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Antioxidants for female subfertility (Review)

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[Intervention Review]

Antioxidants for female subfertility

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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 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 (ICSIs). 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.

PLAIN LANGUAGE SUMMARY

Vitamins and minerals for female subfertility

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 folic acid < 1 mg).

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 April 2013.

Study characteristics: The review included 28 randomised controlled trials that compared antioxidants with placebo or no treatment/ standard treatment, or with another antioxidant in a total of 3548 women.

Funding sources: Funding sources were reported by only six of the 28 included trials.

Key results: Antioxidants were not found to be effective for increasing rates of live birth or clinical pregnancy. Based on these results, we would expect that out of 100 subfertile women not taking antioxidants, 23 would become pregnant, compared with between 22 and 36 per 100 who would become pregnant if taking antioxidants to improve their chances of becoming pregnant. Antioxidants did not appear to be associated with the adverse events of miscarriage or multiple or ectopic pregnancy.

Quality of the evidence: The quality of the evidence in this review for live birth, clinical pregnancy and adverse effects was rated 'very low' to 'low'.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antioxidant(s) versus placebo or no treatment/standard treatment for female subfertility

Population: Subfertile women
Settings: Attending a reproductive clinic
Intervention: Antioxidant(s) versus placebo or no treatment/standard treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control Placebo or no treatment/ standard treatment	Antioxidant(s)				
Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	367 per 1000	420 per 1000 (99 to 827)	OR 1.25 (0.19 to 8.26)	97 (2 studies)	⊕◯◯◯ very low[1,2,3,4]	
Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	231 per 1000	281 per 1000 (217 to 357)	OR 1.3 (0.92 to 1.85)	2441 (13 studies)	⊕◯◯◯ very low[1,2,3,4]	
Adverse events - Miscarriage	63 per 1000	56 per 1000 (37 to 84)	OR 0.88 (0.57 to 1.36)	1456 (8 studies)	⊕⊕◯◯ low[1,3,4]	
Adverse events - Multiple pregnancy	67 per 1000	48 per 1000 (29 to 80)	OR 0.7 (0.41 to 1.21)	1022 (2 studies)	⊕⊕◯◯ low[3,5]	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Most trials described the randomisation adequately but did not describe methods of allocation concealment
[2] The I squared statistic was >50%
[3] Trials contained women with different indications of subfertility and the antioxidants used were also different.
[4] There were wide confidence intervals in some of the trials
[5] One trial described method of randomisation but not allocation concealment and the other described allocation concealment but not randomisation

BACKGROUND

Description of the condition

A couple that has tried to conceive for a year or longer without success is considered to be subfertile (Evers 2002) or less fertile than a typical couple. Over the past two decades, the reported prevalence of subfertility has increased markedly. Forty to fifty percent of cases of subfertility are due to female causes. Influencing factors include ovulatory failure, tubal damage, endometriosis, poor egg quality and unexplained subfertility. It is suggested that up to 25% of couples who are planning a baby have difficulty (Hart 2003).

To overcome these fertility problems, many couples undergo assisted fertility techniques (assisted reproductive techniques (ART)). These include ovulation stimulation, intrauterine insemination, in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

Women use antioxidant supplements in preparation for ART and/or simultaneously with the treatment, and some women use supplements alone with no ART in an attempt to improve their fertility.

The global vitamin and supplement market is a growth industry estimated to be worth $68 billion (US) (Reportlinker 2010). In 2009 sales of vitamins and dietary supplements in the United Kingdom "totalled £674.6 million, a growth of about 16% over the previous five years, with the two biggest selling areas being multivitamins (£138.6 million) and fish oils (£139.1 million)" (NHS News 2011).

Vitamins and supplements are not regulated and are dispensed through various retail outlets, including health food shops, online retailers, health centres, fitness clubs, supermarkets and pharmacies.

Description of the intervention

Antioxidants are biological and chemical compounds that reduce oxidative damage. They are a group of organic nutrients that include vitamins, minerals and polyunsaturated fatty acids (PUFAs). Some of the predominant antioxidants used in female subfertility are *N*-acetyl-cysteine; melatonin; vitamins A, C and E; folic acid; myo-inositol; zinc and selenium. They may be administered as a single antioxidant or as combined therapy.

PUFAs are classified into omega-3, omega-6 and omega-9. Omega-9 is synthesised by animals, but omegas-3 and -6 need to be supplemented in the diet. The main sources of omega-6 are vegetable oils. Sources of omega-3 are vegetable and fish oils. The ratio of omega-6 to omega-3 has risen in recent times (as the result of increased intake of vegetable oils) to the point where there is a reduced need for intake of omega-6 and an increased need for intake of omega-3 (Wathes 2007).

Pentoxifylline is a conventional medicine, a tri-substituted xanthine derivative usually prescribed for intermittent claudication (Drugs.com). Pentoxifylline is also used in fertility treatment as it is known to have a strong antioxidant effect by generating reactive oxygen species (Vircheva 2010). It has been shown to benefit men who have varicocoele-associated infertility (Oliva 2009).

The amino acid L-arginine also has antioxidant properties that aid in the inflammatory response and act against oxidative damage (Ko 2012).

When oxidative damage occurs, toxins are produced as a consequence of all cells using oxygen to survive. Toxic end products may include molecules that have unpaired electrons, which may lead to the formation of free radicals. Free radicals may cause further harmful reactions with lipids in membranes, amino acids in proteins and carbohydrates within nucleic acids. An antioxidant molecule is thought to be capable of slowing or preventing the oxidation of other molecules and potentially of reducing the production of free radicals, which may cause this cellular damage.

Two major types of free radicals have been identified: reactive oxygen species (ROS) and reactive nitrogen species (RNS). Reactive oxygen species are products of normal cellular metabolism and consist of oxygen ions, free radicals and peroxides. The addition of one electron to oxygen forms the superoxide anion radical, which then can be converted to hydroxyl radical, peroxyl radical or hydrogen peroxide. Free radicals seek to participate in chemical reactions that relieve them of their unpaired electron, resulting in oxidation (Ruder 2008; Tremellen 2008). The presence of ROS within the ovary and the endometrium has significant physiological and pathological implications for women when they try to conceive. Oxidative stress is a result of an imbalance between the amount of ROS and the quantity of natural antioxidants present within the body. Natural antioxidants present in the body include catalase, glutathione peroxidase, superoxide dismutase and glutathione reductase, in addition to some non-enzymic agents such as vitamins C and E and ferritin and transferrin (Gupta 2007).

Indirect evidence from smoking and alcohol trials suggests that these factors have a negative impact on female fertility, potentially through the generation of excessive oxidative stress (Ruder 2008). Other lifestyle factors such as diet, disease, pollution, stress and allergies also contribute to increased levels of free radicals.

In an effort to enhance fertility, couples are increasingly resorting to ART; however, these techniques do not cure the causes of subfertility; rather they may overcome some of its barriers. Adjunct measures, including courses of dietary supplements such as oral antioxidants, may be beneficial (Ebisch 2007). However, most antioxidant supplements are uncontrolled by regulation, and thus their effects may be unpredictable in the population.

How the intervention might work

Antioxidants are said to have an important role in the regulation of all processes involved in the birth of a healthy baby (Gupta

2007). The local development of oxidative stress will have significant adverse effects on these processes. Conditions with which the adverse effects of oxidative stress may be associated in subfertile women include endometriosis, hydrosalpinges (dilated fallopian tubes), polycystic ovarian syndrome (PCOS), fetal malformations and potentially unexplained subfertility (Ruder 2008; Zhao 2006).

At the time of conception, oxidative stress can lead to cell membrane lipid peroxidation, cellular protein oxidation and DNA damage, causing a negative effect upon the oocyte, the embryo and implantation (Ruder 2008). Antioxidants would be expected to counteract the negative impact of oxygen free radicals by acting as free radical scavengers.

Supplementary antioxidants may have several methods of action. Fertility benefits of vitamin E include improvement in epithelial growth in blood vessels and in the endometrium (Ledee-Bataille 2002). Higher vitamin D levels are associated with an increased likelihood of successful pregnancy and may be of particular benefit to women with PCOS in lowering hyperandrogenism (Thomson 2012). Myo-inositol helps ovarian function and decreases hyperandrogenism and insulin resistance (Nestler 1998); L-arginine improves endometrial blood flow (Battaglia 1999); *N*-acetyl-cysteine is needed for fertile cervical mucus and ovulation (Badawy 2007); and PUFAs influence prostaglandin synthesis and steroidogenesis and also play a role in the composition of cell membranes of the sperm and oocyte, which is important during fertilisation (Wathes 2007). Cohort studies have shown some evidence suggesting that in some instances, taking a multivitamin tablet may increase fertility (Haggarty 2006) or even regulate ovulation (Charvarro 2008).

Why it is important to do this review

Currently evidence as to whether antioxidants improve fertility is limited, and ongoing trials in this area show varied results. This review assessed the effectiveness of different antioxidants and different dosages.

Subfertile women are highly motivated to explore all avenues of treatment in their desire to have a healthy baby. Antioxidants are mostly unregulated and are readily available for purchase by consumers. Research has suggested that a significant number of women undergoing fertility treatment are taking oral supplements in the expectation that this will improve their chances of conception (Stankiewicz 2007). Consumer perception is that antioxidant therapy is not associated with harm and is associated only with benefit. It is important to establish whether or not this therapy does improve fertility and whether it is associated with any harm.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Randomised controlled trials (RCTs).
- Cross-over trials were included; however, only first-phase data were used in the analysis. Achieving outcomes such as pregnancy and live birth would preclude entry of couples into the next trial phase (Dias 2006).

Exclusion criteria

- Any quasi-randomised trials.

Types of participants

Inclusion criteria

- Trials that included subfertile women who had been referred to a fertility clinic and might or might not be undergoing assisted reproductive techniques (ART) such as in vitro fertilisation (IVF), intrauterine insemination (IUI) or intracytoplasmic sperm injection (ICSI).

Exclusion criteria

- Trials enrolling only fertile women attending a fertility clinic exclusively as the result of male partner infertility.

Types of interventions

We included trials if they investigated the following:

- Any type of oral antioxidant supplementation versus control- placebo (plus or minus a co-intervention) or no treatment/standard treatment (standard treatment includes folic acid < 1 mg);
- Individual or combined oral antioxidants versus any antioxidant (head-to-head trials); or
- Pentoxifylline versus control (placebo or no treatment/standard treatment).

