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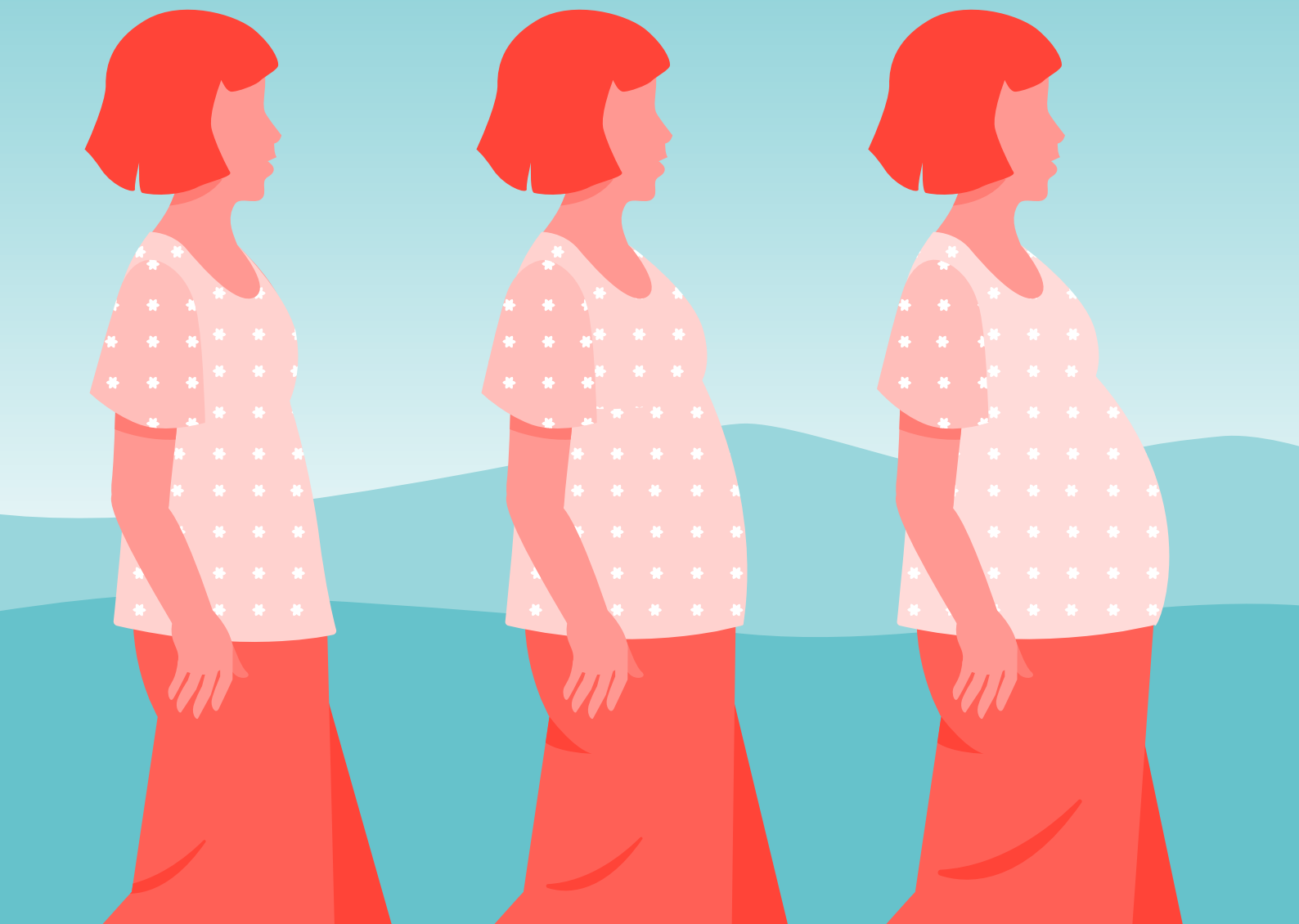
WHO antenatal care recommendations for a positive pregnancy experience

Nutritional interventions update: Vitamin D supplements during pregnancy



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WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Vitamin D supplements during pregnancy

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Acronyms and abbreviations

ANC	antenatal care
CI	confidence interval
CREP	Centro Rosarino de Estudios Perinatales (Argentina)
DECIDE	Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence
DOI	declaration of interest
eLENA	WHO e-Library of Evidence for Nutrition Actions
ERG	External Review Group
EtD	evidence-to-decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GDM	gestational diabetes mellitus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADE-CERQual	Confidence in the Evidence from Reviews of Qualitative Research
GSG	Guideline Steering Group
HIC	high-income country
ICM	International Confederation of Midwives
IFA	iron and folic acid
LMIC	low- and middle-income country
MCA	Maternal, Newborn, Child and Adolescent Health and Ageing
NFS	Nutrition and Food Safety
PICO	population, intervention, comparator, outcome
PPH	postpartum haemorrhage
QES	qualitative evidence syntheses
RCT	randomized controlled trial
RHL	WHO Reproductive Health Library
RNI	recommended nutrient intake
RR	risk ratio
SGA	small for gestational age
SHR	Sexual and Reproductive Health and Research
UN	United Nations
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
UNIMMAP	United Nations International Multiple Micronutrient Antenatal Preparation
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

The World Health Organization's comprehensive antenatal care (ANC) guideline *WHO recommendations on antenatal care for a positive pregnancy experience* was first published in 2016 with the objective of improving the quality of routine health care that all women and adolescent girls receive during pregnancy. The overarching principle – to provide pregnant service users with a positive pregnancy experience – aims to encourage countries to expand their health-care agendas beyond survival, with a view to maximizing health, human rights and the potential of their populations.

Recognizing that ANC provides a strategic platform for important health-care functions, including health promotion and disease prevention, 14 out of the 49 recommendations in the WHO 2016 ANC guideline relate to nutritional interventions in pregnancy. In April 2019, the Executive Guideline Steering Group (GSG) prioritized two of these antenatal nutrition recommendations for updating in response to new evidence on these interventions, namely:

1. Vitamin D supplements during pregnancy
2. Multiple micronutrient supplements during pregnancy.

Evidence on these interventions was evaluated by a Guideline Development Group (GDG) composed of an international group of experts convened during an online GDG meeting held on 4–5 December 2019. The respective recommendations were updated in accordance with WHO's living guidelines approach. For consistency and continuity, the GDG, including the chair, comprised the same members as the ANC guideline GDG.

This guideline presents that evidence and updated recommendation on antenatal vitamin D supplements, which updates and does not alter the corresponding recommendation previously issued.

Target audience

The target audience of this updated recommendation is the same as that of the comprehensive ANC guideline and includes national and local public health policy-makers, maternal and child health programme implementers and managers, concerned organizations, professional bodies, health professionals and academic staff involved in health professional training.

Guideline development methods

The updating of this recommendation was guided by the standardized operating procedures described in the *WHO handbook for guideline development.* This involves: (i) identification of priority questions and outcomes (done as part of the ANC guideline development process); (ii) evidence retrieval and synthesis; (iii) assessment of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations. The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) approaches, for quantitative and qualitative evidence, respectively. Up-to-date systematic reviews were used to prepare evidence profiles for the two recommendations prioritized for updating. The DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) framework – an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability and feasibility criteria – was used to guide the formulation and approval of the recommendations by the GDG.

Recommendation

The WHO technical consultation led to the formulation of one recommendation related to the use of antenatal vitamin D supplements. The GDG had the option to recommend the intervention, not to recommend the intervention, or to recommend the intervention under certain conditions (in specific contexts, targeted

monitoring and evaluation, in the context of rigorous research). The GDG experts also provided additional remarks where they considered them necessary. Users of the guideline should refer to these remarks, as well as to the evidence summary, for further information about the basis of this WHO recommendation.

The updated WHO recommendation on antenatal oral vitamin D supplements for a positive pregnancy experience

This recommendation applies to pregnant women and adolescent girls within the context of routine ANC.

WHO recommendation on antenatal oral vitamin D supplements

Oral vitamin D supplementation is not recommended for all pregnant women to improve maternal and perinatal outcomes. *(Not recommended)*

Remarks

- This recommendation updates and does not alter the respective WHO recommendation on vitamin D supplementation during pregnancy found in the WHO ANC guideline *(1)*.
- Pregnant women should be encouraged to receive adequate nutrition – which is best achieved through consumption of a healthy, balanced diet – and to refer to guidelines on healthy eating *(2)*.
- Pregnant women should be advised that sunlight is the most important source of vitamin D. The amount of time needed in the sun is not known and depends on many variables, such as the amount of skin exposed, the time of day, latitude and season, skin pigmentation (darker skin pigments synthesize less vitamin D than lighter pigments) and sunscreen use *(3)*.
- For pregnant women with suspected vitamin D deficiency, vitamin D supplements may be given at the current recommended nutrient intake of 200 IU (5 µg) per day *(1,4)*. This may include women in populations where direct sun exposure is limited.

