283; RR 0.80, 95% CI 0.61 to 1.06). Low certainty evidence suggests that this intervention makes little or no difference to the risk of **severe pre-eclampsia** (1 study, 579 women; 52/296 vs 60/283; RR 0.83, 95% CI 0.59 to 1.16) when compared with placebo or no calcium supplementation.

Severe maternal morbidity:
It is unclear whether calcium affects the risk of **pulmonary oedema, placental abruption, cerebrovascular accidents**, or **maternal intensive care unit (ICU) admission**, because the evidence was very low-certainty; there were few events in either group for these outcomes.

The Cochrane review also reported on the incidence of **renal failure, liver failure** and **HELLP syndrome**. In the only study included, reporting of these complications is conditional on the woman developing pre-eclampsia. However, because women with these complications were a very small fraction of the original sample randomized, the outcomes were not analysed. The review did not identify data for any other severe maternal morbidities.

Recurrent seizures, maternal adverse effects of intervention, maternal wellbeing and maternal satisfaction: The study included in the Cochrane review did not report on these outcomes.

Fetal/neonatal outcomes

Perinatal death: The review did not report on perinatal death as a separate outcome. However, low-certainty evidence suggests that starting calcium supplementation before and early in pregnancy may make little or no difference to the composite outcomes of **pre-eclampsia and/or pregnancy loss/stillbirth at any gestational age** (1 study, 633 women; 107/323 vs 126/310; RR 0.82, 95% CI 0.66 to 1.00); **pregnancy loss/stillbirth at any gestational age** (1 study, 633 women; 58/323 vs 67/310; RR 0.83, 95% CI 0.61 to 1.14), **stillbirth** when considered as an independent outcome (1 study, 579 babies; 27/296 vs 33/283; RR 0.78, 95% CI 0.48 to 1.27); and **pregnancy loss, stillbirth or neonatal death before discharge** (1 study, 632 babies; 65/323 vs 76/309; RR 0.82, 95% CI 0.61 to 1.10). Low-certainty evidence also suggests that the intervention may make little or no difference to **pregnancy loss before 20 weeks' gestation** (1 study, 633 women; 27/323 vs 27/310, RR 0.96, 95% CI 0.58 to 1.60).

Admission to neonatal intensive care unit (NICU)/special nursery: The review did not report on admission to NICU/special nursery as a separate outcome. However, low-certainty evidence suggests that pre-pregnancy calcium supplementation may make little or no difference to the composite outcome of **perinatal death and/or NICU admission >24 hours** (1 study, 508 babies; 52/265 vs 43/243; RR 1.11, 95% CI 0.77 to 1.60).

Apgar scores: It is unclear whether starting calcium supplementation before and/or early in pregnancy has an effect on **Apgar scores <7 at 5 minutes**, because the evidence was very low-certainty.

Additional considerations

The single included study reported a per-protocol analysis of the primary outcomes for women who consumed >80% of their tablets. In women with >80% compliance for the duration of early pregnancy (from their last pre-pregnancy clinic visit until 20 weeks' gestation), a reduction in risk of pre-eclampsia was reported (30/144 vs 47/149; RR 0.66, 95% CI 0.44 to 0.98), suggesting a possibly important clinical benefit for women who adhered to the intervention. However, a considerable number of women were lost to follow-up at various stages during the trial, including missing data on compliance for some women (22 vs 14) known to reach 20 weeks' gestation. Furthermore, subgroup analysis by compliance was not pre-specified in the Cochrane review or this recommendation.

Desirable effects

How substantial are the desirable anticipated effects of calcium supplementation when started before and/or early in pregnancy for preventing hypertensive disorders of pregnancy?

Judgement

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

Undesirable effects

How substantial are the undesirable anticipated effects of calcium supplementation when started before and/or early in pregnancy for preventing hypertensive disorders of pregnancy?

Judgement

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

Certainty of the evidence

What is the overall certainty of the evidence on effects?

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

Additional considerations

None.

3.2 VALUES

Is there important uncertainty about, or variability in, how much women value the main outcomes associated with use of calcium supplementation before and/or early in pregnancy for preventing hypertensive disorders of pregnancy?

Research evidence

No direct evidence on how much women value the main outcomes associated this intervention was identified.

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*) *(29)*.

