

Antioxidants for female subfertility.

[Showell MG](#)¹, [Brown J](#), [Clarke J](#), [Hart RJ](#).

Abstract

BACKGROUND:

A couple may be considered to have fertility problems if they have been trying to conceive for over a year with no success. This difficulty with conception may affect up to a quarter of all couples planning a child. The reported prevalence of subfertility has increased significantly over the past twenty years. It is estimated that for 40% to 50% of couples, subfertility may be a result of female problems, including ovulatory disorders, poor egg quality, fallopian tube damage and endometriosis. Antioxidants are thought to reduce the oxidative stress brought on by these conditions. Currently, limited evidence suggests that antioxidants improve fertility, and trials have explored this area with varied results. This review assessed the evidence for the effectiveness of different antioxidants in female subfertility.

OBJECTIVES:

To determine whether supplementary oral antioxidants compared with placebo, no treatment/standard treatment or another antioxidant improve fertility outcomes for subfertile women.

SEARCH METHODS:

We searched the following databases (from inception to April 2013) with no language restrictions applied: Cochrane Menstrual Disorders and Subfertility Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS and OpenSIGLE. We also searched conference abstracts and citation lists in the ISI Web of Knowledge. Ongoing trials were searched in the Trials Registers. Reference lists were checked, and a search on Google was performed.

SELECTION CRITERIA:

We included randomised controlled trials (RCTs) that compared any type, dose or combination of oral antioxidant supplement with placebo, no treatment or treatment with another antioxidant, among women attending a reproductive clinic. Trials comparing antioxidants with fertility drugs alone and trials that exclusively included fertile women attending a fertility clinic because of male partner infertility were excluded.

DATA COLLECTION AND ANALYSIS:

Three review authors independently screened 2127 titles and abstracts, and 67 of these potentially eligible trials were appraised for inclusion and quality through review of full texts and contact with authors. Three review authors were involved in data extraction and assessment of risk of bias. Review authors also collected data on adverse events as reported from the trials. Studies were pooled using fixed-effect models; however, if high heterogeneity was found, a random-effects model was used. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the dichotomous outcomes of live birth, clinical pregnancy and adverse events. Analyses were stratified by type of antioxidant, by indications for subfertility and by those women also undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection techniques (ICSI). The overall quality of the evidence was assessed by applying GRADE criteria.

MAIN RESULTS:

A total of 28 trials involving 3548 women were included in this review. Investigators compared oral antioxidants, including combinations of antioxidants, pentoxifylline, N-acetyl-cysteine, melatonin, L-arginine, vitamin E, myo-inositol, vitamin C, vitamin D+calcium and omega-3-polyunsaturated fatty acids with placebo, with no treatment/standard treatment or another antioxidant. Antioxidants were not associated with an increased live birth rate compared with placebo or no treatment/standard treatment (OR 1.25, 95% CI 0.19 to 8.26, P = 0.82, 2

RCTs, 97 women, $I(2) = 75\%$, very low-quality evidence). This suggests that among subfertile women with an expected live birth rate of 37%, the rate among women taking antioxidants would be between 10% and 83%. Antioxidants were not associated with an increased clinical pregnancy rate compared with placebo or no treatment/standard treatment (OR 1.30, 95% CI 0.92 to 1.85, $P = 0.14$, 13 RCTs, 2441 women, $I(2) = 55\%$, very low-quality evidence). This suggests that among subfertile women with an expected clinical pregnancy rate of 23%, the rate among women taking antioxidants would be between 22% and 36%. Only one trial reported on live birth in the antioxidant versus antioxidant comparison, and two trials reported on clinical pregnancy in this comparison. Only subtotals were used in this analysis, and meta-analysis was not possible as each trial used a different antioxidant. Pentoxifylline was associated with an increased clinical pregnancy rate compared with placebo or no treatment (OR 2.03, 95% CI 1.19 to 3.44, $P = 0.009$, 3 RCTs, 276 women, $I(2) = 0\%$). Adverse events were reported by 14 trials in the meta-analysis and included miscarriage, multiple pregnancy, ectopic pregnancy and gastrointestinal effects. No evidence revealed a difference in adverse effects between antioxidant groups and control groups, but these data were limited. The overall quality of evidence was 'very low' to 'low' because of poor reporting of outcomes, the number of small studies included, high risk of bias within studies and heterogeneity in the primary analysis.

AUTHORS' CONCLUSIONS:

The quality of the evidence in the 'antioxidant versus placebo/no treatment' and in the 'antioxidant versus antioxidant' comparisons was assessed to be 'very low'. Antioxidants were not associated with an increased live birth rate or clinical pregnancy rate. There was some evidence of an association of pentoxifylline with an increased clinical pregnancy rate; however, there were only three trials included in this comparison. Future trials may change this result. Variation in the types of antioxidants given meant that we could not assess whether one antioxidant was better than another. There did not appear to be any association of antioxidants with adverse effects for women, but data for these outcomes were limited.