Introduction

Background

The World Health Organization's comprehensive antenatal care (ANC) guideline, *WHO recommendations on antenatal care for a positive pregnancy experience,* was first published in 2016 with the objective of improving the quality of routine health care that all women and adolescent girls receive during pregnancy *(1)*. The overarching principle – to provide pregnant service users with a positive pregnancy experience – aims to encourage countries to expand their health-care agendas beyond survival, with a view to maximizing health, human rights and the potential of their populations. Recognizing that ANC provides a useful platform for important health-care functions, including health promotion and disease prevention, 14 out of the 49 recommendations in the WHO 2016 ANC guideline relate to nutritional interventions in pregnancy.

In April 2019, in response to new evidence, the Executive Guideline Steering Group (GSG) prioritized the updating of the recommendation on vitamin D supplements. This updated recommendation updates and does not alter the corresponding recommendation on vitamin D supplements issued in the 2016 WHO ANC guideline *(1)*.

Pregnancy and vitamin D

Pregnancy requires a healthy diet that includes an adequate intake of energy, protein, vitamins and minerals to meet increased maternal and fetal needs. Vitamin D is a fat-soluble vitamin that is mainly produced by the human body from exposure to sunlight. However, it can also be consumed from a few foods such as fish-liver oils, fatty fish, mushrooms, egg yolks and liver *(5)*. Vitamin D is important for maintaining normal blood levels of calcium and phosphate, which are needed for general cell functioning in all cells of the body, but especially for bone health *(3)*. Daily vitamin D intake is difficult to quantify because accurate food composition data for vitamin D are not available and because of the many variables that influence skin synthesis, which is reduced with dark skin pigmentation, insufficient exposure to sunlight, living in latitudes above 40 degrees, colder seasons, older age and sunscreen use *(3)*. Fetuses acquire their vitamin D from their mothers, and this acquired store forms the main source of vitamin D for infants in the first few months of life, particularly among breastfed infants *(6)*.

Deficiency of vitamin D is common worldwide, with a high prevalence occurring among pregnant women in Middle Eastern and Asian countries *(7,8)*. In pregnancy, it has been implicated in the development of pre-eclampsia, gestational diabetes mellitus (GDM), preterm birth and low birthweight *(9)*.

The updated recommendation in the context of the WHO ANC guideline

In 2016, the WHO ANC Guideline Development Group (GDG) considered the evidence on effects of vitamin deficiency, as well as evidence on values, resources, equity, acceptability and feasibility. They judged the evidence to be insufficient to make a recommendation in favour of vitamin D supplementation at that time. Since the publication of the WHO ANC guideline, the Cochrane review on vitamin D supplementation in pregnancy has been updated to include several additional trials *(7)*. This framework presents the latest evidence (search date 12 July 2018) on the effects and other GDG considerations relevant to vitamin D supplements in the context of routine ANC provision.

Rationale and objectives

As part of WHO's normative work on supporting evidence-informed policies and practices and its living guidelines approach *(10)*, the Department of Sexual and Reproductive Health and Research (SRH), the Department of Maternal, Newborn, Child, Adolescent Health and Ageing (MCA) and the Department of Nutrition and Food Safety (NFS) prioritized the updating of this recommendation on the provision of vitamin D supplements during pregnancy following the identification of new evidence on this intervention.

Target audience

The recommendation in this guideline is intended to inform the development of relevant national- and local-level health policies and clinical protocols. Therefore, the target audience of this guideline includes national

and local public health policy-makers, implementers and managers of national and local maternal and child health programmes, concerned nongovernmental and other organizations, professional societies involved in the planning and management of maternal and child health services, health professionals (including obstetricians, midwives, nurses and general medical practitioners) and academic staff involved in training the health workforce.

Scope of the recommendation

This updated recommendation is relevant to all pregnant women and adolescent girls receiving ANC in any health-care facility or community-based setting, and to their unborn fetuses and newborns. The question was originally prioritized during the WHO ANC guideline development process. In 2019, it was prioritized for updating in the context of WHO's living guideline commitment, after the authors of the Cochrane reviews on which the existing ANC guideline panel's recommendation was based updated their review to include new studies. The outcomes of interest are therefore the same as those prioritized for the WHO ANC guideline relevant to nutritional interventions (see Box 1).

Box 1. ANC nutritional interventions outcomes of interest

Maternal outcomes	Fetal/neonatal outcomes
Infections	Neonatal infections
Anaemia	Small for gestational age
Pre-eclampsia/eclampsia	Low birthweight
Gestational diabetes mellitus	Preterm birth
Mode of delivery	Congenital anomalies
Excessive weight gain	Macrosomia/large for gestational age
Side effects	Fetal/neonatal mortality
Maternal mortality	
Maternal satisfaction	

Methods

This recommendation is an update of one of 49 recommendations that were published in the *WHO recommendations on antenatal care for a positive pregnancy experience* (2016) guideline *(1)*. The recommendation was developed initially using the standardized operating procedures described in the *WHO handbook for guideline development (11)*. In summary, the process included: (i) identification of priority questions and outcomes, (ii) retrieval of evidence, (iii) assessment and synthesis of the evidence, (iv) formulation of recommendations, and (v) planning for the implementation, dissemination, impact evaluation and updating of the recommendation. This recommendation was identified by the Executive GSG as a high priority for updating in response to new evidence on this question.

Contributors to the guideline

Executive Guideline Steering Group (Executive GSG)

The Executive GSG is an independent panel of external experts and relevant stakeholders from the six WHO regions. This group advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating.

WHO Steering Group

The WHO Steering Group that managed the updating process comprised the same staff members from the WHO Departments of SRH, MCA and NFS who were part of the Steering Group for the WHO ANC guideline of 2016 (see Annex 1 for the list of members). The Steering Group drafted the key recommendation question in PICO (population, intervention, comparator, outcome) format and identified individuals to be invited to participate as guideline methodologists, as well as the guideline development and external review groups. In addition, the WHO Steering Group supervised the evidence retrieval and synthesis, organized the technical consultation, and drafted and finalized the guideline document. The Steering Group in collaboration with WHO regional offices will oversee the dissemination of the updated recommendation.

Guideline Development Group (GDG)

The Steering Group identified and invited 15 external experts and stakeholders from the six WHO regions to constitute the GDG, ensuring geographic representation, gender balance, and no important conflicts of interest. These were the experts who had also served in the GDG for the WHO ANC guideline's nutrition recommendations of 2016. This is a diverse group of individuals with expertise in research, guideline development methods, and clinical policy and programmes relating to ANC interventions, and includes a patient/consumer representative. The GDG appraised the evidence used to inform the recommendation, advised on the interpretation of this evidence, and formulated the final recommendation during an online GDG meeting on 4–5 December 2019. In addition, GDG members reviewed and approved the final guideline document before its submission to the WHO Guidelines Review Committee for approval. A list of the GDG members can be found in Annex 1.

External Review Group (ERG)

The ERG was a geographically and gender-balanced group with no important conflicts of interest (see Annex 1 for ERG members). There were five members, including technical experts and other stakeholders with interests in the provision of evidence-informed ANC. This group peer-reviewed a preliminary version of the guideline document to identify any factual errors and comment on the clarity of the language, contextual issues, and implications for implementation. The group ensured that the guideline decision-making processes had considered and incorporated the contextual values and preferences of persons affected by the recommendation, including pregnant women and adolescent girls, health-care professionals and policy-makers. It was not within the ERG's remit to change recommendations previously formulated by the GDG.

Systematic review team and guideline methodologists

The managing editors of the Cochrane Pregnancy and Childbirth Group coordinated the updating of the quantitative systematic review and facilitated collaboration between systematic review authors and guideline methodologists. Methodologists from the Evidence-based Medicine Consultancy Ltd in the United Kingdom worked closely with the WHO Steering Group to conduct the additional pre-specified analysis required by the GDG for this recommendation, and with methodologists from the Centro Rosarino de Estudios Perinatales (CREP) in Argentina, who appraised the quantitative evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology *(12).* Two qualitative evidence experts from the University of Central Lancashire in the United Kingdom systematically reviewed qualitative studies related to women's and health professionals' views on ANC, and synthesized this evidence.