On clinical advice, trials that used folic acid (standard treatment) and those that included a co-intervention (a fertility drug such as clomiphene citrate or metformin) in both arms were analysed in the antioxidant versus placebo or no treatment/standard treatment comparison and not in the head-to-head comparison, as the controls were not considered to be active treatments. Pentoxifylline trials were analysed as a separate comparison as it was not possible to separate the antioxidant effects from the other medical effects of the drug.

Exclusion criteria

- Interventions that included antioxidants alone versus fertility drugs as controls. These fertility drugs included metformin and clomiphene citrate.

Types of outcome measures

Primary outcomes

Live birth rate per woman randomly assigned (defined as the delivery of one or more living infants).

Secondary outcomes

- Clinical pregnancy rate per woman (as confirmed by the identification of a gestational sac on ultrasound at $\geq$ 7 weeks' gestation).

- Any adverse effects reported by the trial. These events were subgrouped by the type of adverse event reported.

Search methods for identification of studies

We searched for all reports, published and unpublished, that described RCTs investigating oral antioxidant supplementation for subfertile women and its impact on live birth, pregnancy and adverse events rates. Both indexed and free text terms were used, and no language restriction was applied.
This review used the information in the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Module regarding search strategies (www.mrw.interscience.wiley.com/cochrane/clabout/articles/MENSTR/frame.html).

Electronic searches

- The Cochrane Menstrual Disorders and Subfertility Group's Trials Search Co-ordinator searched the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials from inception to April 2013 (Appendix 1). This register contains published and unpublished trials and abstracts.
- We searched the following databases using the Ovid platform:
    - Cochrane Central Register of Controlled Trials (CENTRAL) (from inception to April 2013) (Appendix 2);
    - MEDLINE (1950 to April 2013) (Appendix 3);
    - EMBASE (inception to April 2013) (Appendix 4);
    - CINAHL (1982 to September 2010) (Appendix 5);
    - PsycINFO (from inception to April 2013) (Appendix 6); and
    - AMED (Allied and Complementary Medicine) (1985 to April 2013) (Appendix 7).

- CINAHL EBSCO Platform search September 2010 to April 2013 (Appendix 5).
- International trial registers: 'ClinicalTrials.gov', a service of the US National Institutes of Health (http://clinicaltrials.gov/ct2/home) (last searched April 2013) and 'The World Health Organization International Trials Registry Platform search portal' (www.who.int/trialsearch/Default.aspx) (last searched April 2013), using the following simple search strategies: 'antioxidants and subfertility', 'antioxidants and infertility', 'vitamin and subfertility', 'vitamin and infertility', '*N*-acetyl-cysteine and subfertility', '*N*-acetyl-cysteine and infertility', 'myo-inositol and subfertility', 'myo-inositol and subfertility', 'fatty acids and subfertility' and 'fatty acids and infertility'.
- Web of Knowledge for conference proceedings and published trials.
- Google, using the keywords 'antioxidants female infertility' and 'antioxidants female subfertility'.Database for Abstracts of Reviews of Effects (DARE) for other reviews on this topic.

The MEDLINE search was limited by the Cochrane highly sensitive search strategy filter for identifying randomised trials, which appears in the *Cochrane Handbook of Systematic Reviews of Interventions* (Version 5.1, Chapter 6, 6.4.11) (Higgins 2011). The EMBASE and CINAHL (OVID platform only) searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/mehodology/filters.html#random). The RCT filters used are also found in the Cochrane Menstrual Disorders and Subfertility Group module (MDSG) .

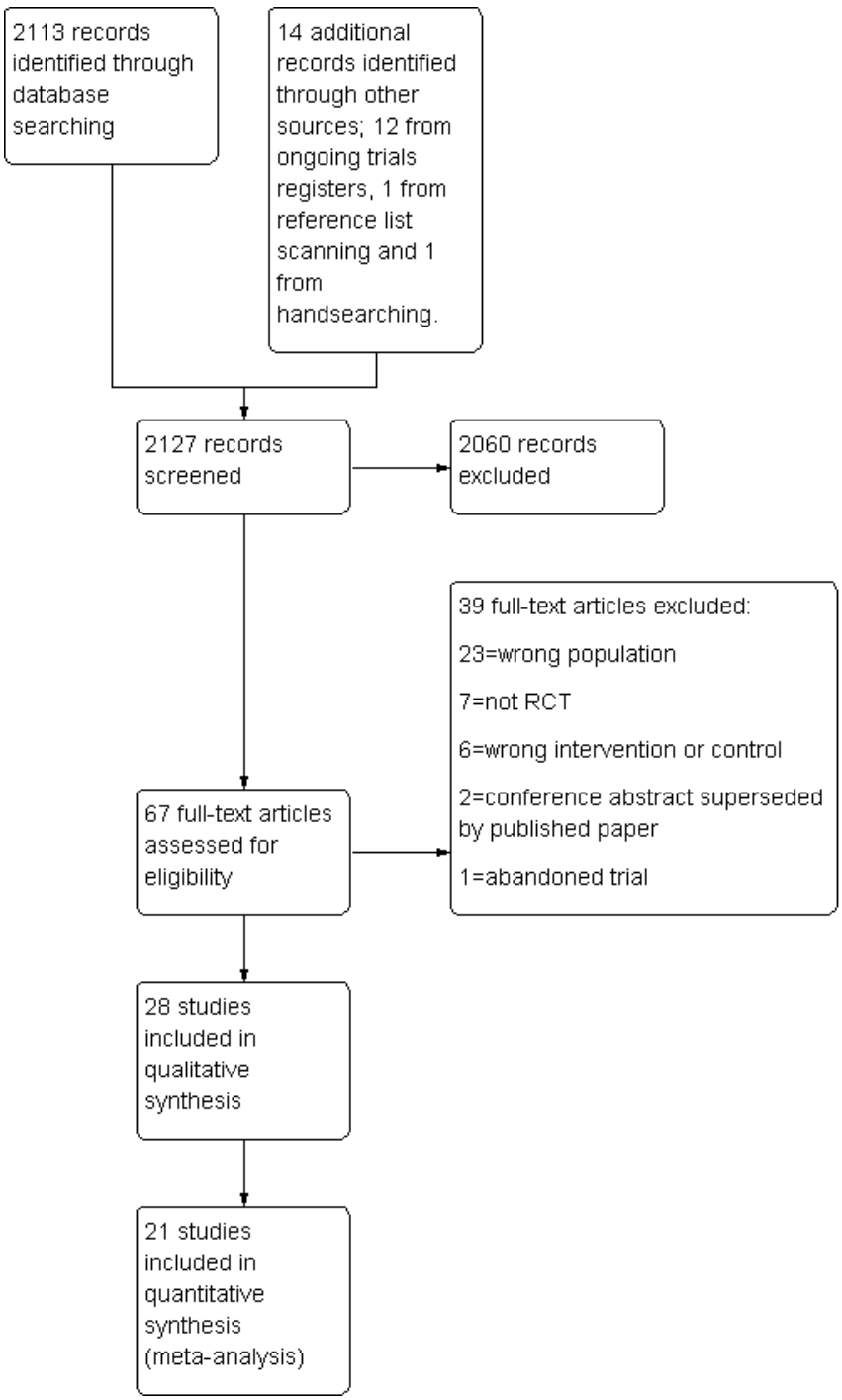
Searching other resources

- Handsearching of selected journals in obstetrics, gynaecology and reproductive medicine, as well as conference proceedings (for abstracts) of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM).
- Grey literature through the openGREY database (http://www.opengrey.eu/).
- Known experts and personal contacts regarding any unpublished materials.
- Citation lists of all articles for any relevant references

Data collection and analysis

We conducted data collection and analysis in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The flow of information through the different phases of this systematic review can be seen in Figure 1.

Figure 1. Study flow diagram.



Selection of studies

Two of three review authors (JC, MGS and JB) independently reviewed titles and abstracts of trials for inclusion eligibility. We obtained the full texts of trials that we considered for potential inclusion. We sought further information from the authors of trials that did not contain sufficient information to make a decision about eligibility. Any disagreements for resolution were referred to a third review author. The selection process was documented with a "PRISMA" flow chart.

Data extraction and management

Two of three authors (JC, MGS and JB) independently extracted data from the included trials using a data extraction form. We compared the two sets of extracted data and resolved discrepancies by discussion. The review authors screened the trials to ensure that there were no duplicate publications.

The data extraction forms were designed to extract data regarding study characteristics and outcomes. We have included this information and presented it in the Characteristics of included studies and the Characteristics of excluded studies tables, in keeping with the guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If any information on trial methodology or any trial data were missing, the study authors were contacted by email and by post. The predominant questions for trial authors concerned live birth data, clinical pregnancy, methods of randomisation and allocation concealment.

Assessment of risk of bias in included studies

The included studies were assessed for risk of bias using the Cochrane risk of bias assessment tool to assess selection bias (sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (completeness of outcome data); reporting bias (selective outcome reporting); and other potential sources of bias. Two of three authors (JC, MGS and JB) assessed the included studies according to these six criteria; any disagreements were resolved by discussion with a third author. We sought published protocols.

Care was taken to search for within-study selective reporting, such as trials failing to report outcomes such as live birth or reporting them in insufficient detail to allow inclusion. Where protocols were available, studies were assessed for differences between published results and study protocols.

In cases where included studies failed to identify the primary outcome of live birth but did report pregnancy rates, we carried out an informal assessment to determine whether pregnancy rates were similar to those in studies that reported live birth.

Measures of treatment effect

The dichotomous data for live birth, pregnancy rate, miscarriage and adverse events were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs) and were combined in a meta-analysis with RevMan software using the Peto method and a fixed-effect model (Higgins 2011). This effect measure is appropriate when subfertility is considered. These data were displayed on forest plots.

Unit of analysis issues

Outcomes of live birth, pregnancy and adverse events were analysed as per woman randomly assigned. Multiple births were counted as one live birth event.

