WHO recommendation regarding Vitamin D supplementation during pregnancy

31 July 2020

Recommendation

Vitamin D supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.

Publication history

First published: October 2011

Updated: December 2016 & July 2020

Assessed as up-to-date: July 2020

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 ?g) per day (1,4). This may include women in populations where direct sun exposure is limited.

Background

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).

Methods

In April 2019, following pre-established prioritization criteria, the Executive Guideline Steering Group prioritized updating of the recommendation on multiple micronutrient supplements (MMS). This resulting recommendation updates and supersedes the previous recommendation on antenatal MMS issued in the 2016 WHO ANC guideline (1). WHO convened a virtual Guideline Development Group (GDG)– an international group of experts assembled for the purpose of developing this guideline – meeting to review and update this recommendation on 4–5 December 2019, organized from Geneva, Switzerland. The recommendation was developed initially using the standardized operating procedures described in the WHO handbook and updated based on the WHO ‘living guideline’ approach for maternal and perinatal health recommendations (10,11).

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. 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.

Evidence profiles (in the form of Grading of Recommendations Assessment, Development and Evaluation [GRADE] tables, for quantitative) were prepared, including assessment of the certainty of the evidence, for comparisons of interest. Data from the Cochrane review were customized to reflect the key comparisons, GDG - specified subgroup analyses, and outcomes relevant to the ANC guideline. 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 recommendation. The latest versions of two qualitative systematic reviews commissioned by the WHO Steering Group for the 2016 guideline development process and systematic reviews of cost-effectiveness informed this framework (12,13). These reviews employed the Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) approach for qualitative evidence. The GDG members reviewed, discussed and made judgements on the impact of the interventions for each of the EtD criteria.

Further information on procedures for developing this recommendation are available.

Recommendation question

For this recommendation, we aimed to answer the following question:

- for pregnant women (P), does vitamin D supplementation (I) compared with no vitamin D supplementation (C) improve maternal and perinatal health outcomes (O)?
Evidence Summary

This evidence was derived from an updated Cochrane systematic review that included 30 trials involving a total of 7033 women (7). Sample sizes ranged from 40 to 1298 women. 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.

The updated review included data for:

- 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

**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. Twelve trials evaluated daily oral vitamin D with 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.

**Maternal outcomes**

Moderate-certainty 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). Low-certainty 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 suggests that vitamin D supplementation may reduce the risk of developing gestational diabetes mellitus (GDM) compared with placebo or no vitamin D (five trials, 1744 women; RR: 0.50, 95% CI: 0.28 to 0.88). The evidence on the effect of vitamin D on maternal mortality is of very low certainty.

**Fetal and neonatal outcomes**

It is unclear whether or not vitamin D makes any difference to the risk of having a low birthweight neonate or to neonatal deaths compared with placebo or no vitamin D, as the certainty of the evidence is very low. Moderate-certainty evidence suggests that vitamin D supplementation makes little or no difference to the risk of preterm birth (< 37 weeks of gestation) (eight trials, 2938 women; RR: 0.78, 95% CI: 0.48 to 1.27) or to the risk of stillbirth (four trials, 1884 women; RR: 0.59, 95% CI: 0.28 to 1.22) compared with placebo or no Vitamin D.

**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. Vitamin D doses ranged from 200 IU to 1200 IU daily and calcium carbonate doses ranged from 375 mg to 1250 mg daily.

**Maternal outcomes**

Moderate-certainty 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). Low-certainty evidence suggests that vitamin D 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). The evidence on the effect of vitamin D plus calcium on GDM is of very low certainty.

**Fetal and neonatal outcomes**

Moderate-certainty evidence indicates that vitamin D plus calcium probably increases preterm birth (< 37 weeks of gestation) (3 trials, 798 women; RR: 1.57, 95% CI: 1.02–2.43). Low-certainty evidence suggests that vitamin D plus calcium has little or no effect on neonatal mortality (1 trial, 660 women; RR: 0.20, 95% CI: 0.01–4.14).

The evidence on the effect of vitamin D plus calcium on low birthweight and on neonatal deaths is of very low certainty. Low-certainty 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).

**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” (14).
- 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 ?g) 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 (15). 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). The moderate-certainty evidence showing that adding vitamin D to calcium supplementation probably increases preterm birth is of concern and this potential harm needs further investigation.
Implementation considerations

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

Research implications

During the recommendation development process, the GDG identified the following important knowledge gap that needs to be addressed through primary research:

- There are several ongoing RCTs on vitamin D supplementation in pregnancy (7,15). 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

Related Links

- [WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia](https://www.who.int/health-topics/pre-eclampsia-(pre-eclampsia-and-preeclampsia)-#section-1) (2011) - full document and [evidence tables](https://www.who.int/phe/edocs/pdf/whocollaboratingcentre/EB32-1EB32-15.pdf) (EB Table 51)
- [Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice](https://apps.who.int/iris/bitstream/handle/10665/44351/9789241548414-eng.pdf;jsessionid=8D9E82211B2C5305C43E2EAE070660C4?sequence=1)
- [WHO Programmes: Department of Maternal, Newborn, Child, Adolescent Health and Ageing](https://www.who.int/programmes/maternal-newborn-health)
- [WHO Programmes: Department of Nutrition and Food Safety](https://www.who.int/nutrition)
- [WHO Programmes: Department of Sexual and Reproductive Health and Research](https://www.who.int/reproductivehealth)

References