External partners and observers

Representatives of the International Federation of Gynecology and Obstetrics (FIGO), the International Confederation of Midwives (ICM), the United Nations Population Fund (UNFPA), the United States Agency for International Development (USAID), the United Nations Children's Fund (UNICEF) and the Bill & Melinda Gates Foundation were invited to the final GDG meeting to serve as observers. All these organizations are potential implementers of the proposed guideline with a history of collaboration with the WHO Departments of SRH and MCA in guideline dissemination and implementation. Observers do not participate in the formulation of recommendations.

Declaration of interests by external contributors

WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflicts of interest. In accordance with the *WHO guidelines for declarations of interest (WHO Experts) (13)*, all GDG members, ERG members and other external collaborators were asked to declare in writing any competing interests (whether academic, financial or other) at the time of the invitation to participate in the ANC guideline development process. The standard WHO form for declarations of interest (DOI) was completed and signed by each expert and sent electronically to the responsible technical officer. The WHO Steering Group reviewed all the DOI forms before finalizing experts' invitations to participate. Where any conflicts of interest were declared, the Steering Group determined whether they were serious enough to affect the individual's ability to make objective judgements about the evidence or recommendation. To ensure consistency, the Steering Group applied the criteria for assessing the severity of a conflict of interest in the *WHO handbook for guideline development (11).*

All findings from DOI statements 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 reduce its credibility, the expert was only required to declare such conflict at the GDG meeting and no further action was taken. A summary of the DOI statements and information on how conflicts of interest were managed are included in Annex 2. In order to strengthen public trust and transparency in connection with WHO meetings involving the provision of expert advice in developing technical norms and standards, the names and brief biographies of individuals considered for participation on this guideline – together with a description of the objectives of relevant meetings – were made public ahead of the first meeting planned to allow time for public notice and comment.

Identifying priority questions and outcomes

The priority question and outcomes were aligned with those of the ANC guideline (2016) *(1).* This question and outcomes were originally informed through an extensive scoping exercise of existing clinical practice guidelines relevant to routine ANC, supplemented by searching the Cochrane Database of Systematic Reviews for existing key systematic reviews relevant to ANC. Critical and important outcomes were informed by these reviews, as well as by a WHO-commissioned scoping qualitative review of what women want during pregnancy *(14).* The findings of the latter revealed that pregnant women want a positive pregnancy experience, defined as maintaining physical and sociocultural normality; maintaining a healthy pregnancy and baby; having an effective transition to positive labour and birth; and achieving a positive motherhood. This composite outcome of a "positive pregnancy experience" became the overarching principle of ANC guideline recommendations.

Evidence identification and retrieval

Evidence to support this recommendation was derived from a number of sources by the methodologists working closely with the WHO Steering Group. An updated Cochrane systematic review published by the Cochrane Pregnancy and Childbirth Group was the primary source of evidence on effectiveness of antenatal oral vitamin D supplements. Earlier versions of this review, in which evidence on effectiveness was derived from randomized controlled trial (RCT) data assessed and synthesized using standardized Cochrane methodology, supported the original ANC guideline recommendation. The up-to-date RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons, GDG-specified subgroup analyses, and outcomes relevant to the ANC guideline. Evidence was evaluated according to standard operating procedures approved by the WHO Steering Group, and evidence profiles (in the form of GRADE tables) were prepared, including assessment of the certainty of the evidence, for comparisons of interest. An additional Cochrane review was conducted to assess the effects and safety of different regimens of vitamin D supplementation alone or in combination with calcium or other vitamins, minerals or nutrients during pregnancy.

The latest versions of two qualitative systematic reviews commissioned by the WHO Steering Group for the 2016 guideline development process informed the values, acceptability and feasibility criteria of these evidence-to-decision (EtD) frameworks *(14,15).* Additionally, systematic reviews of cost-effectiveness were identified through PubMed searches of the literature.

Quality assessment and grading of the evidence

The GRADE approach *(12)* to appraising the certainty of quantitative evidence was used. For each outcome the certainty of the evidence was rated as "high", "moderate", "low", or "very low" based on a set of established criteria. As a baseline, the evidence from the Cochrane reviews was rated "high certainty" because it was derived from RCTs; this rating was then downgraded according to considerations of risk of bias, inconsistency, imprecision, indirectness, and publication bias or other considerations.

Qualitative evidence was derived from qualitative evidence syntheses (QES) performed for the WHO 2016 ANC guideline *(14,15).* Previously subjected to quality appraisal using the Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) tool, the evidence was not re-graded for this updated recommendation. The GRADE-CERQual tool, which uses a similar approach conceptually to other GRADE tools, rates the level of confidence that can be placed in QES evidence according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a QES finding *(16).*

Preparation of the evidence summary

The WHO Steering Group supervised and finalized the preparation of the evidence summary and profile, in collaboration with the guideline methodologists, using the DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) framework. DECIDE is an EtD tool that includes explicit and systematic consideration of research evidence on interventions according to six criteria, namely, effects, values, resources, equity, acceptability and feasibility *(17).* These six EtD criteria were populated with the research evidence, where available; in addition, information from other sources was described in the "additional considerations" subsections of each criterion. Certainty of the graded evidence on intervention effectiveness was systematically interpreted in EtD frameworks according to Cochrane Effective Practice and Organisation of Care guidance *(18).*

Formulation of the recommendation

GDG members and other participants were provided with the evidence summary in advance of the online GDG meeting held on 4–5 December 2019, organized by the Steering Group from Geneva, Switzerland. During the technical consultation, under the leadership of the GDG chair, the GDG members reviewed, discussed and made judgements on the impact of the interventions for each of the EtD criteria. GDG judgements were summarized in a table before finalization of the recommendation and remarks. The intervention could either be recommended, not recommended, or recommended in specific contexts, namely, rigorous research, targeted monitoring and evaluation, or another GDG-specified context.

Decision-making process

The online GDG meeting was guided by a clear protocol, designed to allow the recommendation to be formulated through a process of group discussion, until consensus was reached. The final adoption of the recommendation and its context, if applicable, was confirmed by unanimous consensus (i.e. full agreement among all GDG members).

Guideline preparation and peer review

Following the online GDG meeting, members of the WHO Steering Group, assisted by a methodologist, drafted a full guideline document to accurately reflect the deliberations and decisions. A preliminary version of the document was sent electronically to participants and the ERG for final review and technical comments. The Steering Group carefully evaluated the input of the peer reviewers for inclusion in the guideline document and made revisions to the guideline draft as needed. After the GDG meetings and peer-review process, further modifications to the guideline by the Steering Group were limited to corrections of factual errors and improvements in language to address any lack of clarity. The document was then submitted for executive clearance according to established WHO publication procedures.

Evidence and recommendation on antenatal vitamin D supplements

This section provides the WHO recommendation on antenatal vitamin D supplementation, with its corresponding evidence summary. Evidence on the effectiveness of vitamin D supplementation during pregnancy is further detailed in GRADE tables in Annex 3, along with selected forest plots. To ensure that the recommendation is correctly understood, additional "remarks" reflecting the summary of the discussion by the GDG are included below the recommendation.

WHO recommendation on antenatal vitamin D supplements

Oral vitamin D supplementation is not recommended for all pregnant women to improve maternal and perinatal outcomes. *(Not recommended)*

Remarks

- This recommendation updates and does not alter the WHO recommendation found in the WHO ANC guideline *(1)*.
- Pregnant women should be encouraged to receive adequate nutrition – which is best achieved through consumption of a healthy, balanced diet – and to refer to guidelines on healthy eating *(2)*.
- Pregnant women should be advised that sunlight is the most important source of vitamin D. The amount of time needed in the sun is not known and depends on many variables, such as the amount of skin exposed; the time of day, latitude and season; skin pigmentation (darker skin pigments synthesize less vitamin D than lighter pigments); and sunscreen use *(3)*.
- For pregnant women with suspected vitamin D deficiency, vitamin D supplements may be given at the current recommended nutrient intake (RNI) of 200 IU (5 µg) per day *(1,4)*. This may include women in populations where sun exposure is limited.

A. The priority question

The following priority question was formulated using the PICO format: For pregnant women (P), does vitamin D supplementation (I) compared with no vitamin D supplementation (C) improve maternal and perinatal health outcomes (O)?

