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SYSTEMATIC REVIEWS AND META-ANALYSES

Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials☆

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Abstract *Aims:* To determine whether oral antioxidant therapies, of various types and doses, are able to prevent or treat women with preeclampsia.
Data synthesis: The following databases were searched: MEDLINE, CENTRAL, LILACS, and Web of Science. Inclusion criteria were: a) randomized clinical trials; b) oral antioxidant supplementation; c) study in pregnant women; d) control group, treated or not with placebo. Papers were excluded if they evaluated antioxidant nutrient supplementation associated with other non-antioxidant therapies. Data were extracted and the risk of bias of each study was assessed. Heterogeneity was analyzed using the Cochran Q test, and I2 statistics and pre-specified sensitivity analyses were performed. Meta-analyses were conducted on prevention and treatment studies, separately. The primary outcome was the incidence of preeclampsia in prevention trials, and of perinatal death in treatment trials. Twenty-nine studies were included in the analysis, 19 for prevention and 10 for treatment. The antioxidants used in these studies were vitamins C and E, selenium, L-arginine, allicin, lycopene and coenzyme Q10, none of which showed beneficial effects on the prevention of preeclampsia (RR: 0.89, CI 95%: [0.79–1.02], P = 0.09; I^2 = 39%, P = 0.04) and other outcomes. The antioxidants used in the treatment studies were vitamins C and E, *N*-acetylcysteine, L-arginine, and resveratrol. A beneficial effect was found in intrauterine growth restriction.
Conclusions: Antioxidant therapy had no effects in the prevention of preeclampsia but did show beneficial effects in intrauterine growth restriction, when used in the treatment of this condition.

Introduction

Pregnancy is considered a sensitive period for the appearance of complications, such as hypertensive diseases and, particularly, preeclampsia (PE) [1,2]. This syndrome is one of the leading causes of maternal and fetal mortality worldwide, together with hemorrhage and

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infections, affecting 2–8% of pregnancies. In Latin America, hypertensive disorders account for almost one quarter of maternal deaths, with lower rates than in developed countries such as the United States, where the incidence is from one up to 8% [1,3] and continues to rise [4]. PE consists of the gradual development of hypertension (systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg), or worsening of preexisting hypertension, proteinuria (300 mg/L or more in 24 h), generalized edema, and sometimes blood clotting disorders that arises after 20 weeks of gestation [1]. The etiology of PE is not fully understood. Oxidative stress, involving the imbalance between the generation of reactive oxygen and nitrogen species (RONS) and antioxidant defense (enzymatic and non-enzymatic), in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage, is among the mechanisms proposed to explain the pathogenesis of PE. Exacerbated production of RONS occurs due to placental abnormalities and consequent deficiency in the defense system performance [5].

Conventional treatment aims at controlling blood pressure levels. However, hypertension is not the cause of the disease, but rather a consequence of the inadequacy of the trophoblastic invasion process with subsequent insufficiency of blood supply and oxygen in the uterus, which increases inflammation and oxidative stress in the placenta [5,6]. These events generate several pro-inflammatory mediators contributing to maintaining the inflammatory process and therefore increasing expression of clinical symptoms of the disease. In this context, the cure is only possible with childbirth – that is, with the elimination of the placenta [6]. Antioxidant therapy has shown beneficial effects in the treatment of various diseases based on oxidative stress and inflammation, such as hypertension [7], inflammatory bowel diseases [8,9] and chronic kidney disease [10]. Therefore, since an effective role of antioxidant therapy has been observed in these isolated situations, it is believed that in PE, when there are combinations of these factors, there could also be benefits in the use of this treatment.

In this context, oral antioxidant therapy with micronutrients and/or drugs has been investigated, for increasing the endogenous antioxidant defense, thereby minimizing the consequences of oxidative stress for mother and fetus and helping in the prevention and/or treatment of PE. There are several meta-analyses related to the proposed theme, but they usually present a narrower scope, once the analyses deal with only one or two antioxidant compounds, as those reported by Xu et al. [11] and Rossi et al. [12]. There are also meta-analyses that show a broader scope, including several antioxidant compounds [13,14]. However, since those reports, several clinical trials on the subject have been conducted [15–18], which motivated us to conduct a new systematic review. In addition, the present meta-analysis is the only one that involves studies related to the treatment of PE [19].

Thus, the present systematic review addressed two research questions: (1) among pregnant women, does the use of oral antioxidants compared to no use prevent preeclampsia and other adverse outcomes such as low birth weight and premature death? Moreover (2) among pregnant women with preeclampsia, does the use of oral antioxidants prevent adverse outcome including growth restriction and perinatal death?

Methods

The present meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement. Two researchers conducted the search, data extraction and assessment of risk of bias, independently. Any disagreement was solved by consensus. A formal protocol was published in PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017062109).

Search strategy and selection of studies

The search was conducted until May 2018, in the following databases: MEDLINE (via PubMed), CENTRAL, LILACS, and Web of Science databases. Besides, the registry database clinicaltrials.gov and the grey literature databases greylit.org and opengrey.eu, were also searched. Keywords related to the conditions and to the intervention were combined with Boolean operators, adjusting for each database. The full search strategy for all the databases is reported in the Supplementary Material. We used terms related to the intervention (antioxidants), such as vitamin C, vitamin E, L-arginine, polyphenols, lycopene, catechin, selenium, glutathione, *N*-acetylcysteine, and other terms related to the condition (PE), such as preeclampsia and pregnancy toxemia. Finally, the reference lists of included studies were also evaluated and relevant references were screened.

All retrieved records had their titles and abstracts evaluated. In addition, there were no restrictions based on year of publication. Duplicate papers were removed. The following eligibility criteria were used: a) randomized clinical trials; b) oral antioxidant supplementation; c) study in pregnant women, regardless of age; d) control group treated or not with placebo. Papers were excluded if they evaluated antioxidant nutrient supplementation associated with other non-antioxidant therapies, such as calcium and essential fatty acid supplementation. Those records in languages other than English, Portuguese and Spanish were excluded. We also excluded articles in which it was not possible to access the full text, even after several attempts to contact the authors and other bibliographic sources. Full-texts of potentially relevant papers were retrieved for further assessment. Finally, included papers were divided according to the therapeutic use of antioxidants, for either prevention or treatment of PE.

For the present study, an antioxidant compound was defined according to Halliwell and Gutteridge [20] as 'any substance that, when present at low concentrations compared with that of an oxidizable substrate,

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