Dealing with missing data

In cases where trial data were missing, we first sought information from the original trial investigators. Details of authors contacted and the questions asked of them are contained in Characteristics of included studies. In addition, and where possible, we performed analyses on all outcomes on an intention-to-treat basis. It was our intention to include in the analyses all women randomly assigned to each group and to analyse all women in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Statistical heterogeneity was assessed according to the guidelines set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We examined heterogeneity between the results of different trials by visually assessing the forest plots and the overlap of confidence intervals (poor overlap suggested heterogeneity), by considering the P value (a low P value or a large Chi^2 statistic relative to the degree of freedom suggests heterogeneity) and by identifying the I^2 statistic. If I^2 was $\geq$ 50%, we assumed high heterogeneity, and a sensitivity analysis with a random-effects model was used to assess the possible reasons. A high I^2 statistic suggests that variations in effect estimates were due to differences between trials rather than to chance alone.

Assessment of reporting biases

The search strategies covered multiple sources without language or publication restrictions. We were alert to the possibility of duplication of data. We used a funnel plot to explore the possibility of

small study effects in cases where estimates of intervention effect can be more beneficial in smaller studies (Higgins 2011).

Data synthesis

Statistical analysis of the data was carried out using Review Manager 5 (RevMan 5). Pregnancy outcomes were considered positive, and higher numbers of pregnancy rates were considered a benefit. The outcomes of miscarriage and adverse events were negative effects, and higher numbers were considered harmful. These aspects were considered when the summary graphs were assessed.
Data from primary studies were combined using a fixed-effect model in the following comparisons:

- Antioxidants versus control (placebo or no treatment/ standard treatment);
- Antioxidants versus antioxidants or head-to-head stratification by type of antioxidant; and
- Pentoxifylline versus control (placebo or no treatment/ standard treatment).

Increases in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), were displayed graphically in meta-analyses to the right of the centre line, and decreases in the odds of a particular outcome were displayed to the left of the centre line.
The aim was to define analyses that were comprehensive and mutually exclusive so that all eligible study results could be slotted into one stratum only. Comparisons were specified, so that any trials falling within each stratum could be pooled for meta-analysis. Stratification allowed for consideration of effects within each stratum, as well as or instead of an overall estimate for comparison. In trials with multiple arms, intervention groups were pooled versus the control group.
If individuals had been re-randomly assigned after failed cycles, we would not have pooled the data in a meta-analysis.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were carried out:

- Type of antioxidant, whether individual or combined (three or more antioxidants combined);
- Trials that enrolled women with different indications for infertility (i.e. PCOS, endometriosis, unexplained infertility or poor responders); and
- Trials that enrolled women who were also undergoing IVF or ICSI.

If we detected substantial heterogeneity, we explored possible explanations by performing sensitivity analyses.

Sensitivity analysis

Sensitivity analyses (using the random-effects model in RevMan software) were performed on the primary outcomes if a high degree of heterogeneity was noted (where the I^2 statistic was $\geq$ 50%), excluding studies:

- with a high risk of bias; or
- that used antioxidants plus folic acid versus standard treatment (folic acid < 1 mg); or
- that used antioxidants plus a fertility drug (a co-intervention) versus placebo plus a fertility drug.

Overall quality of the body of evidence: Summary of Findings Table

A Summary of findings table was generated using GRADEPRO software. This table evaluated the overall quality of the body of evidence for main review outcomes, using GRADE criteria (study limitations; i.e. risk of bias, consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality ('high', 'moderate', 'low' or 'very low') were justified, documented and incorporated into reporting of results for the outcomes of live birth, clinical pregnancy and adverse events.
The protocol for this review was provided by Clarke 2009.

RESULTS

Description of studies

Results of the search

The search retrieved 2127 abstracts and titles. These were screened to identify trials that met inclusion criteria. We retrieved the full manuscripts of 67 trials for appraisal. This process is shown in the PRISMA flow chart (Figure 1). Only one study was not published in English (Bonakdaran 2012). The full text was in Persian; however, the English abstract contained enough information to show that it did not meet the inclusion criteria, and the study was therefore excluded. Of the 67 studies assessed, 28 were included and 39 were excluded. Please see Characteristics of included studies and Characteristics of excluded studies for study details. A repeat search in April 2013 revealed seven studies that were placed into the awaiting classification section of the review (Characteristics of studies awaiting classification). A total of 12 ongoing trials were found in searches of the trials registers (see Ongoing studies).

Included studies

A total of 28 trials met the criteria for inclusion. Seven trials were based in Italy (Battaglia 2002; Ciotta 2011; Gerli 2007; Lisi 2012; Papaleo 2009; Rizzo 2010; Unfer 2011). Five were based in Iran (Alborzi 2007; Aleyasin 2009; Firouzabadi 2012; Rashidi 2009; Salehpour 2009), four in Egypt (Aboulfoutouh 2011; Badawy 2006; Rizk 2005; Nasr 2010), four in Turkey (Batioglu 2012;

Cicek 2012; Eryilmaz 2011; Ozkaya 2011), two in Korea (Kim 2006; Kim 2010), two in Spain (Creus 2008; Balasch 1997) and one each in the UK (Agrawal 2012), Hungary/Austria (Griesinger 2002), Mexico (Mier-Cabrera 2008) and the USA (Westphal 2006).

Three of these trials did not provide data for meta-analysis (Kim 2006; Kim 2010; Ozkaya 2011), and two did not report on the outcomes included in this review (Salehpour 2009; Firouzabadi 2012). Attempts were made to contact all authors of included trials to obtain further details and clarification. In one trial (Gerli 2007) (see Table 1), only half of the participants declared that they wanted to become pregnant before the study began; therefore, this trial was included, but the data have not been used in the meta-analysis (see Characteristics of included studies).

Duration of treatment ranged from 12 days (Battaglia 2002) to two years (Firouzabadi 2012).

Participants

The trials randomly assigned 3548 subfertile women who were attending a fertility clinic and might or might not be undergoing ART procedures such as IVF, IUI or ICSI. The age range of randomly assigned participants was 18 to 42 years.

Four trials (Nasr 2010; Papaleo 2009; Rizk 2005; Unfer 2011) included women with PCOS. Other participants in the trials were enrolled as the result of endometriosis, ovulation failure, tubal blockages and unexplained subfertility. One trial included women aged 35 to 42 years with poor oocyte quality (Rizzo 2010).

Five trials included women with more than one fertility problem: these reasons included male partner subfertility, unexplained subfertility, ovulatory problems and endometriosis (Agrawal 2012; Aleyasin 2009; Batioglu 2012; Griesinger 2002 and Westphal 2006). One trial (Gerli 2007) included participants in whom "infertility was an ailment in only half of the participants in each group". The author of this trial states that there was "no difference in the proportions of infertile women in the groups".

Four trials included a percentage of women whose subfertility was caused by the male partner (Aleyasin 2009; Creus 2008; Balasch 1997 and Griesinger 2002).

Further details of inclusion and exclusion criteria are found in the Characteristics of included studies table.

Interventions

A variety of antioxidants were used in the included trials. Comparisons consisted of antioxidants versus placebo, no treatment or standard treatment (folic acid < 1 mg), head-to-head comparisons (antioxidant vs antioxidant) and pentoxifylline versus placebo, no treatment or standard treatment.

Comparison antioxidants versus placebo, no treatment and standard treatment included the following: combinations (Octatron^{R}, multiple micronutrients and Fertility Blend- details of these combination antioxidants are given in the Characteristics of included studies), *N*-acetyl-cysteine, melatonin, L-arginine, vitamin E, myo-inositol, vitamin C, vitamin D+calcium and omega-3 polyunsaturated fatty acids.

The comparison 'antioxidants versus antioxidants' included the antioxidants myo-inositol, melatonin and d-chiro-inositol and differing doses of vitamin C. The head-to-head comparisons were included in an attempt to assess whether one antioxidant was more effective than another:

- 9 included trials compared antioxidants versus placebo (Alborzi 2007; Battaglia 2002; Griesinger 2002; Kim 2006; Mier-Cabrera 2008; Nasr 2010; Ozkaya 2011; Salehpour 2009; Westphal 2006);
- 9 trials (Aboulfoutouh 2011; Agrawal 2012; Batioglu 2012; Cicek 2012; Ciotta 2011; Eryilmaz 2011; Gerli 2007; Lisi 2012; Papaleo 2009) compared antioxidants with 'no treatment' or standard treatment;
- 2 trials compared one antioxidant with another antioxidant (head-to-head comparisons) (Rizzo 2010; Unfer 2011);
- 2 trials (Balasch 1997; Creus 2008) compared pentoxifylline with placebo;
- 1 trial (Aleyasin 2009) compared pentoxifylline plus vitamin E with no treatment;
- 4 trials compared antioxidants plus a co-intervention with a placebo plus a co-intervention at the same dosage (Badawy 2006; Firouzabadi 2012; Rashidi 2009; Rizk 2005). The co-interventions used were clomiphene citrate and metformin; and
- In one trial, the control was unspecified (Kim 2010), and unsuccessful attempts were made to contact this author by mail and by email.

Outcomes

Live birth

The primary outcome for this review was live birth. Four trials reported on live birth (Aleyasin 2009; Battaglia 2002; Nasr 2010; Unfer 2011). Emails and letters were sent to all other authors of included trials to ask whether they had any data on live birth. Live birth data from Battaglia 2002 were received by email.

Pregnancy

21 trials reported on 'clinical pregnancy' or 'ongoing pregnancy' rates in the text of the trial reports or through direct communication with the authors (Aboulfoutouh 2011; Agrawal 2012; Aleyasin 2009; Badawy 2006; Balasch 1997; Batioglu 2012; Battaglia 2002; Cicek 2012; Creus 2008; Eryilmaz 2011; Gerli 2007; Griesinger 2002; Kim 2010; Lisi 2012; Nasr 2010; Papaleo 2009; Rashidi 2009; Rizk 2005; Rizzo 2010; Unfer 2011; Westphal 2006). Two trials reported only biochemical pregnancy or conception (Ciotta 2011; Firouzabadi 2012), and another two

trials reported only 'pregnancy rates' (Alborzi 2007; Mier-Cabrera 2008) (see data from these four trials in Table 2). Three trials did not report any pregnancy outcomes (Kim 2006; Ozkaya 2011; Salehpour 2009). Attempts were made to contact all authors of the trials that did not report clinical pregnancy rates.