B. Assessment

1) Effects of the intervention

What are the effects of vitamin D supplementation on maternal and perinatal outcomes?

Research evidence

This evidence was derived from an updated Cochrane systematic review that included 30 trials involving a total of 7033 women *(7)*. Of the 30 trials, 22 were conducted in low- and middle-income countries (LMICs), namely: Bangladesh *(19,20)*, Brazil *(21)*, China *(22)*, India *(23–27)*, the Islamic Republic of Iran *(28–39)* and Pakistan *(40)*. Eight trials were conducted in high-income countries (HICs), namely: Australia *(41)*, France *(42,43)*, New Zealand *(44)*, the Russian Federation *(45)* and the United Kingdom *(46–48)*.

Sample sizes ranged from 40 to 1298 women. Six trials had more than two arms *(20,22,30,37,43,44)*. Twenty-three trials compared the effects of vitamin D alone versus no supplementation or a placebo; and nine trials compared the effects of vitamin D plus calcium with no supplementation. The dose and regimen of vitamin D varied widely between the trials, as did the gestational age at enrolment. All included studies provided vitamin D supplements orally.

Anaemia, infection, congenital anomalies, perinatal mortality, small for gestational age (SGA) and positive pregnancy experience outcomes were not included among the review outcomes.

The updated review included data for three comparisons:

1. Vitamin D versus no vitamin D (or placebo) (22 trials)
2. Vitamin D + calcium versus no vitamin D + calcium (or placebo) (nine trials)
3. Vitamin D + calcium + other micronutrients versus calcium + other micronutrients (one trial).

During the review evidence evaluation, it became apparent that the trial included in the review Comparison 3 *(20)* should be included in review Comparison 1, as it evaluated effects of vitamin D plus routine ANC supplements (in this case, calcium and iron and folic acid [IFA] supplements) compared with routine ANC supplements only (i.e. all participants received calcium and IFA; therefore, the comparison was essentially vitamin D versus no vitamin D supplementation). Review authors contacted the authors of the included studies for additional information on routine supplements given to all participants and retrieved the following data:

- in two trials, all women received calcium plus IFA;
- in two trials, all women received IFA;
- in 14 trials, women received no other supplements; and
- in five trials, there was no information on baseline supplements.

WHO guideline methodologists revised the Comparison 1 analysis accordingly, subgrouping trials according to routine supplements given. Thus, the comparisons presented in this framework are as per the 2016 ANC guideline; that is:

Comparison 1: Oral vitamin D supplement versus no vitamin D (placebo or no supplement); and
Comparison 2: Oral vitamin D + calcium supplement versus no vitamin D (placebo or no supplement) + calcium.

At a late stage in the framework preparation, guideline methodologists were informed by the Cochrane editors and review authors that serious concerns had been raised about four studies included in the Cochrane review. Three of these studies contributed data to the analyses – one to Comparison 1 and two to Comparison 2. No other information was given; therefore, guideline methodologists addressed this issue by performing additional sensitivity analyses that excluded all data from these three studies.

Comparison 1: Oral vitamin D supplement versus placebo or no vitamin D (placebo or no supplement)

Twenty-three trials involving a total of 5023 women contributed data to this comparison in the review, including four 3-arm trials *(30,44)* and one 5-arm trial *(20).* Trials were carried out from the 1980s to 2017 in Australia *(41),* Bangladesh *(19,20),* France *(42,43),* India *(23,25–27),* the Islamic Republic of Iran *(29–32,34–36,38,39)*, New Zealand *(44),* Pakistan *(40),* and the United Kingdom *(46–48).*

Twelve trials evaluated daily oral vitamin D with daily doses ranging from 200 IU to 2000 IU, with five trials using a dose of 1000 IU daily. In one trial the initial dose was 2000 IU daily, but this dose was increased to 4000 IU if the women remained deficient at 28 weeks. Two trials evaluated a single dose of 200 000 IU given at approximately 28 weeks of gestation; two trials evaluated 50 000 IU every two weeks; one trial evaluated 5000 IU weekly; one trial evaluated a single dose of 100 000 IU; two trials evaluated two doses of 60 000 IU during the third trimester; one trial evaluated a weekly dose of 35 000 IU during the third trimester; and one trial administered one to four vitamin D doses (60 000 IU to 480 000 IU in total) depending on the participant's baseline serum 25-hydroxy vitamin D levels. The 5-arm trial randomized women to one of four different weekly doses of vitamin D, ranging from 4200 IU to 28 000 IU per week, or to placebo.

All data were derived from studies conducted north or south of the Tropics of Cancer and Capricorn, respectively, and skin pigmentation was unknown, mixed or not reported. Thus, the review subgroup analysis by these variables was uninformative. Few trials contributed data to each outcome.

Maternal outcomes

Caesarean section: The evidence suggests that vitamin D supplementation probably makes little or no difference to the risk of caesarean section compared with placebo or no vitamin D (11 trials, 2402 women; risk ratio [RR]:

1.02, 95% confidence interval [CI]: 0.87 to 1.20; *moderate-certainty evidence, downgraded for publication bias concerns*).

Pre-eclampsia: The evidence suggests that vitamin D supplementation may reduce the risk of developing pre-eclampsia compared with placebo or no vitamin D (four trials, 499 women; RR: 0.48, 95% CI: 0.30 to 0.79; *low-certainty evidence, downgraded for concerns about applicability)* (see Annex 3 for forest plot).

GDM: The evidence suggests that vitamin D supplementation may reduce the risk of developing GDM compared with placebo or no vitamin D (five trials, 1744 women; RR: 0.50, 95% CI: 0.28 to 0.88; *low-certainty evidence, downgraded for concerns about applicability)* (see Annex 3 for forest plot).

Maternal mortality: The evidence on the effect of vitamin D on maternal mortality is of very low certainty.

Side effects: The evidence on the relative risks of nephritic syndrome and hypercalcaemia with vitamin D supplementation is also of very low certainty.

Fetal/neonatal outcomes

Low birthweight (less than 2500 g): It is unclear whether or not vitamin D makes any difference to the risk of having a low birthweight neonate compared with placebo or no vitamin D, as the certainty of the evidence is very low.

Preterm birth: The evidence suggests that vitamin D probably makes little or no difference to the risk of preterm birth (< 37 weeks of gestation) compared with placebo or no vitamin D (eight trials, 2938 women; RR: 0.78, 95% CI: 0.48 to 1.27; *moderate-certainty evidence, downgraded for imprecision*).

Neonatal mortality: It is not clear whether or not vitamin D makes any difference to neonatal mortality compared with placebo or no vitamin D as the certainty of the evidence is very low.

Stillbirth: The evidence suggests that vitamin D probably makes little or no difference to the risk of stillbirth compared with placebo or no vitamin D (four trials, 1884 women; RR: 0.59, 95% CI: 0.28 to 1.22; *moderate-certainty evidence due to imprecision*).

Statistical tests suggested that there were no significant subgroup differences for these outcomes.

Sensitivity analysis

Sensitivity analysis involved removing one study with a total of 54 participants from the analysis. The effects estimate for pre-eclampsia remained similar (original analysis – RR: 0.48, 95% CI: 0.30 to 0.79; sensitivity analysis – RR: 0.49, 95% CI: 0.30 to 0.81). However, for GDM, whilst the original result suggested a clear reduction in GDM with vitamin D supplementation (RR: 0.51, 95% CI: 0.27 to 0.97), the removal of this study meant that the reduction was no longer statistically significant (RR: 0.52, 95% CI: 0.27 to 1.03). For other outcomes, removal of the study made little difference.

Comparison 2: Oral vitamin D + calcium supplement versus no vitamin D + calcium (placebo or no supplement)

Nine trials involving 1916 women contributed data to this comparison. Trials were conducted in Brazil *(21),* China *(22),* India *(24),* the Islamic Republic of Iran *(28–30,33,37)* and the Russian Federation *(45).* Vitamin D doses ranged from 200 IU to 1200 IU daily and calcium carbonate doses ranged from 375 mg to 1250 mg daily. Data on other routine antenatal supplements given, if any, were not available for these studies.

Maternal outcomes

Caesarean section: The evidence suggests that vitamin D plus calcium has little or no effect on caesarean section rates compared with placebo or no vitamin D plus calcium (two trials, 146 women; RR: 1.16, 95% CI: 0.87 to 1.54; *moderate-certainty evidence, downgraded due to imprecision*).

