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[Intervention Review]

# Antioxidants for female subfertility

Marian G Showell[1], Rebecca Mackenzie-Proctor[2], Vanessa Jordan[1], Roger J Hart[3]

[1]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [2]Department of Obstetrics and Gynaecology, Auckland City Hospital, Auckland, New Zealand. [3]School of Women's and Infants' Health, The University of Western Australia, King Edward Memorial Hospital and Fertility Specialists of Western Australia, Subiaco, Perth, Australia

**Contact address:** Marian G Showell, Department of Obstetrics and Gynaecology, University of Auckland, Park Road Grafton, Auckland, 1142, New Zealand. m.showell@auckland.ac.nz.

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## 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 may affect up to a quarter of all couples planning a child. It is estimated that for 40% to 50% of couples, subfertility may result from factors affecting women. 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 assesses 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 their inception to September 2016) with no language or date restriction: Cochrane Gynaecology and Fertility Group (CGFG) specialised register, the Cochrane Central Register of Studies (CENTRAL CRSO), MEDLINE, Embase, PsycINFO, CINAHL and AMED. We checked reference lists of appropriate studies and searched for ongoing trials in the clinical trials registers.

### 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. We excluded trials comparing antioxidants with fertility drugs alone and trials that only included fertile women attending a fertility clinic because of male partner infertility.

### Data collection and analysis

Two review authors independently selected eligible studies, extracted the data and assessed the risk of bias of the included studies. The primary review outcome was live birth; secondary outcomes included clinical pregnancy rates and adverse events. We pooled studies using a fixed-effect model, and calculated odds ratios (ORs) with 95% confidence intervals (CIs) for the dichotomous outcomes of live birth, clinical pregnancy and adverse events. We assessed the overall quality of the evidence by applying GRADE criteria.

### Main results

We included 50 trials involving 6510 women. Investigators compared oral antioxidants, including combinations of antioxidants, *N*-acetyl-cysteine, melatonin, L-arginine, myo-inositol, *D*-chiro-inositol, carnitine, selenium, vitamin E, vitamin B complex, vitamin C, vitamin D

+calcium, CoQ10, pentoxifylline and omega-3-polyunsaturated fatty acids versus placebo, no treatment/standard treatment or another antioxidant.

Very low-quality evidence suggests that antioxidants may be associated with an increased live birth rate compared with placebo or no treatment/standard treatment (OR 2.13, 95% CI 1.45 to 3.12, P > 0.001, 8 RCTs, 651 women, $I^2$ = 47%). This suggests that among subfertile women with an expected live birth rate of 20%, the rate among women using antioxidants would be between 26% and 43%.

Very low-quality evidence suggests that antioxidants may be associated with an increased clinical pregnancy rate compared with placebo or no treatment/standard treatment (OR 1.52, 95% CI 1.31 to 1.76, P < 0.001, 26 RCTs, 4271 women, $I^2$ = 66%). This suggests that among subfertile women with an expected clinical pregnancy rate of 22%, the rate among women using antioxidants would be between 27% and 33%. Heterogeneity was moderately high.

There was insufficient evidence to determine whether there was a difference between the groups in rates of miscarriage (OR 0.79, 95% CI 0.58 to 1.08, P = 0.14, 18 RCTs, 2834 women, $I^2$ = 23%, very low quality evidence). This suggests that, among subfertile women with an expected miscarriage rate of 7%, use of antioxidants would be expected to result in a miscarriage rate of between 4% and 7%. There was also insufficient evidence to determine whether there was a difference between the groups in rates of multiple pregnancy (OR 1.00, 95% CI 0.73 to 1.38, P = 0.98, 8 RCTs, 2163 women, $I^2$ = 4%, very low quality evidence). This suggests that among subfertile women with an expected multiple pregnancy rate of 8%, use of antioxidants would be expected to result in a multiple pregnancy rate between 6% and 11%. Likewise, there was insufficient evidence to determine whether there was a difference between the groups in rates of gastrointestinal disturbances (OR 1.55, 95% CI 0.47 to 5.10, P = 0.47, 3 RCTs, 343 women, $I^2$ = 0%, very low quality evidence). This suggests that among subfertile women with an expected gastrointestinal disturbance rate of 2%, use of antioxidants would be expected to result in a rate between 1% and 11%. Overall adverse events were reported by 35 trials in the meta-analysis, but there was insufficient evidence to draw any conclusions.