Adverse events

The following adverse events were reported:

- Miscarriage: 15 trials reported on miscarriage (Aboulfoutouh 2011; Agrawal 2012; Aleyasin 2009; Badawy 2006; Balasch 1997; Battaglia 2002; Cicek 2012; Creus 2008; Eryilmaz 2011; Nasr 2010; Papaleo 2009; Rizzo 2010; Rizk 2005; Unfer 2011; Westphal 2006). The data from Rizk 2005 were not included in the meta-analysis for miscarriage as no pregnancies were reported in the control group, and adding these miscarriage data would have skewed the analysis. Battaglia 2002 also could not be included in the meta-analysis as no events were noted in the treatment or control groups;
- Multiple pregnancy: Five trials reported on multiple pregnancy (Aboulfoutouh 2011; Aleyasin 2009; Badawy 2006; Nasr 2010; Rizk 2005). Rizk 2005 was not included in the meta-analysis for multiple pregnancy as no pregnancies occurred in the control group, and adding these data would have skewed the analysis. Nasr 2010 reported no multiple pregnancies in the antioxidant or placebo groups, so this study was not included in the meta-analysis;
- Gastrointestinal disturbances: Two trials reported on nausea (Cicek 2012; Westphal 2006). No cases of gastrointestinal disturbances were reported in treatment or control groups in the trial by Cicek 2012;
- Ectopic pregnancy: Two trials reported ectopic pregnancies (Agrawal 2012; Aleyasin 2009);
- Ovarian hyperstimulation syndrome (OHSS): three trials reported on OHSS (Kim 2006; Papaleo 2009; Rizk 2005).There were no cases of OHSS in treatment or control groups in the trials by Papaleo 2009 and Rizk 2005. Kim 2006 did not provide data for OHSS; and
- Preterm birth: One trial (Nasr 2010) reported on preterm birth.

Attempts were made to contact all authors of the trials that did not report adverse events. We could not conclude that there were no adverse events in cases where these were not reported.

Design

All 28 included trials were of parallel-group design. One trial (Griesinger 2002) was a four-arm trial in which different dosages of vitamin C versus placebo were used.

The sample size of the included trials ranged from 36 participants (Mier-Cabrera 2008) to 804 participants (Badawy 2006). Only nine trials included in the meta-analysis (Agrawal 2012; Battaglia 2002; Cicek 2012; Ciotta 2011; Eryilmaz 2011; Lisi 2012; Mier-Cabrera 2008; Nasr 2010; Papaleo 2009) reported carrying out a power calculation.

Excluded studies

We retrieved the full text of trials that were identified as potentially eligible for inclusion (see Figure 1). We excluded 39 trials; 23 of these were excluded because the population did not meet criteria for inclusion in this review (Ardabili 2012; Baillargeon 2004; Bonakdaran 2012; Cheang 2008; Ciotta 2012; Costantino 2009; Elgindy 2008; Elgindy 2010; Genazzani 2008; Hernndez-Yero 2012; Iuorno 2002; Kilicdag 2005; Le Donne 2012; Moosavifar 2010; Nestler 1999; Nestler 2001; Nordio 2012; Oner 2011; Santanam 2003; Vargas 2011; Yoon 2010; Kamencic 2008; Thiel 2006). Many of these trials recruited women with PCOS who were not attending a subfertility clinic and whose main concern was not pregnancy but rather ways to control their symptoms of PCOS. Seven were found to be quasi-controlled trials and therefore were not randomised (Aksoy 2010; Al-Omari 2003; Crha 2003; Henmi 2003; Nazzaro 2011; Papaleo 2007; Tamura 2008). Four had inappropriate controls for inclusion (Elnashar 2007; Hashim 2010; Papaleo 2008; Raffone 2010). Two had an inappropriate treatment for inclusion (Farzadi 2006; Twigt 2011). Two were conference abstracts of another published trial (Elnashar 2005; Rezk 2004). We excluded Nichols 2010 after the lead investigator confirmed that this trial had been abandoned before recruitment because of lack of funding.

Ongoing trials

Twelve trials are ongoing (Agrawal 2012a; Bentov 2010; Lindqvist 2009; Mahdian 2012; Mane 2012; Ortega 2013; Unfer 2011a; Mohammadbeigi 2011; Pasha 2011; Pourghassem 2010; Unfer 2010; Youssef 2011). We may be able to include data from these trials in future updates of this review. One ongoing trial (Youssef 2011) was in press, and any published article will supersede the included conference abstract (Aboulfoutouh 2011).

Trials awaiting classification

Seven trials are awaiting classification (see Characteristics of studies awaiting classification).

Risk of bias in included studies

See Figure 2 for a summary of risk of bias in individual trials and Figure 3 for a summary of each risk of bias item across all included trials.

Figure 2. Methodological risk of bias summary: review authors' judgements about each methodological bias item for each included study.

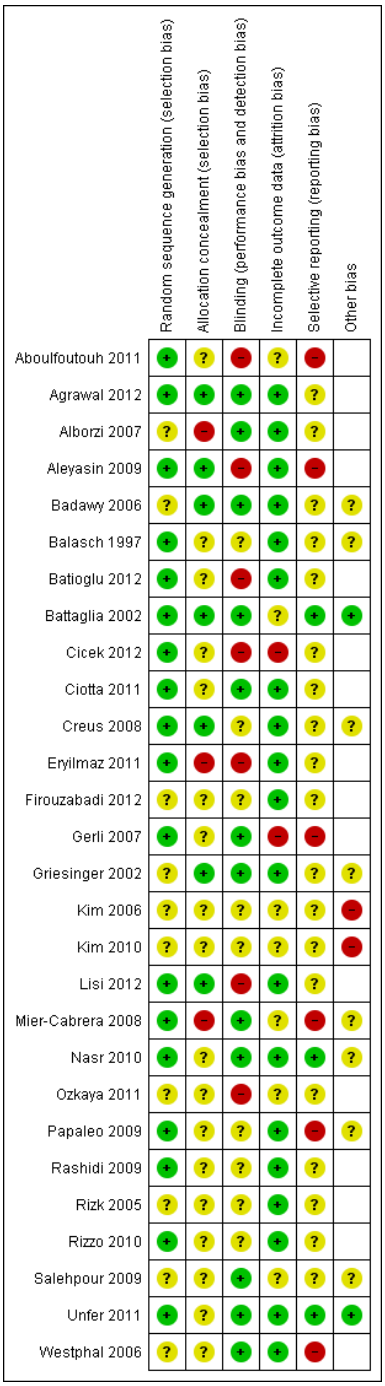
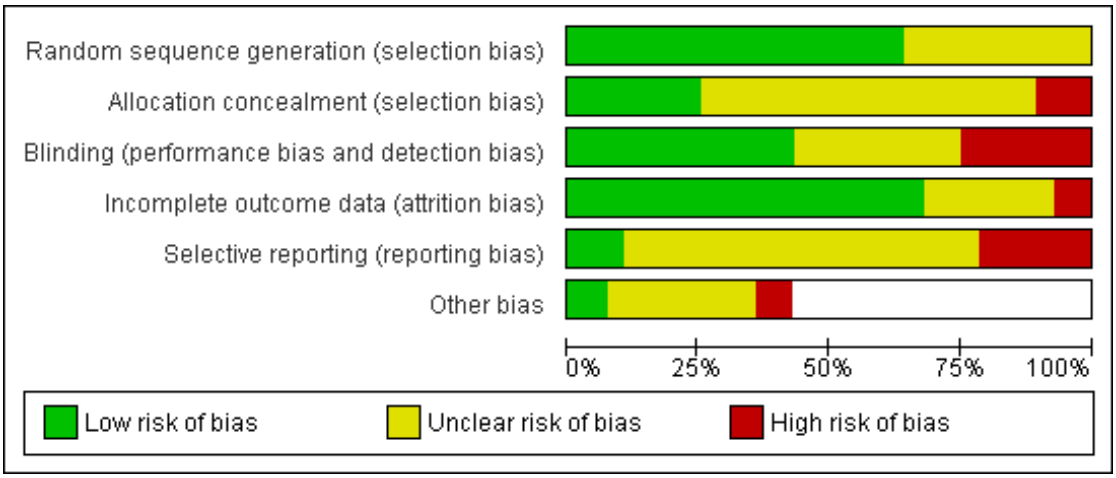


Figure 3. Methodological risk of bias graph: review authors' judgements about each methodological bias item presented as percentages across all included trials.



Sequence Generation

All of the 28 included trials were randomised with a parallel design. 19 trials describe their methods of sequence generation, which typically were computer generated or used a random number table (Aboulfoutouh 2011; Agrawal 2012; Aleyasin 2009; Balasch 1997; Batioglu 2012; Battaglia 2002; Cicek 2012; Ciotta 2011; Creus 2008; Eryilmaz 2011; Firouzabadi 2012; Gerli 2007; Lisi 2012; Nasr 2010; Ozkaya 2011; Papaleo 2009; Rashidi 2009; Rizzo 2010; Unfer 2011). Eight trials (Badawy 2006; Griesinger 2002; Kim 2006; Kim 2010; Mier-Cabrera 2008; Rizk 2005; Salehpour 2009; Westphal 2006) simply reported the trial as randomised with no description of method. One trial (Alborzi 2007) reported the method, but it remained unclear whether randomisation was performed by coin flip or with the use of odd and even numbers. Sensitivity analysis was performed on exclusion of trials that lacked a clear explanation of randomisation.

Allocation

Six trials (Aleyasin 2009; Badawy 2006; Battaglia 2002; Creus 2008; Griesinger 2002; Lisi 2012) described their allocation concealment as using 'sequentially numbered closed opaque envelopes'. Seven trials described the envelopes as sealed but did not mention sequential numbering (Aboulfoutouh 2011; Agrawal 2012; Balasch 1997; Ciotta 2011; Nasr 2010; Rizk 2005; Unfer 2011). Attempts were made to contact these authors regarding the numbering. One trial (Eryilmaz 2011) replied through email correspondence that no allocation concealment was used. The remainder did not describe any methods of allocation concealment, and unsuccessful attempts were made to contact these authors regarding allocation concealment techniques.

Blinding

We did not consider that blinding was likely to influence findings for the outcomes of live birth or pregnancy; however, for adverse effects, blinding status could have affected the findings. In all, 17 trials from the 28 included trials described some form of blinding of participants and/or investigators. Four were triple-blinded, with participants, clinicians/investigators and outcome assessors blinded (Agrawal 2012; Badawy 2006; Battaglia 2002; Mier-Cabrera 2008). Seven were double-blinded with blinding of participants and clinicians (Alborzi 2007; Ciotta 2011; Griesinger 2002; Nasr 2010; Rizk 2005; Salehpour 2009; Westphal 2006). Four stated that they were double-blinded but did not declare who was blinded (Creus 2008; Gerli 2007; Griesinger 2002; Unfer 2011). Three were single-blinded: the participants were blinded in Balasch 1997, the embryologist was blinded in Papaleo 2009 and the outcome assessors were blinded in Lisi 2012.