Pre-eclampsia: The evidence suggests that vitamin D supplements plus calcium may reduce the risk of developing pre-eclampsia compared with placebo or no vitamin D plus calcium (four trials, 1174 women; RR: 0.50, 95% CI: 0.32 to 0.78; *low-certainty evidence, downgraded due to design limitations*) (see Annex 3 for forest plot).

GDM: The evidence on the effect of vitamin D plus calcium on GDM is of very low certainty.

Reviewers found no data on maternal mortality, infection and side effects for this comparison.

Fetal/neonatal outcomes

Low birthweight (less than 2500 g): The evidence on the effect of vitamin D plus calcium on low birthweight is of very low certainty.

Preterm birth: The evidence suggests that vitamin D plus calcium may increase the risk of preterm birth (< 37 weeks of gestation) compared with placebo or no vitamin D plus calcium (five trials, 942 women; RR: 1.52, 95% CI: 1.01 to 2.28; *low-certainty evidence, downgraded due to design limitations*) (see Annex 3 for forest plot).

Neonatal mortality: The evidence on the effect of vitamin D plus calcium on neonatal mortality is of very low certainty.

Data for stillbirth and infection were not found by reviewers, and perinatal mortality, SGA and congenital anomalies were not review outcomes.

Sensitivity analysis

Sensitivity analysis involved removing two studies with a total of 114 participants from the analysis. There were no important differences for most outcomes. However, the low-certainty finding that the risk of preterm birth may be increased with vitamin D and calcium (original analysis – RR: 1.52, 95% CI: 1.01 to 2.28) was no longer statistically significant when these studies were removed (sensitivity analysis – RR: 1.48, 95% CI: 0.98 to 2.26).

Summary of effects

The main findings of vitamin D supplements compared with no vitamin D supplements are that vitamin D supplements may reduce the risk of pre-eclampsia and GDM; however, the evidence is of low certainty and, in the sensitivity analysis, the effect on GDM was no longer present.

The evidence from the analyses of vitamin D plus calcium supplements compared with no vitamin D plus calcium also suggests, with low certainty, that vitamin D plus calcium supplements may reduce the risk of pre-eclampsia. The other low-certainty finding, suggesting that supplementation with vitamin D plus calcium may increase the risk of preterm birth, was no longer present on sensitivity analysis when two studies with potentially high risk of bias were removed.

Desirable effects

How substantial are the desirable anticipated effects of vitamin D supplementation?

Judgement					
☒ Don't know	☐ Varies	☐ Trivial	☐ Small	☐ Moderate	☐ Large

Rationale for judgement: Whilst 50% reductions in the risk of pre-eclampsia and GDM are large reductions, findings were influenced by studies conducted among women at high risk of the respective conditions, data were sparse, and studies were from India and the Islamic Republic of Iran only. Sensitivity analyses cast further doubt on the certainty of the already uncertain evidence.

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement					
☒ Don't know	☐ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Rationale for judgement: There was insufficient evidence to judge the magnitude of undesirable effects, if any.

Certainty of the evidence

What is the overall certainty of the evidence of effects?

Judgement				
☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Rationale for judgement: Most evidence is graded low or very low certainty and is further undermined by the findings of sensitivity analyses.

Additional considerations

- With regard to calcium supplementation, the 2018 WHO recommendation on *Calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications* states the following: "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" *(49)*.
- For pregnant women with documented low concentrations of 25-hydroxy vitamin D in nmol/L (a marker of vitamin D status), vitamin D supplements may be given at the current RNI of 200 IU (5 µg) per day, alone or as part of a multiple micronutrient supplement *(1,4)*.
- The Cochrane review *(7)* on which this evidence on effects is based also reported with moderate certainty that oral vitamin D supplementation probably reduces the risk of severe postpartum haemorrhage (PPH) compared with placebo or no vitamin D supplementation, based on the findings from one trial involving 1134 women (RR: 0.68, 95% CI: 0.51 to 0.91). The incidence of severe PPH in this trial was high (14%) and the definition of severe PPH was not provided in the report.
- A further Cochrane review looked at the effect of different doses of vitamin D on pre-eclampsia, GDM, preterm birth and low birthweight, among other outcomes *(50)*. Comparing a daily dose of more than 600 IU with a daily dose of 600 IU or less, the review found low-certainty evidence that the higher dose may reduce the risk of GDM more than the lower dose but that effects on the other three outcomes were similar. Comparing higher doses of 4000 IU daily or more with doses of less than 4000 IU daily did not reveal any clear differences, and most evidence was graded as being of low certainty by the reviewers.
- The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) comprises 15 micronutrients in its formulation, including 200 IU of vitamin D (but no calcium).

Values

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

A scoping review of what women want from ANC informed the outcomes for the ANC guideline *(14)*. Evidence showed that women from various resource settings valued having a positive pregnancy experience comprising three equally important components: effective clinical practices (interventions and tests), relevant and timely information, and psychosocial and emotional support – each provided by practitioners with good clinical and interpersonal skills within a well-functioning health system *(high confidence in the evidence)*.

Judgement			
☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Rationale for judgement: The evidence indicates that women value effective clinical practices; the evidence on whether vitamin D is effective or not is very uncertain.

Balance of effects

Does the balance between desirable and undesirable effects favour vitamin D supplements or no vitamin D supplements?

Judgement						
☒ Don't know	☐ Varies	☐ Favours no vitamin D	☐ Probably favours no vitamin D	☐ Does not favour vitamin D or no vitamin D	☐ Probably favours vitamin D	☐ Favours vitamin D

Rationale for judgement: There is insufficient evidence on this domain for vitamin D supplementation.

2) Resources

How large are the resource requirements (costs) associated with vitamin D supplementation?

Research evidence

One economic analysis of vitamin D supplementation in England and Wales was identified *(51)*. This analysis, based on a reduction in pre-eclampsia of approximately 14%, estimated that a reduction in cases of pre-eclampsia by 4126 cases annually would result in a net saving of £18.6 million for the health service of these countries.

Additional considerations

- Pricing varies widely but, at a daily dose of 400 IU, a six-month supply (180 tablets) of vitamin D is available in the United Kingdom for about £5.10 (approximately US$ 6.50) *(52)*.
- Vitamin D is included in the UNIMMAP multiple micronutrient supplement (200 IU), which has been estimated to cost US$ 3.42 per pregnant woman per six-month treatment period *(53,54)*.

Resources required

How costly are the resources required for vitamin D supplements?

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

Rationale for judgement: The estimated costs of vitamin D are overall higher than IFA supplements and multiple micronutrient supplements.

Certainty of evidence on required resources

What is the certainty of the evidence on costs of vitamin D supplements?

Judgement				
☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Rationale for judgement: Estimated costs are supply costs only and are derived from one country only (United Kingdom).

Cost-effectiveness

How cost-effective are vitamin D supplements compared with no vitamin D supplementation?

Judgement						
☒ Don't know	☐ Varies	☐ Favours no vitamin D	☐ Probably favours no vitamin D	☐ Does not favour vitamin D or no vitamin D	☐ Probably favours vitamin D	☐ Favours vitamin D

Rationale for judgement: Cost-effectiveness cannot be judged if there is no or very uncertain evidence of effectiveness.

3) Equity

What would be the impact of antenatal vitamin D supplementation on health equity?

Research evidence

The WHO *State of inequality* report (2015) shows that 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 LMICs *(55).* ANC coverage of at least four visits differed according to education and income; inequalities in ANC coverage of at least one visit were also demonstrated, though to a lesser extent. In 50% of study countries, infant mortality was at least eight deaths per 1000 live births higher in rural than in urban areas and, in about a quarter of the study countries, neonatal mortality was at least 15 deaths per 1000 live births higher among the least educated. Stunting prevalence in children under 5 was also substantially unequal between the least and most educated mothers.

Additional considerations

- Nutritional gaps are common in disadvantaged populations. Effective interventions to improve the general nutritional status of pregnant women and adolescent girls in LMICs could help to address maternal and neonatal health inequalities by improving general health and preventing poor maternal health related to vitamin and mineral malnutrition.
- Cultural norms may be associated with vitamin D deficiency if women are required to wear clothing that limits exposure to sunlight.

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

Rationale for judgement: It is possible that vitamin D supplements may improve health equity in populations where women and girls are required to wear clothing that limits exposure to sunlight.

4) Acceptability

Is vitamin D supplementation acceptable to key stakeholders?