Only one trial reported on live birth, clinical pregnancy or adverse effects in the antioxidant versus antioxidant comparison, and no conclusions could be drawn.

Very low-quality evidence suggests that pentoxifylline may be associated with an increased clinical pregnancy rate compared with placebo or no treatment (OR 2.07, 95% CI 1.20 to 3.56, P = 0.009, 3 RCTs, 276 women, $I^2$ = 0%). This suggests that among subfertile women with an expected clinical pregnancy rate of 25%, the rate among women using pentoxifylline would be between 28% and 53%.

There was insufficient evidence to determine whether there was a difference between the groups in rates of miscarriage (OR 1.34, 95% CI 0.46 to 3.90, P = 0.58, 3 RCTs, 276 women, $I^2$ = 0%) or multiple pregnancy (OR 0.78, 95% CI 0.20 to 3.09, one RCT, 112 women, very low quality evidence). This suggests that among subfertile women with an expected miscarriage rate of 4%, the rate among women using pentoxifylline would be between 2% and 15%. For multiple pregnancy, the data suggest that among subfertile women with an expected multiple pregnancy rate of 9%, the rate among women using pentoxifylline would be between 2% and 23%.

The overall quality of evidence was limited by serious risk of bias associated with poor reporting of methods, imprecision and inconsistency.

**Authors' conclusions**

In this review, there was very low-quality evidence to show that taking an antioxidant may provide benefit for subfertile women, but insufficient evidence to draw any conclusions about adverse events. At this time, there is limited evidence in support of supplemental oral antioxidants for subfertile women.

## PLAIN LANGUAGE SUMMARY

**Vitamins and minerals for subfertility in women**

**Review question:**
Do supplementary oral antioxidants compared with placebo, no treatment/standard treatment or another antioxidant improve fertility outcomes for subfertile women (standard treatment includes less than 1 mg of folic acid).

**Background:**
Many subfertile women undergoing fertility treatment also take dietary supplements in the hope of improving their fertility. This can be a very stressful time for women and their partners. It is important that these couples be given high-quality evidence that will allow them to make informed decisions on whether taking a supplemental antioxidant when undergoing fertility treatment will improve their chances or cause any adverse effects. This is especially important, as most antioxidant supplements are uncontrolled by regulation. This review aimed to assess whether supplements with oral antioxidants increase a subfertile woman's chances of becoming pregnant and having a baby.

**Search date:**
The evidence is current to September 2016.

**Study characteristics:**

The review includes 50 randomised controlled trials that compare antioxidants with placebo or with no treatment/standard treatment, or with another antioxidant, in a total of 6510 women.

**Funding sources:**
Funding sources were reported by only 14 of the 50 included trials.

**Key results:**
Very low-quality evidence suggests that antioxidants may be associated with an increased live birth and clinical pregnancy rate. Based on these results, we would expect that out of 100 subfertile women not taking antioxidants, 20 would have a baby, compared with between 26 and 43 women per 100 who would have a baby if taking antioxidants. There was insufficient evidence to draw any conclusions about the adverse effects of miscarriage, multiple births or gastrointestinal effects. Very low-quality evidence suggests that pentoxifylline may also be associated with increased rates of clinical pregnancy, but there were only three trials in this analysis. In this case we would expect that out of 100 subfertile women not taking pentoxifylline, 25 would become pregnant, compared with between 28 and 53 women per 100 who would become pregnant if taking pentoxifylline to improve their chances of getting pregnant. There was also insufficient evidence to draw any conclusions about the adverse effects of pentoxifylline. Only one trial measured one antioxidant against another,so there was no evidence available to draw any conclusion from this comparison.

**Quality of the evidence:**
The overall quality of evidence was limited by serious risk of bias associated with poor reporting of methods, imprecision and inconsistency.