Five trials (Aboulfoutouh 2011; Aleyasin 2009; Batioglu 2012; Cicek 2012; Eryilmaz 2011) used no treatment as the control; therefore, there was no blinding in these trials. The six remaining trials did not report any blinding (Firouzabadi 2012; Kim 2006; Kim 2010; Ozkaya 2011; Rashidi 2009; Rizzo 2010).

Incomplete outcome data

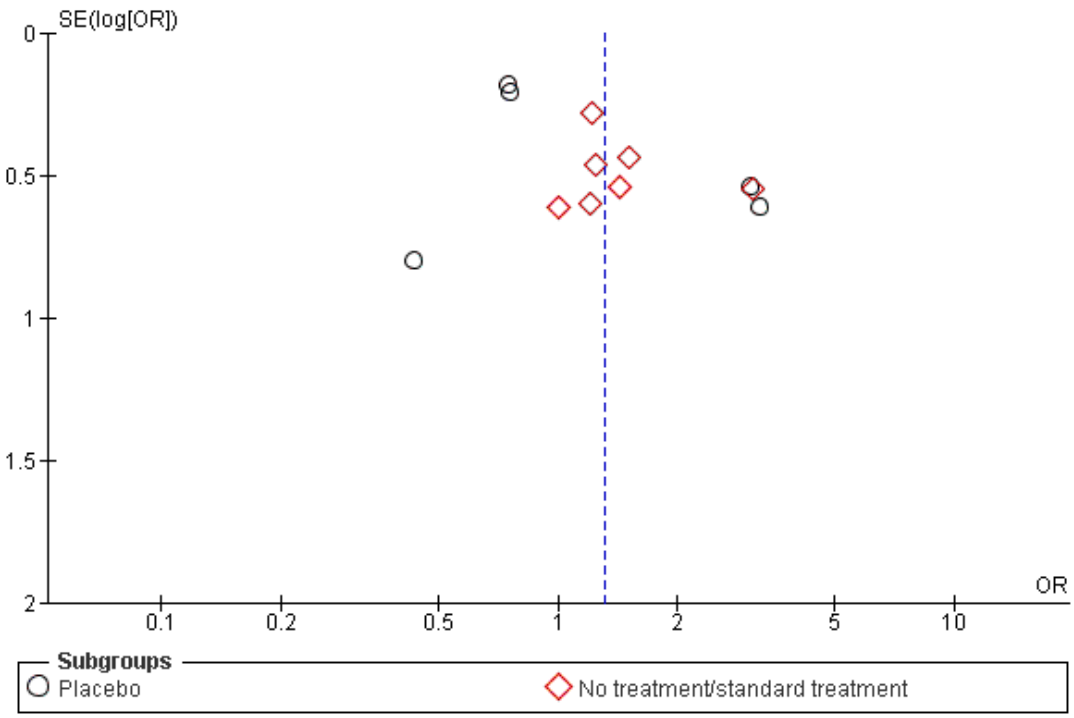
Thirteen trials (Alborzi 2007; Aleyasin 2009; Badawy 2006; Batioglu 2012; Ciotta 2011; Firouzabadi 2012; Lisi 2012; Nasr 2010; Papaleo 2009; Rashidi 2009; Rizk 2005; Rizzo 2010; Westphal 2006) had no losses to follow-up. Three trials reported losses but used intention-to-treat (ITT) analysis (Aboulfoutouh 2011; Agrawal 2012; Unfer 2011). Four trials (Balasch 1997; Battaglia 2002; Creus 2008; Mier-Cabrera 2008) had losses and described from which groups they were lost but did not use ITT in the reporting of trials; however, ITT was used in the meta-analysis. Salehpour 2009 also had explained losses, but because outcomes reported in the trial were different from outcomes in this review, this study was not included in the meta-analysis. Four trials had loss to follow-up with no explanation as to which groups these women were lost from. Data were taken from Cicek 2012; Eryilmaz 2011 and Griesinger 2002, as totals were given after dropouts, and the assumption was made that the groups were equal on allocation. The remaining four trials were not included in the meta-analysis: Gerli 2007 had greater than 30% dropout from the treatment group, and data were unavailable from Kim 2006; Kim 2010 and Ozkaya 2011. Attempts were made to contact authors when the data were unavailable.

Selective reporting

Trial protocols were unavailable for all 28 included trials; therefore, it cannot be claimed that on the basis of published reports alone, the authors included all expected outcomes. Failure to report live birth in subfertility trials is common, is a major source of bias (Clarke 2010) and should be the default primary outcome in fertility trials. Only four trials reported live birth (Aleyasin 2009; Battaglia 2002; Nasr 2010; Unfer 2011). Mier-Cabrera 2008 and Papaleo 2009 stated that they would report live birth, but then they reported only pregnancy. Adverse events were not well reported.

A funnel plot for clinical pregnancy (Figure 4) was nearly symmetrical, indicating that there may not be a small study effect. Estimates of the intervention effect tend to be more beneficial in smaller studies and thus introduce the potential for selective reporting and publication bias; however, this does not seem to be the case in this review.

Figure 4. Funnel plot of comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment, outcome: 1.5 Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).



Other potential sources of bias

Funding sources were reported by only six of the 28 included trials. One trial was self-funded (Agrawal 2012), and the remaining five gained funding from their institutions (Aleyasin 2009; Creus 2008; Mier-Cabrera 2008; Salehpour 2009; Westphal 2006). See details in Characteristics of included studies.

Studies included within the review but not in the analysis

Gerli 2007 (see Table 1) was not incorporated into the analysis, as only half the women randomly assigned reported a desire to become pregnant. 92 women were randomly assigned, 45 to the treatment group and 47 to the control group. 23 from the treatment group and 19 from the control wished to conceive; four from the treatment group and one from the control group became pregnant. This trial also had greater than 30% dropouts from the treatment group.

Rashidi 2009 reported on clinical pregnancy; however, there were no events in either the antioxidant or no treatment arms of the trial.

Effects of interventions

See: **Summary of findings for the main comparison** Antioxidant(s) versus placebo or no treatment/standard treatment for female subfertility

1. Antioxidant supplement versus placebo, no treatment/standard treatment

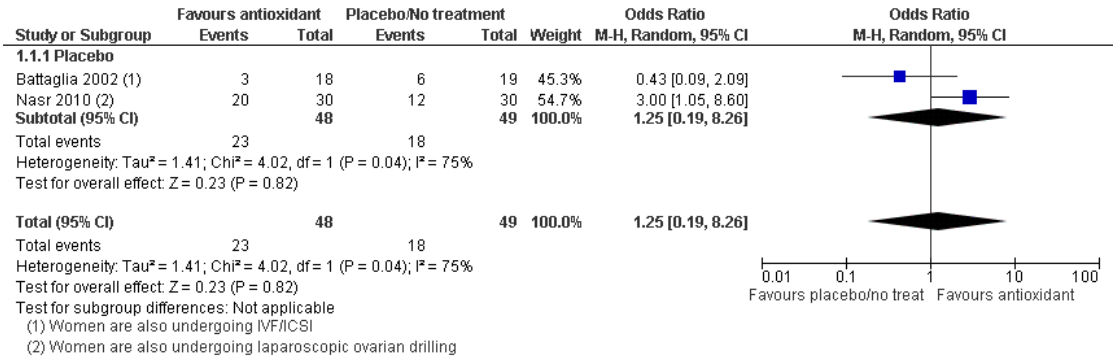
Primary outcome: Live birth

1.1 Live birth; antioxidants versus placebo or no treatment/standard treatment

See Analysis 1.1.

Antioxidants were not associated with an increased live birth rate compared with placebo or no treatment (OR 1.60, 95% CI 0.70 to 3.69, P = 0.27, 2 RCTs, 97 women, I^2 = 75%, very low-quality evidence). As the I^2 statistic was greater than 50%, we repeated the analysis using a random-effects model, and here again, antioxidants were not associated with an increased live birth rate compared with placebo or no 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) (Figure 5). This suggests that among subfertile women with an expected live birth rate of 37%, the rate among women using antioxidants would be between 10% and 83% (Summary of findings for the main comparison). Heterogeneity remained high, with an I^2 statistic of 75%.

Figure 5. Forest plot of comparison: 1 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).



In the two trials that reported live birth (Battaglia 2002; Nasr 2010), the OR for live birth was 1.25 and for clinical pregnancy was 1.26. However, when we pooled all 16 studies that reported clinical pregnancy, the OR for clinical pregnancy was higher, at 1.30. This suggests that the clinical pregnancy rate in the two trials that reported live birth was not an overestimation of the effect of the antioxidants, and hence that the live birth rate in these trials is probably not an overestimate.

1.1.1 Live birth; antioxidants versus placebo

No evidence of a statistically significant difference in live birth was noted between antioxidant and placebo groups (OR 1.25, 95% CI 0.19 to 8.26, P = 0.82, 2 RCTs, 97 women, I^2 = 75%). The high heterogeneity was possibly due to the differing populations. Battaglia 2002 enrolled women with tubal infertility undergoing IVF, and Nasr 2010 enrolled women with PCOS undergoing laparoscopic ovarian drilling. We could not perform a sensitivity analysis as only two trials were included in the placebo analysis.

1.2 Live birth; type of antioxidant

See Analysis 1.2.

Subtotals only were used for this analysis. Each comparison included only one trial.

1.2.1 Nasr 2010; *N*-acetyl-cysteine versus placebo (OR 2.87, 95% CI 1.05 to 7.84, P = 0.04).

1.2.2 Battaglia 2002; compared L-arginine with placebo (OR 0.45, 95% CI 0.10 to 2.00, P = 0.30).

1.3 Live birth rate; indications for subfertility

See Analysis 1.3.

Battaglia 2002 enrolled women with tubal subfertility undergoing IVF (OR 0.45, 95% CI 0.10 to 2.00, P = 0.30, 37 women), and Nasr 2010 enrolled women with PCOS (OR 2.87, 95% CI 1.05 to 7.84, P = 0.04, 60 women).

1.4 Live birth; IVF/ICSI

See Analysis 1.4.