Research evidence

A systematic review of qualitative research exploring women's views and experiences of ANC suggests that women tend to view ANC 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) (15).*

The same review explored health professionals' views of ANC, which suggested that health professionals are keen to offer general health-care advice and specific pregnancy-related information *(low confidence in the evidence)* but sometimes feel they do not have the appropriate training and lack the resources and time to deliver the service in the informative, supportive and caring manner that women want *(high confidence in the evidence) (15).*

Additional considerations

- If women are expected to pay for supplements, vitamin D may not be acceptable.
- Increasing the number of daily antenatal supplements by adding vitamin D supplementation to IFA supplements (plus calcium) may reduce adherence.

Judgement

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

Rationale for judgement: Women and health providers in different settings may have different views on vitamin D supplementation depending on various factors, such as cost, other antenatal supplements, and risk factors for deficiency.

5) Feasibility

Is it feasible to implement vitamin D supplementation?

Research evidence

Evidence derived from a QES conducted to support the guideline development shows that where there are likely to be additional costs associated with supplementation *(high confidence in the evidence)* or where the recommended intervention is unavailable because of resource constraints *(low confidence in the evidence)* women may be less likely to engage with services *(15)*. In addition, in a number of LMIC settings, providers felt that a lack of resources – in terms of both the availability of the supplements and the lack of suitably trained staff to deliver nutritional information – may limit the implementation of this intervention *(high confidence in the evidence)*.

Additional considerations

- From the demand side, if supplements are free and available, vitamin D supplements may be feasible. However, on the supply side there may be several barriers to overcome or considerations to take into account, such as changes in regulatory norms and policies (e.g. tariffs, labelling, imports, government oversight, quality), how sustainable the production is (local or imported), and how to guarantee product availability *(56)*.
- Multiple micronutrient supplements such as UNIMMAP may be a feasible way in which to deliver vitamin D supplementation.
- Vitamin D supplements are listed in the Model List of Essential Medicines: https://list.essentialmeds.org/?indication=625.

Judgement

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

Rationale for judgement: The additional cost and logistics of vitamin D supplementation are not feasible, given the lack of evidence of effectiveness and in the face of competing resource needs from effective interventions.

C. Summary of GDG judgements on antenatal vitamin D supplements

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 no vitamin D	- Probably favours no vitamin D	- Does not favour vitamin D or no vitamin D	- Probably favours vitamin D	- Favours vitamin D
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 no vitamin D	- Probably favours no vitamin D	- Does not favour vitamin D or no vitamin D	- Probably favours vitamin D	- Favours vitamin D
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

Dissemination and implementation of recommendations

Recommendation dissemination

This updated guideline will be available online for download and also as a printed publication. Online versions will be available via the websites of the WHO Departments of SRH, NFS and MCA, and through the WHO Reproductive Health Library (RHL)[1] and e-Library of Evidence for Nutrition Actions (eLENA).[2] Print versions will be distributed to WHO regional and country offices, ministries of health, WHO collaborating centres, nongovernmental organization partners, among others, using the same distribution list that was developed for the WHO 2016 ANC guideline *(1)*.

The updated recommendation and updated derivative products, in particular, the WHO Antenatal Care Recommendations Adaptation Toolkit and its Instruction Manual, will be disseminated during meetings and scientific conferences attended by WHO staff. To increase awareness of the updated recommendation, social media channels will be used. The executive summary and recommendation from this publication will be translated into the six United Nations languages for dissemination through the WHO regional offices and during meetings organized by, or attended by, WHO staff.

Implementation considerations and applicability issues

This updated recommendation updates and does not alter the respective WHO ANC guideline recommendation on vitamin D supplementation (recommendation A9) *(1)*. The GDG agreed that there were no new implementation considerations or applicability issues specific to this recommendation, as the intervention is not recommended. For GDG considerations relevant to this recommendation, stakeholders should refer to the "Remarks" section beneath the recommendation in the "Evidence and recommendations" section. For general implementation considerations related to *WHO recommendations on antenatal care for a positive pregnancy experience,* please refer to this 2016 guideline *(1)* and associated derivative products, which are available on the WHO website.

1 RHL is available at: http://apps.who.int/rhl/en/.
2 eLENA is available at: https://www.who.int/elena/en/.

Research implications

During the recommendation development process, the GDG identified some important knowledge gaps that need to be addressed through primary research. These are listed in Box 2 below.

Box 2. Priority research questions for antenatal vitamin D supplementation

There are several ongoing RCTs on vitamin D supplementation in pregnancy *(7,50)*. These should aim to provide clear evidence on:

- Effectiveness
- Adverse effects
- Any additional benefits or harms of vitamin D when combined with other vitamins or minerals, particularly calcium
- Optimal dose and timing (daily, intermittent, single-dose)
- Optimal timing of initiation.

Updating the guideline

WHO convenes the Executive GSG biannually to review WHO's current portfolio of maternal and perinatal health recommendations, and to advise on the prioritization of new and existing questions for recommendation development and updating. Accordingly, these recommendations will be reviewed and updated in the event that new evidence is identified that could potentially impact the current evidence base. Any concern about the validity of the recommendations will be promptly communicated via the guideline website[3] and plans will be made to update the recommendation, as necessary. WHO will prioritize its independent normative guidance informed by the strategic shifts embedded in its Constitution and the Thirteenth General Programme of Work 2019–2023.

All technical products developed during the process of developing this recommendation – including the Cochrane RevMan[4] file customized for priority outcomes – and the basis for quality rating of outcomes within the GRADE process will be archived in the departmental shared folder for future reference and use.

3 Available at: https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/
4 For further information, see: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.

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Annex 2. Summary of declarations of interest from the Guideline Development Group (GDG) members and how they were managed

Name (with title)	Gender	Expertise	Disclosure of interest	Conflict of interest and management
Dr Niveen Abu-Rmeileh	F	Community and public health, statistical epidemiology	None declared.	Not applicable.
Dr Luz Maria De-Regil	F	Nutrition, epidemiology, systematic reviews, programme implementation	Authored two publications on multiple micronutrient supplements for pregnant women and two on vitamin D supplementation. Former full-time staff employee of Nutrition International (2013–2018), not-for-profit organization that delivers micronutrient interventions, including IFA supplementation to women, in multiple countries in Asia and Africa. Nutrition International received grants from the Government of Canada to support research and implementation of IFA supplementation programmes.	The conflict was not considered serious enough to affect GDG membership or participation in the GDG meeting.
Dr Atf Ghérissi	F	Systematic reviews, qualitative evidence, maternal and perinatal health, community health	None declared.	Not applicable.
Ms Gill Gyte	F	Consumer representative, pregnancy and childbirth	None declared.	Not applicable.
Dr Rintaro Mori	M	Perinatology, neonatology, systematic reviews, evidence synthesis and guideline development using GRADE	None declared.	Not applicable.
Prof. Jim Neilson	M	General obstetrics, perinatology, gynaecology, systematic reviews, evidence synthesis and guideline development using GRADE	None declared.	Not applicable.
Dr Lynnette Neufeld	F	Micronutrients, programmes, epidemiology	None declared.	Not applicable.

Name (with title)	Gender	Expertise	Disclosure of interest	Conflict of interest and management
Dr Lisa Noguchi	F	Midwifery, delivery of care, implementation science	Employer anticipated research funding from Bill & Melinda Gates Foundation related to studying introduction of innovations and improving quality of care in ANC and postnatal care.	The conflict was not considered serious enough to affect GDG membership or participation in the technical consultation.
Prof. Nafissa Osman	F	Obstetrics and gynaecology, implementation research	None declared.	Not applicable.
Dr Erika Ota	F	Nutrition, evidence synthesis, guideline development	None declared.	Not applicable.
Prof. Robert Pattinson	M	Obstetrics and gynaecology, delivery of care, evidence synthesis	None declared.	Not applicable.
Prof. Harshi Sachdev	M	Paediatrics, nutrition, systematic reviews	Contributed data from India to subsequent meta-analyses and contributed to a published opinion paper on the subject of multiple micronutrients in pregnancy. Was involved in the epidemiological design and analysis of this publication; however, did not receive funding for this work.	The conflict was not considered serious enough to affect GDG membership or participation in the technical consultation.
Ms Rusidah Selamat	F	Maternal and infant nutrition, community-based programmes, implementation research	None declared.	Not applicable.
Dr Charlotte Warren	F	Maternal and perinatal health, systematic reviews, implementation research	None declared.	Not applicable.
Prof. Charles Wiysonge	M	Health systems, systematic reviews, delivery of care	None declared.	Not applicable.