A qualitative study of 30 women who had experienced pre-eclampsia in the United Kingdom of Great Britain and Northern Ireland (conducted in the context of developing a core outcome set for pre-eclampsia) reported that women value a range of outcomes relating to their childbirth experience, their physical and emotional health, as well as their child's physical health and future wellbeing *(30)*.

Additional considerations

The occurrence of hypertensive disorders (such as pre-eclampsia or eclampsia) during pregnancy can increase the risk of adverse outcomes to the woman and baby and can increase the use of additional interventions and hospital admissions *(31)*. It is unlikely that there would be important variability in how women value these outcomes.

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 the intervention or the comparison?

Judgement

☐ Don't know	☑ Varies	☐ Favours placebo/no treatment	☐ Probably favours placebo/no treatment	☐ Does not favour either	☐ Probably favours intervention	☐ Favours intervention

3.3 RESOURCES

How large are the resource requirements (costs) of calcium supplementation before and/or early in pregnancy for preventing hypertensive disorders of pregnancy?

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 of calcium supplementation for women before and/or during pregnancy were identified. However, a USAID report estimates the cost of calcium supplementation as US$ 3-6 per pregnancy *(32)*, while the cost of one tablet (600 mg) daily of calcium is estimated, based on OneHealth tool, to be under US$ 8 per person per year *(10, 33)*.

In the Calcium And Pre-eclampsia (CAP) Trial, women were randomized to 500 mg elemental calcium (as calcium carbonate) or placebo daily from enrolment pre-pregnancy until 20 weeks' gestation (all participants received unblinded calcium 1.5 g daily after 20 weeks' gestation) *(10)*.

The cost of calcium supplementation prior to pregnancy may vary, depending on the duration of supplementation. Costs for calcium supplementation in pregnancy may also be higher considering that supplementation with 1.5 g to 2 g daily from 20 weeks onwards is currently recommended by WHO for pregnant women with low calcium intake. Adopting OneHealth tool unitary cost of US$ 0.0213 per 600 mg calcium tablet *(33)*, an illustrative example is provided:

Time period	Supplement cost (US$)
Pre-pregnancy: 6 months of 1 x 600 mg calcium tablet per day	$3.83
First half of pregnancy: 20 weeks of 1 x 600 mg calcium tablet per day	$2.98
Second half of pregnancy: 20 weeks of 3 x 600 mg calcium tablets per day	$8.95
Total	$15.76

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. 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 *(32)*. The weight and volume of the supplements needed may have cost and logistics implications with regards to storage and transport for health services.

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 placebo/no treatment	☐ Probably favours placebo/no treatment	☐ Does not favour either	☐ Probably favours treatment	☐ Favours treatment

3.4 EQUITY

What would be the impact of calcium supplementation before and/or early in pregnancy for preventing hypertensive disorders of pregnancy on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

A systematic review of 105 studies assessed global inequities in calcium intake during pregnancy *(11)*. The weighed arithmetic mean of calcium intake was 948.3 mg/day (95% CI 872.1–1024.4 mg/day) for women in high-income countries and 647.6 mg/day (95% CI 568.7–726.5 mg/day) for women in LMICs. Using 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. It is therefore likely that pre-pregnancy and early pregnancy calcium supplementation as a public health intervention could alleviate/rectify low calcium intake and associated problems in disadvantaged populations.

However, if poor pre-pregnant women and those in early gestation would have to routinely procure calcium supplements, which may not necessarily improve critical outcomes of their pregnancy, it may enhance inequity.

Judgement

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

3.5 ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

Research evidence

No direct evidence on the acceptability of this intervention to key stakeholders was identified. However, a qualitative evidence synthesis exploring provision and uptake of routine antenatal services *(19)* suggests that women tend to view antenatal care as a source of knowledge and information, and generally appreciate advice or interventions that may lead to a healthy baby and a positive pregnancy experience (*high confidence in the evidence*). Evidence from this review also suggests that women who experienced a previous pregnancy complication (e.g. hypertension) are more likely to utilize antenatal services early and regularly during subsequent pregnancies (l*ow confidence in the evidence*). However, in some low-income settings, the indirect costs associated with procuring drugs and/or travelling to clinics for pre-pregnancy (or additional) check-ups may restrict access (*high confidence in the evidence*) and a reliance on traditional beliefs or practices to treat common pregnancy-related conditions may limit engagement in these contexts (*moderate confidence in the evidence*).