Only one trial (Battaglia 2002) compared antioxidants with placebo or no treatment in women having IVF/ICSI treatment and reported live birth (OR 0.45, 95% CI 0.10 to 2.00, P = 0.30, 1 RCT, 37 women) (Battaglia 2002).

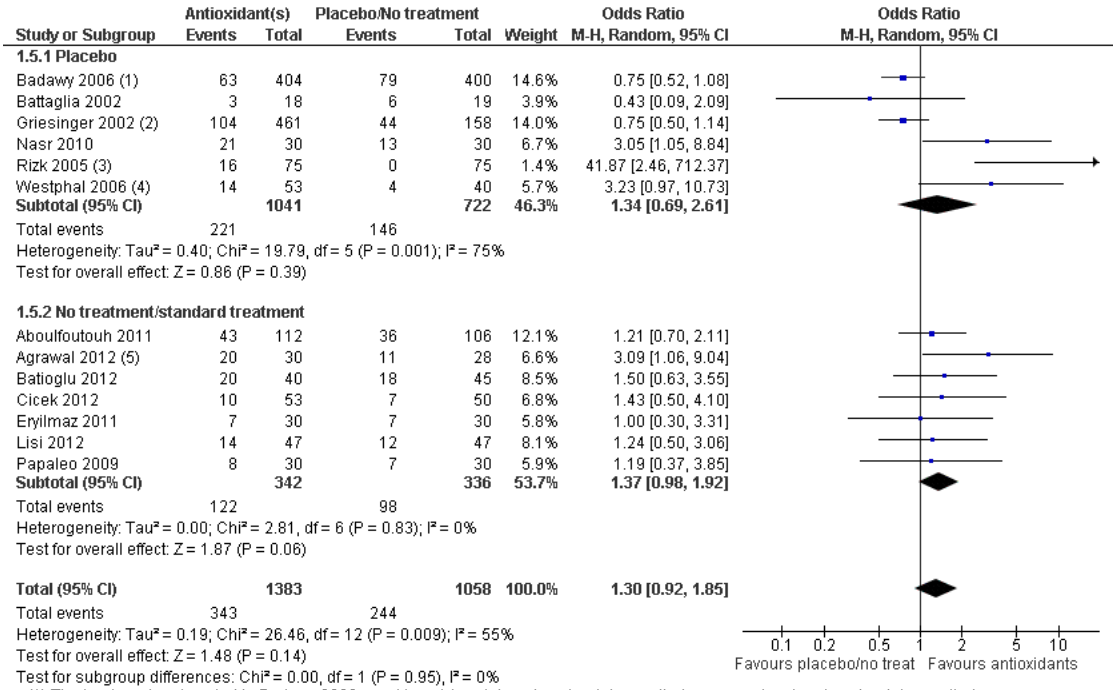
Secondary outcome: Clinical pregnancy

1.5 Clinical pregnancy; antioxidants versus placebo or no treatment/standard treatment.

See Analysis 1.5.

Antioxidants were not associated with an increased clinical pregnancy rate compared with placebo or no treatment (OR 1.12, 95% CI 0.92 to 1.36, P = 0.27, 13 RCTs, 2441 women, I^2= 67%, very low-quality evidence). As the I^2 statistic was greater than 50%, we repeated the analysis using a random-effects model, and here again, antioxidants were not associated with an increased clinical pregnancy rate when compared with placebo or no 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) (Figure 6). This suggests that among subfertile women with an expected clinical pregnancy rate of 23%, the rate among women using antioxidants would be between 22% and 36% (Summary of findings for the main comparison). However, the 1^2 statistic in the random-effects model of 55% remained high.

Figure 6. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment, outcome: 1.5 Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).



Westphal 2006 was the only included trial reporting on clinical pregnancy where the women conceived naturally without ovulation induction, IVF/ICSI or laparoscopic ovarian drilling.

Sensitivity analysis for trials with a high risk of bias

Two trials (Rizk 2005; Westphal 2006) did not describe details of sequence generation or allocation concealment in their reports and were removed in a sensitivity analysis. This result indicated that antioxidants were not associated with an increased clinical pregnancy rate compared with placebo or no treatment/standard treatment when high risk studies were removed (OR 1.11, 95% CI 0.83 to 1.50, P = 0.47, 11 RCTs, 2198 women, I^2 = 37%).

Sensitivity analysis for trials using placebo plus co-intervention as a control

Two trials (Badawy 2006; Rizk 2005) used placebo plus a co-intervention as a control and were removed in a sensitivity analysis (OR 1.32, 95% CI 0.94 to 1.85, P = 0.11, 11 RCTs, 1487 women, I^2 = 35%). On removal of these trials from the analysis, the heterogeneity decreased but there remained no association with antioxidants and clinical pregnancy rates in this comparison.

Sensitivity analysis for trials using folic acid (standard treatment) as a control

On removing the three trials (Agrawal 2012; Lisi 2012; Papaleo 2009) that reported using folic acid (standard treatment) as a control, we found no evidence of an association between antioxidants and the clinical pregnancy rate (OR 1.24, 95% CI 0.83 to 1.85, P = 0.30, 10 RCTs, 2229 women, I^2 = 59%).

1.5.1 Clinical pregnancy; antioxidants versus placebo

No evidence was found of a statistically significant difference in clinical pregnancy rates between the antioxidant and placebo

groups (OR 1.34, 95% CI 0.69 to 2.61, P = 0.39, 6 RCTs, 1763 women, I^2 = 75%).

1.5.2 Clinical pregnancy; antioxidants versus no treatment or standard treatment

Antioxidants were not associated with an increased clinical pregnancy rate compared with no treatment or standard treatment (OR 1.37, 95% CI 0.98 to 1.92, P = 0.06, 7 RCTs, 678 women, I^2 = 0%). Six of the seven trials in this analysis enrolled fewer than 50 women.

1.6 Clinical pregnancy; type of antioxidant

See Analysis 1.6.

Only subtotals were used in the stratification by antioxidant type (Figure 7).

N-acetyl-cysteine was not associated with an increased clinical pregnancy rate when compared with placebo, no treatment or standard treatment (OR 1.10, 95% CI 0.80 to 1.53, P = 0.55, 3 RCTs, 1014 women, I^2 = 92%). Heterogeneity was extremely high, perhaps as a result of the high risk of bias in Badawy 2006 and Rizk 2005 or the additional treatment of laparoscopic drilling that women received in Nasr 2010.

Combined antioxidants (similar antioxidants were combined in each trial) were associated with an increased clinical pregnancy rate (OR 1.66, 95% CI 1.07 to 2.58, P = 0.02, 3 RCTs, 369 women, I^2 = 43%). However, heterogeneity was moderately high, and the trials enrolled small numbers of women.

No association of increased clinical pregnancy rates was seen in those women receiving melatonin (OR 1.30, 95% CI 0.65 to 2.60, P = 0.45, 2 RCTs, 145 women, I^2 = 0%).

Myo-inositol plus folic acid was not associated with an increased clinical pregnancy rate (OR 1.22, 95% CI 0.60 to 2.48, P = 0.59, 2 RCTs, 154 women, I^2 = 0%).

Only one trial was included in each of the other subgroups; therefore results could not be pooled. Vitamin E (OR 1.42, 95% CI 0.50 to 4.00, P = 0.51, 103 women); ascorbic acid (OR 0.75, 95% CI 0.49 to 1.14, P = 0.18, 619 women); and L-arginine (OR 0.45, 95% CI 0.10 to 2.00, P = 0.30, 37 women).

1.7 Clinical pregnancy rate; indications for subfertility

See Analysis 1.7.

1.7.1 Clinical pregnancy rate; polycystic ovary syndrome

Antioxidants were associated with an increased pregnancy rate in women with PCOS (OR 3.40, 95% CI 1.84 to 6.29, P < 0.0001, 3 RCTs, 270 women, I^2 = 71%) (Analysis 1.7). However, heterogeneity was very high, and this was assumed to be due to the very wide confidence intervals in Rizk 2005. This trial had 16 events in the treatment group and nil in the control group, which is unusual. The trials in this analysis all had small numbers of women randomly assigned.

1.7.2 Clinical pregnancy rate; unexplained subfertility

Antioxidants were not associated with an increase in clinical pregnancy rate in women with unexplained subfertility (OR 0.82, 95% CI 0.59 to 1.14, P = 0.23, 3 RCTs, 967 women, I^2 = 0%) (Analysis 1.7).

1.7.3 Clinical pregnancy rate; tubal subfertility

Only one trial (Battaglia 2002) enrolled women with tubal subfertility (OR 0.45, 95% CI 0.10 to 2.00, P = 0.30).

1.7.4 Clinical pregnancy rate; varying indications

Five trials (Aboulfoutouh 2011; Agrawal 2012; Batioglu 2012; Griesinger 2002; Westphal 2006) enrolled women who presented with different indications within the trials. Antioxidants were not associated with an increase in clinical pregnancy rate in women enrolled in trials with varying indications of subfertility (OR 1.14, 95% CI 0.85 to 1.52, P = 0.38, 5 RCTs, 1073 women, I^2 = 62%) (Analysis 1.7).

1.8 Clinical pregnancy rate; IVF/ICSI

See Analysis 1.8.

No evidence was found of an effect of antioxidants versus placebo or no treatment in the subgroup of women undergoing IVF/ICSI (OR 0.97, 95% CI 0.74 to 1.27, P = 0.83, 7 RCTs, 1173 women, I^2 = 0%) (Analysis 1.8).