Annex 3. Antenatal vitamin D supplements: GRADE tables and forest plots

GRADE tables for effects of vitamin D supplements vs no vitamin D supplements: Comparison 1

Question: Vitamin D alone compared with placebo or no intervention for women during pregnancy.

Settings: Studies were conducted in several countries (Australia, Bangladesh, Brazil, China, France, India, the Islamic Republic of Iran, New Zealand, Pakistan, the Russian Federation and the United Kingdom), but most outcome data are derived from studies conducted in India and the Islamic Republic of Iran.

Source: *Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2019;(7):CD008873.* Data from this review were used in the revised 2019 WHO meta-analysis.

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D alone	Placebo or no intervention (subgrouped by other routine micronutrients specified)	Relative (95% CI)	Absolute (95% CI)		
Caesarean section												
11	randomized trials	not serious	not serious	not serious	not serious	serious[a]	765/1641 (46.6%)	331/761 (43.5%)	**RR 1.02** (0.87 to 1.20)	**9 more per 1000** (from 57 fewer to 87 more)	⊗⊗⊗○ MODERATE	CRITICAL
Pre-eclampsia												
4	randomized trials	not serious	not serious	none	not serious	very serious[b,c]	21/273 (7.7%)	38/226 (16.8%)	**RR 0.48** (0.30 to 0.79)	**87 fewer per 1000** (from 118 fewer to 35 fewer)	⊗⊗○○ LOW	CRITICAL
Gestational diabetes mellitus												
5	randomized trials	not serious	not serious	none	not serious	very serious[b,d]	18/1288 (1.4%)	28/456 (6.1%)	**RR 0.50** (0.28 to 0.88)	**31 fewer per 1000** (from 44 fewer to 7 fewer)	⊗⊗○○ LOW	CRITICAL

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D alone	Placebo or no intervention (subgrouped by other routine micronutrients specified)	Relative (95% CI)	Absolute (95% CI)		
Maternal death (death while pregnant or within 42 days of termination of pregnancy)												
2	randomized trials	not serious	not serious	serious[b]	very serious[e,f]	none	1/1160 (0.1%)	1/320 (0.3%)	**RR 0.25** (0.02 to 3.98)	**2 fewer per 1000** (from 3 fewer to 9 more)	⊗○○○ VERY LOW	CRITICAL
Maternal adverse events – Nephritic syndrome												
1	randomized trial	serious[g]	not serious	not serious	very serious[e,f]	none	0/90 (0.0%)	1/45 (2.2%)	**RR 0.17** (0.01 to 4.06)	**18 fewer per 1000** (from 22 fewer to 68 more)	⊗○○○ VERY LOW	CRITICAL
Maternal adverse events – Hypercalcaemia												
2	randomized trials	not serious	not serious	not serious	very serious[h]	none	0/1604 (0.0%)	0/828 (0.0%)	not pooled	–	⊗⊗○○ LOW	CRITICAL
Low birthweight (less than 2500 g)												
6	randomized trials	very serious[i]	serious[j]	serious[b]	serious[e]	none	227/1405 (16.2%)	112/590 (19.0%)	**RR 0.65** (0.40 to 1.04)	**66 fewer per 1000** (from 114 fewer to 8 more)	⊗○○○ VERY LOW	CRITICAL
Preterm birth (less than 37 weeks of gestation)												
8	randomized trials	not serious	not serious	not serious	serious[e]	none	134/1895 (7.1%)	71/1043 (6.8%)	**RR 0.78** (0.48 to 1.27)	**15 fewer per 1000** (from 35 fewer to 18 more)	⊗⊗⊗○ MODERATE	CRITICAL

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D alone	Placebo or no intervention (subgrouped by other routine micronutrients specified)	Relative (95% CI)	Absolute (95% CI)		
Stillbirth												
4	randomized trials	not serious	not serious	not serious	serious[e]	none	22/1404 (1.6%)	11/480 (2.3%)	**RR 0.59** (0.28 to 1.22)	**9 fewer per 1000** (from 16 fewer to 5 more)	⊗⊗⊗○ MODERATE	CRITICAL
Neonatal death												
3	randomized trials	not serious	not serious	serious[c]	very serious[e,f]	none	12/1232 (1.0%)	8/392 (2.0%)	**RR 0.53** (0.20 to 1.39)	**10 fewer per 1000** (from 16 fewer to 8 more)	⊗○○○ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Publication bias strongly suspected.

b. Regional differences in skin pigmentation and clothing that limit exposure to sunlight could lead to the evidence not being applicable to all regions.

c. One study (Sasan et al., 2017) *(35)* that recruited women with high risk of eclampsia contributed the most weight to this analysis.

d. One study (Shahgheibi et al., 2016) *(36)* that recruited women at high risk of gestational diabetes mellitus contributed the most weight to this analysis.

e. Wide CI crossing the line of no effect.

f. Few events occurred (< 30).

g. All the pooled effect provided from studies with some risk of bias concerns.

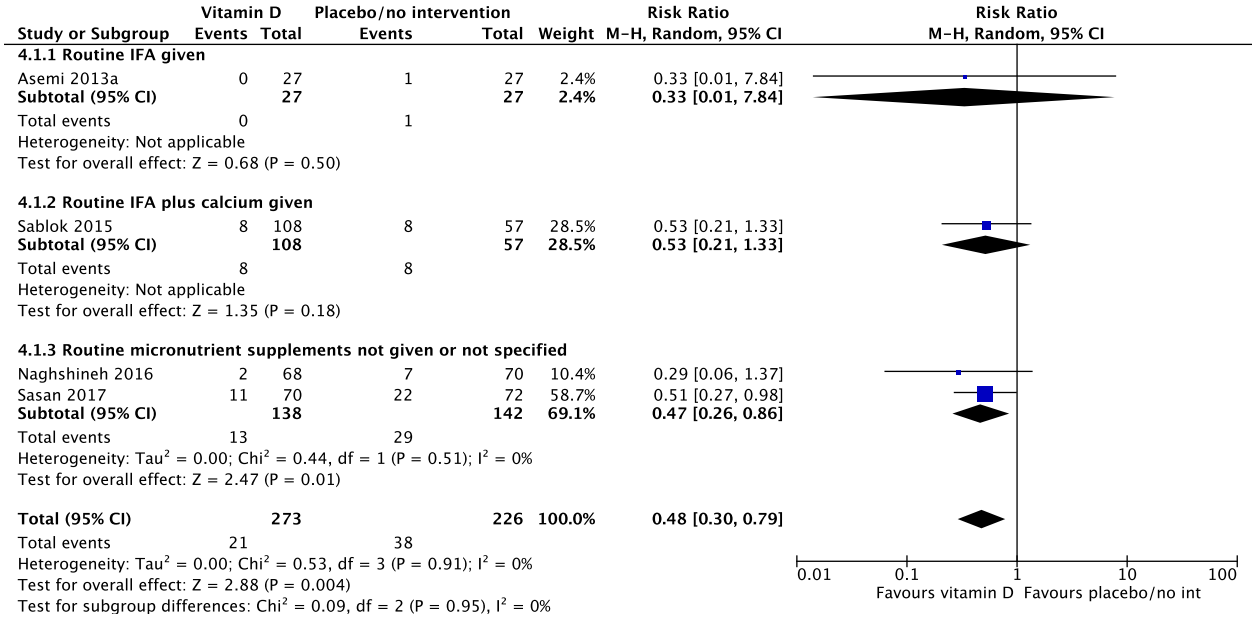
h. No events occurred.

i. All the pooled effect provided from studies with high risk of bias concerns.

i. Severe unexplained heterogeneity ($I^2 \geq 60\%$ or P value ≤ 0.05).