This intervention involves taking one or more tablets every day for a prolonged period, which may be in addition to other micronutrient supplements (e.g. pregnant women also need to take iron and folic acid daily). Conventional calcium tablets are typically swallowed intact, though chewable calcium tablets are also available in some settings, and they can be easier for some women to consume. The conventional tablets can be large, powdery in texture and unpalatable *(34)*. Although, a discrete-choice study of 132 pregnant women in Bangladesh, found that women preferred conventional calcium tablets to chewable tablets, and to unflavoured and flavoured powder calcium *(35)*.

Additional considerations

Pre-pregnant women at risk of hypertensive disorders of pregnancy may not be in regular contact with health services. In addition, health services may not routinely offer pre-conception care to women who are not pregnant. The intervention may therefore be less acceptable to both women and healthcare providers in some settings.

Judgement

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

3.6 FEASIBILITY

Is the intervention feasible to implement?

Research evidence

In the CAP trial, approximately half of the randomized women (with compliance data available) took at least 80% of expected tablets from the last visit before pregnancy to 20 weeks' gestation *(10)*. Women were provided with a bottle of 84 tablets and were required to visit a healthcare provider for re-supply every 12 weeks.

Qualitative evidence suggests that where there are likely to be additional costs associated with supplements (*high confidence in the evidence*), or where the recommended interventions, such as calcium tablets, are unavailable because of resource constraints (*low confidence in the evidence*), pregnant women may be less likely to engage with antenatal care services *(19)*. Qualitative evidence on healthcare providers' views suggests that resource constraints (lack of supplement availability and lack of trained staff) may also limit implementation (*high confidence in the evidence*) *(21)*.

Additional considerations

Regular visits by women to health facilities to re-stock calcium supplements may be less feasible for women who are not pregnant, and for those who live far away from where preconception or antenatal care services are sited.

In addition to the cost, providing calcium supplements may be associated with difficult logistical issues. Among other challenges, such as forecasting, the tablets can be bulky, and there can be need for adequate transportation and storage to maintain stock in medical facilities.

Judgement

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

4. SUMMARY OF JUDGEMENTS TABLE

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 placebo/no treatment	– Probably favours placebo/no treatment	– Does not favour either	– Probably favours intervention	– Favours the intervention
Resources required	– Don't know	– Varies	– Large costs	✔ **Moderate costs**	– Negligible costs or savings	– Moderate savings	– Large savings
Certainty of the evidence on required resources	✔ **No included studies**			– Very low	– Low	– Moderate	– High
Cost–effectiveness	✔ **Don't know**	– Varies	– Favours placebo/no treatment	– Probably favours placebo/no treatment	– Does not favour either	– Probably favours intervention	– Favours 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	–	– Yes

5. Summary of Findings tables

Question: Calcium supplementation compared to placebo before or early in pregnancy for preventing hypertensive disorders of pregnancy

Setting: Hospital (Argentina, South Africa and Zimbabwe)

