WHO recommendation against vitamin C or vitamin E supplementation during pregnancy for the prevention of pre-eclampsia

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Recommendation

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

Publication history

First published: October 2011

Updated: December 2016

Assessed as up-to-date: December 2016

Remarks

- The GDG noted that vitamin E and C combined supplements were evaluated mainly in the context of preventing pre-eclampsia. Vitamin C is important for improving the bioavailability of oral iron, but this was not considered within the context of the Cochrane reviews. In addition, low-certainty evidence on vitamin C alone suggests that it may prevent prelabour rupture of membranes (PROM). Therefore, the GDG agreed that future research should consider vitamin C supplements separately from vitamin E and C supplements.
- 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. It is relatively easy to consume sufficient quantities of vitamin C from food sources.

Background

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

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

**Methods**

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(3, 4) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (2011), and WHO recommendations on antenatal care for a positive pregnancy experience.(5, 6)

Two Cochrane systematic reviews were conducted on the effects of Vitamin C and Vitamin E supplementation on pregnancy outcomes. (7, 8) In the reviews, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

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

Both GDGs discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

**Recommendation question**

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

- in pregnant women (P), does a supplementation with antioxidants (I) compared to placebo or no change to diet (C), affect maternal and neonatal outcomes (O)?
- If so, what combination is most beneficial?

**Evidence Summary**

*Effects of vitamin E and C supplements compared with no vitamin E and C supplements (EB Table A.8)*

The evidence was derived from two Cochrane systematic reviews that included 17 trials conducted in low-, middle- and high-income countries contributed data. (7, 8) The trials assessed vitamin E plus vitamin C combined supplements compared with placebo or no vitamin E and C supplements. The most commonly used dose of vitamin E was 400 IU daily (15 trials) and vitamin C was 1000 mg daily (13 trials). The primary outcome of 14 trials was pre-eclampsia and nine of the trials recruited women at “high” or “increased” risk of pre-eclampsia. Most of the trials commenced supplementation in the second trimester.

*Maternal outcomes*
Moderate-certainty evidence shows that vitamin E and C combined supplements probably have little or no effect on the risk of developing pre-eclampsia (14 studies, 20,878 women; RR: 0.91, 95% CI: 0.79–1.06) and eclampsia (8 trials, 19,471 women; RR: 1.67, 95% CI: 0.82–3.41). Moderate-certainty evidence also shows that vitamin E and C supplements probably have little or no effect on maternal mortality (7 trials, 17,120 women; RR: 0.60, 95% CI: 0.14–2.51) and caesarean section (6 trials, 15,297 women; RR: 1.02, 95% CI: 0.97–1.07).

Side-effects: High-certainty evidence shows that vitamin E and C supplementation is associated with an increased risk of abdominal pain during pregnancy (1 trial, 1,877 women; RR: 1.66, 95% CI: 1.16–2.37; absolute effect of 32 more per 1,000 women).

Fetal and neonatal outcomes

High-certainty evidence indicates that vitamin E and C supplementation does not have an important effect on SGA (11 trials, 20,202 women; RR: 0.98, 95% CI: 0.91–1.06). Moderate-certainty evidence shows that vitamin E and C supplements probably have little or no effect on preterm birth (11 trials, 20,565 neonates; RR: 0.98, 95% CI: 0.88–1.09), neonatal infections (5 trials, 13,324 neonates; RR: 1.10, 95% CI: 0.73–1.67) and congenital anomalies (4 trials, 5,511 neonates; RR: 1.16, 95% CI: 0.83–1.63).

Additional considerations

The high-certainty evidence on abdominal pain is derived from a large, well designed trial in which abdominal pain occurred in 7.9% of women in the vitamin E and C supplement group and 4.8% of women in the placebo group.

Despite the certainty of these effects of vitamin E and C supplementation, the biological explanations for these adverse effects are not established. Moderate-certainty evidence indicates that vitamin E and C supplements probably reduce the risk of placental abruption (7 trials, 14,922 women; RR: 0.64, 95% CI: 0.44–0.93; absolute effect of 3 fewer abruptions per 1000) but make little or no difference to the risk of antepartum haemorrhage from any cause (2 trials, 12,256 women; RR: 1.25, 95% CI: 0.85–1.82).

High-certainty evidence shows vitamin E and C supplementation increases PROM at term (37 weeks of gestation or more) (2 trials, 2,504 women; RR: 1.77, 95% CI: 1.37–2.28; absolute effect of 52 more cases of PROM per 1000).

The trial contributing the most data on PROM was stopped early, based on their PROM data, when only a quarter of the planned sample (10,000 women) had been accrued.

Low- to moderate-certainty evidence on vitamin C only suggests that vitamin C alone (in doses ranging from 100 mg to 1000 mg) may reduce preterm PROM (5 studies, 1,282 women; RR: 0.66, 95% CI: 0.48–0.91) and term PROM (1 study, 170 women; RR: 0.55, 95% CI: 0.32–0.94).

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

The 2011 GDG did not identify any high-priority research questions on this intervention.

A research priority was identified by the 2016 antenatal care GDG:

- Does vitamin C reduce PROM and improve maternal and perinatal outcomes?

Related Links

WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (2011) - full document
and evidence tables (EB Table 51)

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

Supporting systematic review:

Rumbold A, Ota E, Hori H, Miyazaki C, Crowther CA. Vitamin E supplementation in pregnancy. Cochrane


References

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   strength of recommendations using the GRADE approach. 2013.
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Citation