Secondary outcome: Adverse events

1.9 Adverse events

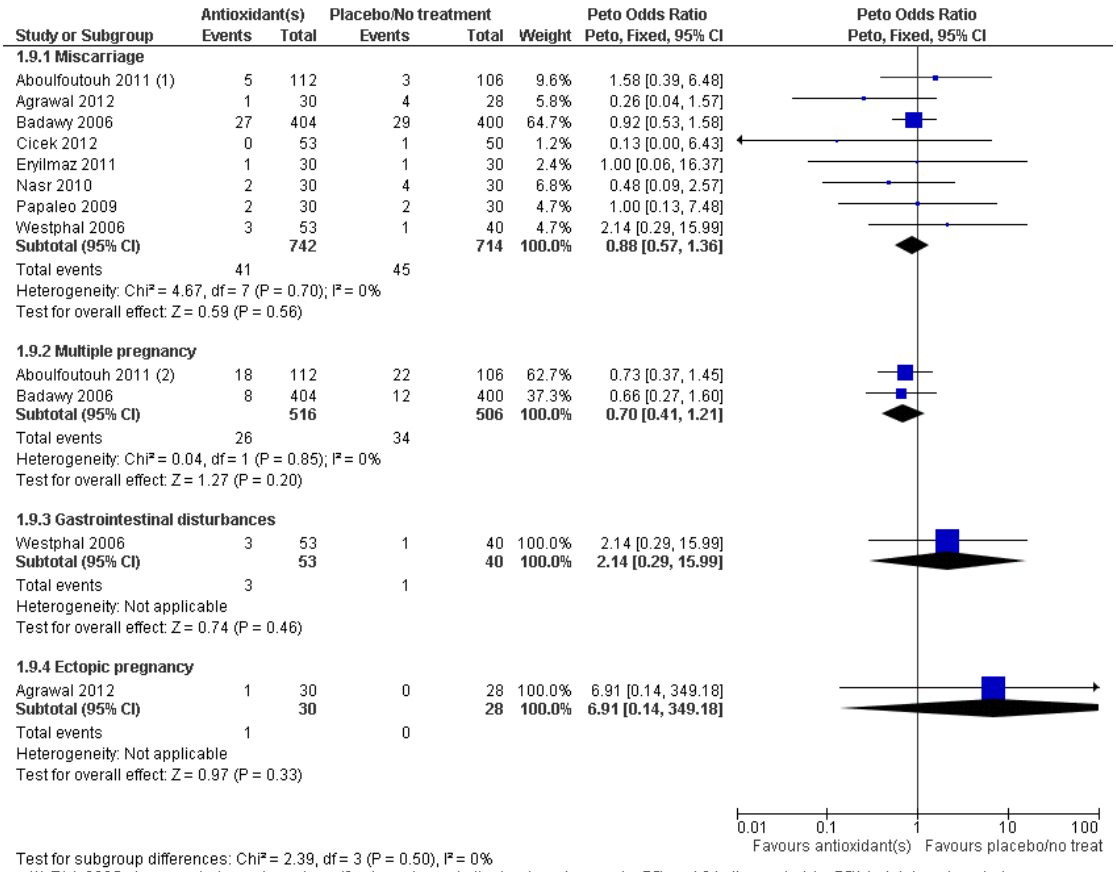
See Analysis 1.9.

Adverse event data were subgrouped according to the types of events that occurred, as reported by the trial. These included miscarriage, multiple pregnancy, gastrointestinal disturbances and ectopic pregnancy. No evidence suggested an association between antioxidants and adverse events, but data were limited, with 8 trials reporting on miscarriage, two trials reporting on multiple pregnancy, and one reporting on gastrointestinal upsets and ectopic pregnancy. Only subtotals were used in the analysis.

1.9.1 Miscarriage

Antioxidants were not associated with miscarriage (OR 0.88, 95% CI 0.57 to 1.36, P = 0.56, 8 RCTs, 1456 women, I^2 = 0%, low-quality evidence) (Figure 7). This means that given the rate of 5% miscarriages in the control population, the use of antioxidants would be expected to result in a miscarriage rate of between 4% and 8% (Summary of findings for the main comparison). Most of the trials in this analysis were small, ranging from 60 women to 218 women randomly assigned; however, one trial (Badawy 2006) did enrol 804 women.

Figure 7. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.9 Adverse event.



Battaglia 2002 also reported on miscarriage but described no events in the treatment or control groups; therefore, this study could not be added to the meta-analysis.

1.9.2 Multiple pregnancy

No association was noted between antioxidants and multiple pregnancy (OR 0.70, 95% CI 0.41 to 1.21, P = 0.20, 2 RCTs, 1022

women, I^2 = 0%, low-quality evidence) (Figure 7). This means that of 7% multiple pregnancies in the control population (with a range from 5% to 14%), use of antioxidants instead would be expected to result in a multiple pregnancy rate between 3% and 8% (Summary of findings for the main comparison). Nasr 2010 also reported on multiple pregnancy events, but no events were reported in the treatment or control groups; therefore this study could not be added to the meta-analysis.

1.9.3 Gastrointestinal disturbances

Two trials (Cicek 2012; Westphal 2006) reported on gastrointestinal disturbances, but no events were reported in treatment or control groups in Cicek 2012; therefore, meta-analysis was not possible for this adverse event; Westphal 2006 (OR 2.14, 95% CI 0.29 to 15.99, P = 0.46).

1.9.4 Ectopic pregnancy

One trial (Agrawal 2012) reported on ectopic pregnancy (OR 6.91, 95% CI 0.14 to 349.18, P = 0.33, 58 women).

2. Head-to-head antioxidants

Primary outcome: Live birth

Only one trial reported on live birth (Unfer 2011).

2.1 Live birth; type of antioxidant

See Analysis 2.1.

2.1.1 Myo-inositol versus d-chiro-inositol

Unfer 2011 reported on live birth (OR 3.44, 95% CI 1.27 to 9.34, P = 0.02), measuring the effects of myo-inositol versus d-chiro-inositol.

2.2 Live birth; indications for subfertility

See Analysis 2.2.

2.2.1 Polycystic ovary syndrome

Unfer 2011 enrolled women with PCOS.

2.3 Live birth; IVF/ICSI

See Analysis 2.3.

The women who were enrolled in Unfer 2011 were also undergoing ICSI.

Secondary outcome: Clinical pregnancy

Two trials (Unfer 2011; Rizzo 2010) reported on clinical pregnancy in the antioxidant versus antioxidant comparison. Only subtotals were used in this analysis, and meta-analysis was not possible as each trial used a different antioxidant.

2.4 Clinical pregnancy; type of antioxidant

See Analysis 2.4.

2.4.1 Myo-inositol versus d-chiro-inositol

One trial (Unfer 2011) reported on clinical pregnancy, measuring the effects of myo-inositol versus d-chiro-inositol (OR 3.44, 95% CI 1.27 to 9.34, P = 0.02).

2.4.2 Myo-inositol plus folic acid plus melatonin versus myo-inositol plus folic acid

Rizzo 2010 reported on the effects of myo-inositol plus folic acid plus melatonin versus myo-inositol plus folic acid (OR 1.85, 95% CI 0.65 to 5.25, P = 0.25).

2.5 Clinical pregnancy; indications for subfertility

See Analysis 2.5

Two trials reported on the indications for subfertility; these included PCOS and poor responders; however, only one trial was included in each subgroup.

2.5.1 Polycystic ovary syndrome

Unfer 2011 enrolled women with polycystic ovary syndrome (OR 3.44, 95% CI 1.27 to 9.34, P = 0.02).

2.5.2 Poor responders

Rizzo 2010 was the only trial to report on clinical pregnancy rate in women who were poor responders (OR 1.85, 95% CI 0.65 to 5.25, P = 0.25).

2.6 Clinical pregnancy; IVF/ICSI

See Analysis 2.6.

Antioxidant 'a' was associated with an increased clinical pregnancy rate in women also having IVF/ICSI compared with antioxidant 'b' (OR 2.56, 95% CI 1.24 to 5.26, P = 0.01, 2 RCTs, 149 women, I^2 = 0%) (Analysis 2.6). However, these two trials were very small, and antioxidant 'a' was very different from antioxidant 'b'. Unfer 2011 compared myo-inositol (antioxidant 'a') with d-chiro-inositol (antioxidant 'b') in women with PCOS. Rizzo 2010 enrolled women who were poor responders and compared myo-inositol plus folic acid plus melatonin (antioxidant 'a') with myo-inositol plus folic acid (antioxidant 'b'), so no conclusions regarding the use of antioxidants for women undergoing IVF/ICSI can be drawn on the basis of this analysis.

Secondary outcome: Adverse events

See Analysis 2.7.

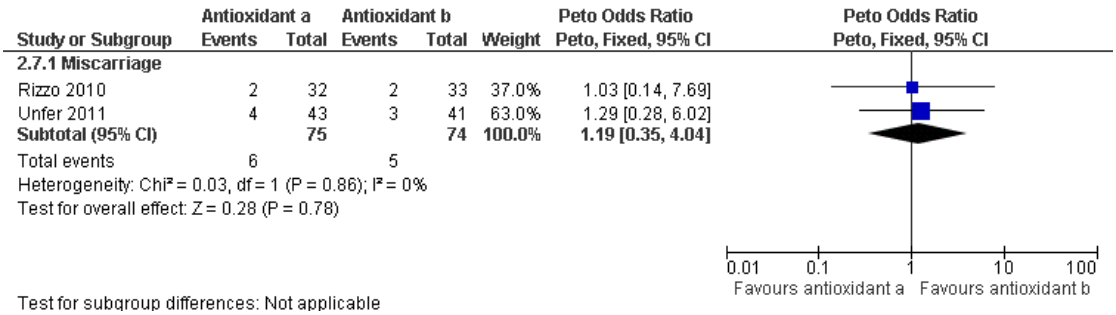
Adverse event data were subgrouped according to the type of event that occurred, and only subtotals were used in the analysis.

2.7 Adverse events

2.7.1 Miscarriage

Antioxidant 'a' was not associated with miscarriage when compared with antioxidant 'b' (OR 1.19, 95% CI 0.35 to 4.04, P = 0.78, 2 RCTs, 149 women, I^2 = 0%) (Figure 8). Antioxidant 'a' was myo-inositol in Unfer 2011 and melatonin plus myo-inositol plus folic acid in Rizzo 2010.

Figure 8. Forest plot of comparison: 2 Head to head antioxidants, outcome: 2.7 Adverse events.



No evidence suggested a difference between the interventions used for miscarriage, but data were limited.

3. Pentoxifylline supplement versus placebo, no treatment/standard treatment

Primary outcome: Live birth

3.1 Live birth; pentoxifylline versus placebo or no treatment/standard treatment

See Analysis 3.1

3.1.1 Live birth; pentoxifylline versus no treatment

Only one trial (Aleyasin 2009) performed this comparison in the pentoxifylline versus no treatment subgroup (OR 1.53, 95% CI 0.68 to 3.44, P = 0.30, 112 women).

3.2 Live birth; type of antioxidant

See Analysis 3.2

3.2.1 Pentoxifylline plus vitamin E versus no treatment.

The type of antioxidant used in Aleyasin 2009 was pentoxifylline plus vitamin E versus no treatment.

