Combined vitamin C and E supplementation during pregnancy for preeclampsia prevention: 
a systematic review

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CRD summary
This review assessed the effects of combined vitamin C and E supplementation during pregnancy on pre-eclampsia and major adverse infant outcomes. No significant effects were found. The authors concluded that vitamin C and E supplementation during pregnancy should be discouraged. The authors’ conclusions are likely to be reliable, however, their applicability is uncertain as the trials included were mainly of high-risk populations.

Authors’ objectives
To evaluate the effect of combined vitamin C and E supplementation during pregnancy on the prevention of pre-eclampsia and major adverse infant outcomes.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched up to August 2006 for relevant trials; some search terms were provided. Three relevant journals were handsearched for the previous 5 years. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Eligible studies were randomised controlled trials (RCTs). All of the included trials were multicentre studies and one was multinational.

Specific interventions included in the review
Eligible studies compared a combination of vitamins C and E with placebo. Studies in which another antioxidant was combined with vitamins C and E, or which studied only vitamin C or vitamin E compared with placebo, were excluded. In all of the included trials, the vitamin C dose was 1,000 mg and the vitamin E dose was 400 mg.

Participants included in the review
Studies of pregnant women were eligible for inclusion. The mean age of the women in the included trials, where reported, was between 26 and 31 years. Three of the 4 included trials enrolled women at high risk of pre-eclampsia, while the remaining trial enrolled patients with no or few risk factors for pre-eclampsia.

Outcomes assessed in the review
Studies where the primary outcome was pre-eclampsia or a hypertensive disorder of pregnancy were eligible. In detail, the maternal outcomes assessed included incidence of pre-eclampsia, severe pre-eclampsia, gestational hypertension and severe gestational hypertension. Infant or foetal outcomes included the incidence of foetal or neonatal loss, pre-term birth (before 37 weeks’ gestation), small for gestational age (below the 10th percentile), low birth weight (under 2.5 kg) and birth weight. The secondary outcomes recorded for mothers and infants included the use of magnesium sulphate for pre-eclampsia, an Apgar score below four at 5 minutes, necrotising enterocolitis, retinopathy of prematurity and the need for mechanical ventilation.

The review only reported outcomes consistently reported across studies in the analyses. For maternal outcomes, this was only the case for pre-eclampsia; for foetuses or neonates, this was the case for foetal or neonatal loss, pre-term birth and small for gestational age.

How were decisions on the relevance of primary studies made?
Three independent investigators performed the searches and selected the studies. The results were compared and a consensus reached with the help of two further reviewers.
Assessment of study quality
The authors did not state how the validity assessment was performed. The following methodological quality criteria were assessed: blinding, adequate randomisation, allocation concealment, withdrawal of participants, description of withdrawals, and intention-to-treat (ITT) analysis.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The data extracted included maternal characteristics and consistently reported outcomes. For all dichotomous variables, relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

Methods of synthesis
How were the studies combined?
The studies were combined statistically in a fixed-effect meta-analysis, unless statistically significant heterogeneity was detected, in which case a random-effects model was used.

How were differences between studies investigated?
Possible heterogeneity between the studies was assessed using the chi-squared (Q) statistic test with a level of significance of 0.1. Sources of heterogeneity were not explored; the authors stated that this was because there were insufficient data available to enable such analyses.

Results of the review
Four RCTs (n=4,680) were included.

All of the included trials were double-blind and described randomisation and allocation concealment adequately. Three of the 4 trials described reasons for withdrawal and used an intention-to-treat analysis.

No significant differences were found between the vitamin and placebo groups in the main outcome measures assessed. Pre-eclampsia occurred in 11% of women in the vitamin groups and in 11.4% of women in the control groups (RR 0.97, 95% CI: 0.82, 1.13). Foetal or neonatal loss occurred in 2.6% of cases in the vitamin groups and 2.3% of cases in the control groups (RR 1.10, 95% CI: 0.78, 1.57). The proportion of small for gestational age infants was 20.6% in the vitamin groups and 20% in the control groups (RR 0.94, 95% CI: 0.74, 1.19). The risk for pre-term birth was 19.5% in the vitamin groups and 18% in the control groups (RR 1.07, 95% CI: 0.96, 1.20). Between-study heterogeneity was only observed for the analysis of small for gestational age.

Authors' conclusions
Combined vitamin C and E supplementation during pregnancy does not reduce the risk of pre-eclampsia, foetal or neonatal loss, small for gestational age infant, or pre-term birth.

CRD commentary
This review had a clearly-stated review question and inclusion criteria. The authors searched two relevant databases and made efforts to identify supplemental information. They described the use of appropriate measures to minimise bias and error in the study selection process, but not in the data extraction or validity assessment, and appropriate criteria to assess validity. The decision to use meta-analysis to combine the studies appeared appropriate, despite some clinical heterogeneity. The authors' conclusions appear to reflect the results of the review and are probably reliable, although the majority of the included studies were conducted in high-risk women and it is not clear how applicable these findings would be to the general population.

Implications of the review for practice and research
Practice: The authors stated that combined vitamin C and E supplementation should be discouraged during pregnancy unless solid supporting data become available.

Research: The authors did not state any implications for further research.

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