Antioxidants for Female Subfertility – a Systematic Review

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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.

Many subfertile women undergoing treatment also take dietary supplements in the hope of improving their fertility. This can be a very costly and 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.

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.

Methods

- Meta-analysis was performed as per the Cochrane manual.
- Databases searched and studies were selected based on the following
- Inclusion criteria:
- Randomised controlled trials 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.
- Excluded:
- Trials comparing antioxidants with fertility drugs alone and trials that only included fertile women attending a fertility clinic because of male partner infertility.
- The primary review outcome was live birth; secondary outcomes included clinical pregnancy rates and adverse events

Results

- 50 trials, **6510 women**.
  - Oral antioxidants:
    - combinations of antioxidants N-acetyl-cysteine,
    - melatonin, L-arginine selenium,
    - myo-inositol D-chiro-inositol carnitine
    - vitamin E vitamin B complex vitamin C
    - CoQ10 pentoxifylline vitamin D+calcium
    - omega-3-polyunsaturated fatty acids
  - versus placebo, no treatment/standard treatment or another antioxidant.
- 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 1.45-3.12, $P > 0.001$, 8 RCTs, 651 women)
  - Subfertile women using antioxidants had a live birth rate (LBR) between **26% and 43%** compared to 20% in subfertile women without supplementation.
  - Combined antioxidants had a significantly higher live births compared to any other individual antioxidant (OR 6.76).

- 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)
  - L-Carintine, Q10 and combined antioxidants and CoQ10 were associated with increased clinical pregnancy rate compared to placebo (OR 82.05, 4.28, and 2.28 respectively).
  - Insufficient evidence to determine a difference between the groups in rates of:
    - miscarriage (OR 0.79, 95% CI 0.58-1.08, $P = 0.14$),
    - multiple pregnancy (OR 1.00, 95% CI 0.73-1.38, $P = 0.98$)
    - gastrointestinal disturbances (OR 1.55, 95% CI 0.47-5.10, $P = 0.47$).

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

Conclusions

- **Taking antioxidants may provide benefit for subfertile women by improving live births and clinical pregnancies.**
- There was insufficient evidence to draw any conclusions about the adverse effects of miscarriage, multiple births or gastrointestinal effects.

In a world with increased access and resources spent on complementary and supportive treatments for subfertility it is important to have good quality evidence to support their use. This increased focus is highlighted by having almost twice as many studies in this review compared to that published in 2013, which found no significant difference in outcomes.

- Unfortunately, the quality of these new studies is poor. High quality research is needed to strengthen the association between antioxidants and subfertility outcomes and provide women with stronger evidence of benefit or harm.

Antioxidant(s) versus placebo or no treatment/standard treatment, outcome: 1.1 Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).