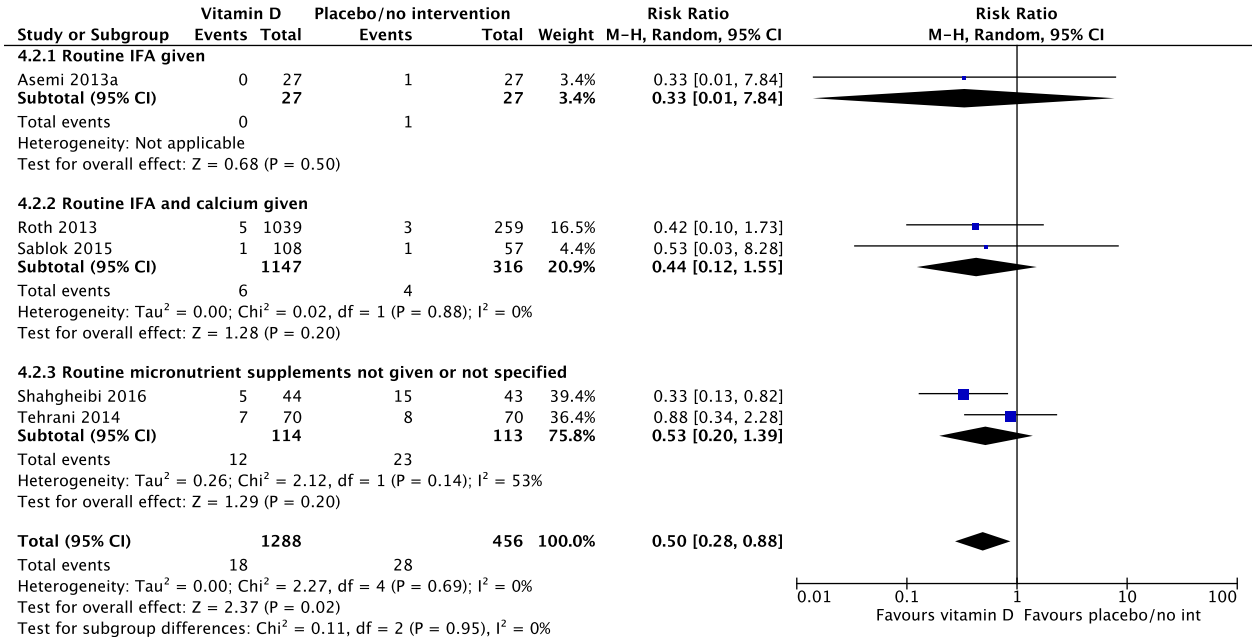
Selected forest plots for effects of vitamin D supplements vs no vitamin D supplements: Comparison 1

a. Pre-eclampsia



IFAS: iron and folic acid supplements
Sensitivity analysis effect estimate: Three trials, RR: 0.49 (95% CI: 0.30 to 0.81).

b. Gestational diabetes mellitus



IFAS: iron and folic acid supplements
Sensitivity analysis effect estimate: Four trials; RR: 0.52 (95% CI: 0.27 to 1.03).

GRADE tables for effects of vitamin D plus calcium supplements vs no vitamin D plus calcium supplements: Comparison 2

Question: Vitamin D + calcium supplementation compared with placebo or no intervention (no vitamin D + calcium).

Setting: Most data are derived from studies conducted in India and the Islamic Republic of Iran.

Source: *Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2019(7):CD008873.*

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supplementation with vitamin D + calcium	Placebo or no intervention (no vitamin or minerals)	Relative (95% CI)	Absolute (95% CI)		
Pre-eclampsia (ALL)												
4	randomized trials	very serious[a]	not serious	not serious	not serious	none	27/587 (4.6%)	55/587 (9.4%)	**RR 0.50** (0.32 to 0.78)	**47 fewer per 1.000** (from 64 fewer to 21 fewer)	⊗⊗○○ LOW	CRITICAL
Gestational diabetes mellitus (ALL)												
1	randomized trials	serious[b]	not serious	not serious	very serious[c,d]	none	0/27 (0.0%)	1/27 (3.7%)	**RR 0.33** (0.01 to 7.84)	**25 fewer per 1.000** (from 37 fewer to 253 more)	⊗○○○ VERY LOW	CRITICAL
Preterm birth (less than 37 weeks of gestation) (ALL)												
5	randomized trials	very serious[a]	not serious	not serious	not serious	none	52/472 (11.0%)	34/470 (7.2%)	**RR 1.52** (1.01 to 2.28)	**38 more per 1.000** (from 1 more to 93 more)	⊗⊗○○ LOW	CRITICAL
Low birthweight (less than 2500 g) (ALL)												
2	randomized trials	very serious[a]	not serious	not serious	very serious[c,d]	none	2/59 (3.4%)	3/51 (5.9%)	**RR 0.68** (0.10 to 4.55)	**19 fewer per 1.000** (from 53 fewer to 209 more)	⊗○○○ VERY LOW	CRITICAL

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supplementation with vitamin D + calcium	Placebo or no intervention (no vitamin or minerals)	Relative (95% CI)	Absolute (95% CI)		
Caesarean section												
2	randomized trials	not serious	not serious	not serious	serious[c]	none	42/72 (58.3%)	37/74 (50.0%)	**RR 1.16** (0.87 to 1.54)	**80 more per 1.000** (from 65 fewer to 270 more)	⊗⊗⊗○ MODERATE	CRITICAL
Neonatal mortality												
1	randomized trial	very serious[a]	not serious	not serious	very serious[c,d]	none	0/330 (0.0%)	2/330 (0.6%)	**RR 0.20** (0.01 to 4.15)	**5 fewer per 1.000** (from 6 fewer to 19 more)	⊗○○○ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Most of the pooled effect provided by "B" or "C" studies but with a substantial proportion (i.e. > 50%) from "C" studies.

b. Most of the pooled effect provided by "B" or "C" studies but without a substantial proportion (i.e. < 50%) from "C" studies.

c. CI is imprecise.

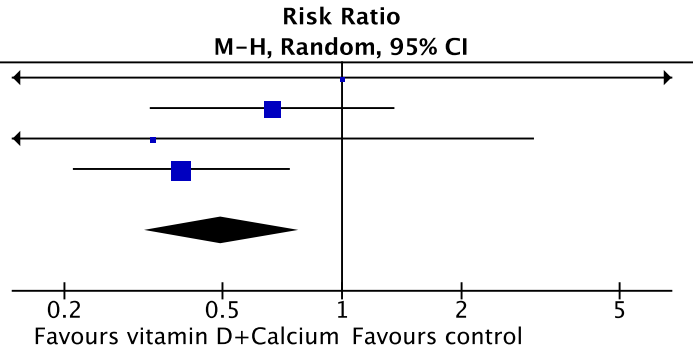
d. Few events.

Selected forest plots for effects of vitamin D plus calcium supplements vs no vitamin D plus calcium supplements: Comparison 2

a. Pre-eclampsia

Study or Subgroup	Vitamin D+Calcium Events	Total	Placebo/no intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Asemi 2012	1	27	1	27	2.7%	1.00 [0.07, 15.18]
Marya 1987	12	200	18	200	40.9%	0.67 [0.33, 1.35]
Samimi 2016	1	30	3	30	4.2%	0.33 [0.04, 3.03]
Taherian 2002	13	330	33	330	52.2%	0.39 [0.21, 0.73]
Total (95% CI)		**587**		**587**	**100.0%**	**0.50 [0.32, 0.78]**
Total events	27		55			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.59$, df = 3 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 3.04 (P = 0.002)

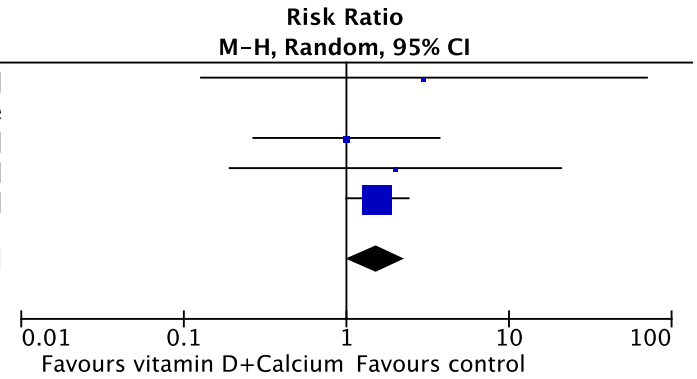


Sensitivity analysis effect estimate: Two trials; RR: 0.50 (95% CI: 0.30 to 0.82).

b. Preterm birth

Study or Subgroup	Vitamin D+Calcium Events	Total	Placebo/no intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Asemi 2012	1	27	0	27	1.7%	3.00 [0.13, 70.53]
Diogenes 2013	0	43	0	41		Not estimable
Mirghafourvand 2013	4	42	4	42	9.6%	1.00 [0.27, 3.74]
Samimi 2016	2	30	1	30	3.0%	2.00 [0.19, 20.90]
Taherian 2002	45	330	29	330	85.7%	1.55 [1.00, 2.41]
Total (95% CI)		**472**		**470**	**100.0%**	**1.52 [1.01, 2.28]**
Total events	52		34			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.63$, df = 3 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 2.00 (P = 0.05)



Sensitivity analysis effect estimate: Three trials; RR: 1.48 (95% CI: 0.98 to 2.26).

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