Bibliography: Hofmeyr GJ, Manyame S. Calcium supplementation commencing before or early in pregnancy, for preventing hypertensive disorders of pregnancy. Cochrane Database Syst. Rev. 2019 (9): CD011192.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium supplementation**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal death												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	2/323 (0.6%)	2/310 (0.6%)	**RR 0.96** (0.14 to 6.77)	**0 fewer per 1000** (from 6 fewer to 37 more)	⨁◯◯◯ VERY LOW	PRIORITY
Eclampsia												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	4/296 (1.4%)	5/283 (1.8%)	**RR 0.76** (0.21 to 2.82)	**4 fewer per 1000** (from 14 fewer to 32 more)	⨁◯◯◯ VERY LOW	PRIORITY
Recurrent seizures – not reported												
-	-	-	-	-	-	-	-	-	**-**	**-**	-	PRIORITY
Pre-eclampsia												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	69/296 (23.3%)	82/283 (29.0%)	**RR 0.80** (0.61 to 1.06)	**58 fewer per 1000** (from 113 fewer to 17 more)	⨁⨁◯◯ LOW	PRIORITY
Severe gestational hypertension												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	93/296 (31.4%)	94/283 (33.2%)	**RR 0.95** (0.75 to 1.20)	**17 fewer per 1000** (from 83 fewer to 66 more)	⨁⨁◯◯ LOW	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium supplementation**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Severe pre-eclampsia												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	52/296 (17.6%)	60/283 (21.2%)	**RR 0.83** (0.59 to 1.16)	**36 fewer per 1000** (from 87 fewer to 34 more)	⨁⨁◯◯ LOW	PRIORITY
Severe maternal morbidity: pulmonary oedema												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	0/296 (0.0%)	1/283 (0.4%)	**RR 0.32** (0.01 to 7.79)	**2 fewer per 1000** (from 3 fewer to 24 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: placental abruption												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	9/295 (3.1%)	5/283 (1.8%)	**RR 1.73** (0.59 to 5.09)	**13 more per 1000** (from 7 fewer to 72 more)	⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: cerebrovascular accident												
1	randomized trials	serious[a]	not serious	not serious	very serious[e]	none	0/296 (0.0%)	0/283 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	PRIORITY
Severe maternal morbidity: intensive care unit (ICU) admission >24h												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	2/296 (0.7%)	3/283 (1.1%)	**RR 0.64** (0.11 to 3.79)	**4 fewer per 1000** (from 9 fewer to 30 more)	⨁◯◯◯ VERY LOW	PRIORITY
Maternal adverse effects of intervention – not reported												
-	-	-	-	-	-	-	-	-	**-**	**-**	-	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium supplementation**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Maternal wellbeing – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Maternal satisfaction – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	PRIORITY
Perinatal death and/or neonatal intensive care unit (NICU) admission for >24 hours												
1	randomized trials	serious[a]	not serious	not serious	serious[f]	none	52/265 (19.6%)	43/243 (17.7%)	**RR 1.11** (0.77 to 1.60)	**19 more per 1000** (from 41 fewer to 106 more)	⨁⨁◯◯ LOW	PRIORITY
Pregnancy loss, stillbirth or neonatal death before discharge												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	65/323 (20.1%)	76/309 (24.6%)	**RR 0.82** (0.61 to 1.10)	**44 fewer per 1000** (from 96 fewer to 25 more)	⨁⨁◯◯ LOW	PRIORITY
Pregnancy loss/stillbirth at any gestational age												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	58/323 (18.0%)	67/310 (21.6%)	**RR 0.83** (0.61 to 1.14)	**37 fewer per 1000** (from 84 fewer to 30 more)	⨁⨁◯◯ LOW	PRIORITY
Pre-eclampsia and/or pregnancy loss/stillbirth at any gestational age												
1	randomized trials	serious[a]	not serious	not serious	serious[g]	none	107/323 (33.1%)	126/310 (40.6%)	**RR 0.82** (0.66 to 1.00)	**73 fewer per 1000** (from 138 fewer to 0 fewer)	⨁⨁◯◯ LOW	PRIORITY

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calcium supplementation**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Stillbirth												
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	27/296 (9.1%)	33/283 (11.7%)	**RR 0.78** (0.48 to 1.27)	**26 fewer per 1000** (from 61 fewer to 31 more)	⨁⨁◯◯ LOW	PRIORITY
Pregnancy loss before 20 week's gestation												
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	32/678 (4.7%)	32/677 (4.7%)	**RR 1.00** (0.62 to 1.61)	**0 fewer per 1000** (from 18 fewer to 29 more)	⨁⨁◯◯ LOW	PRIORITY
Apgar <7 at 5 min												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	5/255 (2.0%)	11/239 (4.6%)	**RR 0.43** (0.15 to 1.21)	**26 fewer per 1000** (from 39 fewer to 10 more)	⨁◯◯◯ VERY LOW	PRIORITY

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

Explanations

a. All of pooled effect provided by single study with moderate risk of bias (due to high rate of attrition pre-conception).
b. Wide confidence interval including both appreciable benefit and appreciable harm.
c. Few events.
d. Wide confidence interval crossing line of no effect whilst also including appreciable benefit.
e. No events, not estimable.
f. Wide confidence interval crossing line of no effect whilst also including appreciable harm.
g. Wide confidence interval touching line of no effect whilst also including appreciable benefit.

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