Antioxidants for preventing pre-eclampsia: a systematic review
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CRD summary
This review found there were no significant differences in the incidence of pre-eclampsia in pregnant women after treatment with antioxidants. The risk of publication bias and variation in patients and treatments across the trials mean that the authors’ conclusions should be interpreted with caution and their reliability is uncertain.

Authors’ objectives
To assess the efficacy of antioxidants, in preventing pre-eclampsia and other maternal and foetal complications, for pregnant women at low, moderate, or high risk of pre-eclampsia.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), metaRegister of Controlled Trials, CRD databases, Web of Science, Scopus, LILACS, and SciELO were searched to October 2011 for relevant studies; search terms were reported. The websites of gynaecology and obstetrics associations and ProQuest Digital Dissertations, and Brazilian theses registration databases were searched for unpublished studies. The references from relevant studies were checked for additional studies. There were no language restrictions.

Study selection
Eligible for inclusion were randomised controlled trials that evaluated the use of antioxidants, compared with placebo or no antioxidant treatment, in pregnant women with a low, moderate, or high risk of pre-eclampsia. Trials were required to report the primary outcome which was the risk of pre-eclampsia. Secondary outcomes were severe pre-eclampsia, pre-term birth, small-for-gestational age births, baby deaths, and adverse events. Trials in which more than 30% of patients were lost to follow-up, and trials for which the full text was not available, were excluded from the review.

The included trials were conducted in the USA, the UK, Australia, China, India, Indonesia, Vietnam, Brazil, Peru, Mexico and South Africa. The antioxidant administered in most of the trials was vitamin C at doses ranging from 200mg to 1g; other antioxidants were vitamins A, B6, B12, and E, selenium (0.1mg), and lycopene (2 or 4mg). The comparators were placebo or no antioxidant treatment.

Two reviewers performed the study selection; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed methodological quality using the Cochrane Collaboration’s recommendations for randomisation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, treatment of incomplete outcome data, use of selective reporting and the risk of other biases.

Data extraction
The data were extracted by two independent reviewers to calculate relative risks and 95% confidence intervals for the outcomes. Trial authors were contacted for missing data. Any disagreements between reviewers were resolved by consensus or by a third reviewer.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a Mantel-Haenszel random-effects model. The statistical heterogeneity was assessed using X², F, and T². Sensitivity analyses were conducted to examine the impact of low-quality trials on the primary outcome. Trials that were excluded from the review due to unavailability of full texts were included in the primary outcome meta-analysis to assess their impact on the global effect, publication bias and heterogeneity. The potential for publication bias was assessed using visual appraisals of funnel plots, and Peters’ test and Harbord’s modified test for small-study effects were used to detect publication bias.

Results of the review
Fifteen studies, with 21,012 women and 21,647 foetuses, were included in the review. Three trials satisfied all quality criteria and three adequately reported all criteria. For all the quality aspects evaluated, at least half of the trials had a low risk of bias. Three trials each had high risks of bias for the treatment of incomplete outcome data, selective reporting, and other biases.

There were no statistically significant differences in the incidence of pre-eclampsia between women who received antioxidants and women who did not (RR 0.92, 95% CI 0.82 to 1.04; I²=37.3%; 15 trials). There were no differences between intervention and control groups in the incidence of severe pre-eclampsia (RR 1.03, 95% CI 0.87 to 1.22; I²=0; six trials). Sensitivity analysis evaluating only high-quality trials (fulfilling all quality criteria) revealed a non-significant increased risk of pre-eclampsia with antioxidant treatment.

There were no statistically significant differences between antioxidants and placebo or no treatment for pre-term birth, small-for-gestational age births, miscarriage, and neonatal deaths (I²=0; I² ranged from 35.6% to 57.9% for the other outcomes). The heterogeneity was attributed by the reviewers to differences in population and interventions.

Larger numbers of complications were observed in women who were given antioxidants, but the differences between groups were not statistically significant. The side-effects of antioxidant treatment included abdominal pain at the end of pregnancy, itching, eczema, vomiting, diarrhoea, headache, constipation, malaise, decreased vision, skin rash and chest pain.

Visual appraisals of the funnel plots indicated some asymmetry, and this risk of publication bias was statistically significant in Peters' test (p=0.005) and Harbord's modified test (p=0.004). The inclusion of the pre-eclampsia risk from trials published as abstracts only resulted in more asymmetry of the funnel plot and more heterogeneity.

**Authors’ conclusions**
The available evidence did not support the use of antioxidants for the prevention of pre-eclampsia in pregnant women.

**CRD commentary**
A range of appropriate databases was searched for relevant trials, without language restrictions, and attempts were made to identify unpublished trials. The potential for publication bias was evaluated, using validated methods, and a risk of publication bias was found. Steps were taken to minimise errors and biases at each stage of the review process. The quality assessment showed that the included trials were of medium-to-high quality. The authors noted that there were differences in methods and clinical factors between the trials and statistical heterogeneity was identified in the results for most outcomes.

The clear potential for publication bias and methodological limitations of combining heterogeneous results in a meta-analysis mean that the authors' conclusions should be interpreted with caution and their reliability is uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that the use of antioxidants during pregnancy should be carefully considered as beneficial effects had not been proven.

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

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