3.3 Live birth; indications for subfertility

See Analysis 3.3

3.3.1 Varying indications

The trial Aleyasin 2009 enrolled women with varying causes of subfertility, and the cause of subfertility in 45% of these women was the male partner.

3.4 Live Birth: IVF/ICSI

See Analysis 3.4

The women enrolled in Aleyasin 2009 were also undergoing IVF/ICSI.

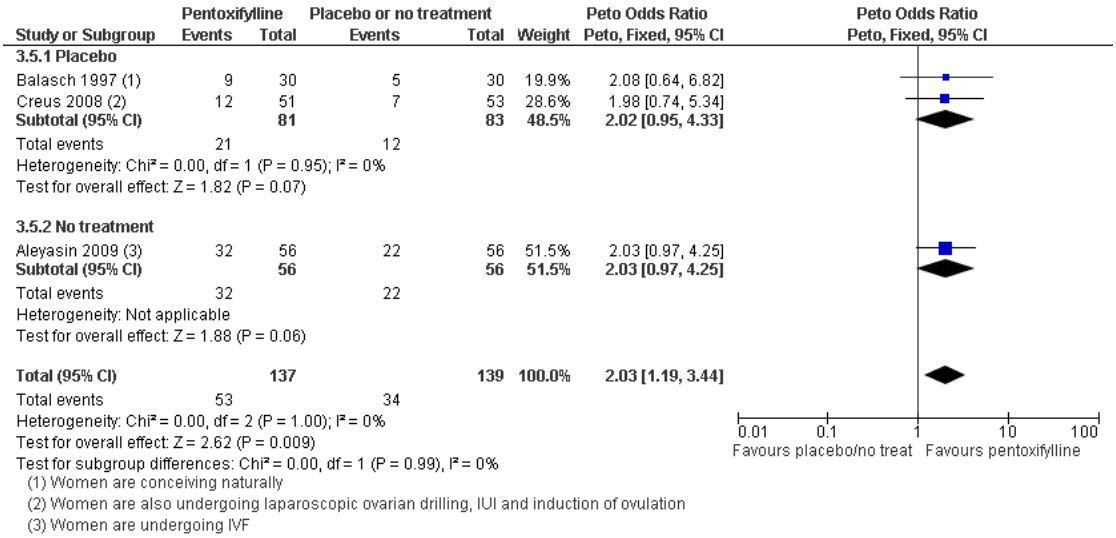
Secondary outcome: Clinical pregnancy

3.5 Clinical pregnancy; pentoxifylline vs placebo or no treatment/standard treatment

See Analysis 3.5

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%) (Figure 9).

Figure 9. Forest plot of comparison: 3 Pentoxifylline versus placebo or no treatment/standard care, outcome: 3.5 Clinical pregnancy; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).



Sensitivity analysis for trials with a high risk of bias

When Balasch 1997 was removed from the analysis (as it did not describe methods of allocation concealment) there remained an association with pentoxifylline and clinical pregnancy rate (OR 2.01, 95% CI 1.11 to 3.64, P = 0.02, 2 RCTs, 216 women, I^2 = 0%).

3.5.1 Clinical pregnancy; pentoxifylline versus placebo

No evidence was found of a statistically significant difference in effect of pentoxifylline versus placebo on clinical pregnancy rate (OR 2.02, 95% CI 0.95 to 4.33, P = 0.07, 2 RCTs, 164 women, I^2 = 0%).

3.5.2 Clinical pregnancy rate; pentoxifylline versus no treatment

Aleyasin 2009 was the only trial in this subgroup (OR 2.03, 95% CI 0.97 to 4.25, P = 0.06, 112 women).

3.6 Clinical pregnancy; type of antioxidant

See Analysis 3.6

3.6.1 Pentoxifylline

Two trials reported on pentoxifylline alone and there was no association with pentoxifylline and clinical pregnancy rate (OR 2.02, 95% CI 0.95 to 4.33, P = 0.07, 2 RCTs, 164 women, I^2 = 0%).

3.6.2 Pentoxifylline plus vitamin E

Only one trial reported on pentoxifylline plus vitamin E and there was no association clinical pregnancy rate (OR 2.03, 95% CI 0.97 to 4.25, P = 0.06, 112 women).

3.7 Clinical pregnancy; indications for subfertility

See Analysis 3.7

3.7.1 Clinical pregnancy rate; endometriosis

Pentoxifylline did not show an association with an increased clinical pregnancy rate (OR 2.02, 95% CI 0.95 to 4.33, P = 0.07, 2 RCTs, 164 women, I^2 = 0%) in women with endometriosis (Analysis 3.7).

3.7.2 Clinical pregnancy rate; varying indications

Only one trial enrolled women who presented with different indications within the trial (OR 2.03, 95% CI 0.97 to 4.25, P = 0.06,

112 women).

3.8 Clinical pregnancy rate; IVF/ICSI

See Analysis 3.8

Only one trial enrolled women who were undergoing IVF/ICSI (OR 2.03, 95% CI 0.97 to 4.25, P = 0.06) .

Secondary outcome: Adverse events

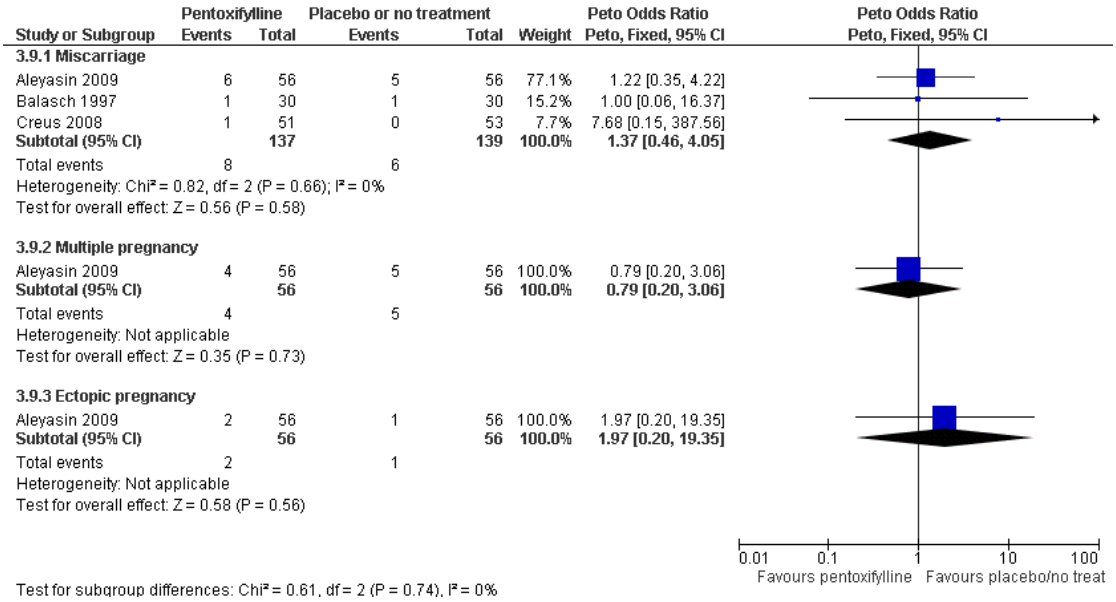
See Analysis 3.9

Adverse event data were subgrouped according to the types of events that occurred, as reported by the trial. These included miscarriage, multiple pregnancy and ectopic pregnancy. No evidence suggested an association with antioxidants and adverse events, but data were limited, with 3 trials reporting on miscarriage, one trial reporting on multiple pregnancy, and one reporting on ectopic pregnancy. Only subtotals were used in the analysis.

3.9.1 Miscarriage

No evidence suggested an association with antioxidants and miscarriage, but data were limited with only 3 trials reporting on this outcome (OR 1.37, 95% CI 0.46 to 4.05, P = 0.58, 3 RCTs, 276 women, I^2 = 0%) (Figure 10).

Figure 10. Forest plot of comparison: 3 Pentoxifylline versus placebo or no treatment/standard care, outcome: 3.9 Adverse events.



3.9.2 Multiple pregnancy

Only one trial reported on multiple pregnancy (OR 0.79, 95% CI 0.20 to 3.06, P = 0.73).

3.9.3 Ectopic pregnancy

Only one trial reported on ectopic pregnancy (OR 1.97, 95% CI 0.20 to 19.35, P = 0.56).

DISCUSSION

Summary of main results

Effectiveness of antioxidants versus placebo or no treatment

The findings of this review indicate that for subfertile women, the use of supplemental antioxidants is not effective in increasing the rates of live birth. Only two trials with a total of 97 women reported on live birth, and the differences between the trials (heterogeneity) were very high (I^2 = 75% with fixed-effect and 75% with random-effects model). We assumed that this was so because

each trial enrolled women with different indications for subfertility and administered varying types of antioxidants. The quality of the evidence in this analysis was deemed to be 'very low' (Summary of findings for the main comparison). As a result of inconsistency between the trials, subgroup analysis was performed by type of antioxidant, indications for subfertility and women who were undergoing IVF or ICSI. No association of an increased live birth rate was noted between antioxidants and placebo or no treatment in any of these subgroups.

Antioxidants were not associated with an increased clinical pregnancy rate when compared with placebo or no treatment; however, the quality of this evidence was assessed to be 'very low' (Summary of findings for the main comparison). A sensitivity analysis was performed excluding trials with high risk of bias and those using standard treatment as their control; there remained no association of clinical pregnancy rates with antioxidants in the analysis when we removed the trials with a high risk of bias and the trials that used a co-intervention plus a placebo as their control.

In the subgroup 'type of antioxidant', only one group, 'combined antioxidants', showed an association with clinical pregnancy rate; however, only three trials were included in this meta-analysis. No association was seen with *N*-acetyl-cysteine, melatonin, vitamin E, ascorbic acid, L-arginine or myo-inositol. At most, these subgroups contained only three trials.

In the analysis for the subgroup 'indications for subfertility', an association was seen between antioxidants and clinical pregnancy in women with PCOS; however, heterogeneity here was extremely high. No association was seen between antioxidants and clinical pregnancy rates in women with endometriosis, unexplained subfertility or tubal subfertility or in trials that enrolled women with varying indications.

No association was evident between antioxidants and clinical pregnancy rates in women undergoing IVF or ICSI.

There was no evidence to suggest that antioxidants were associated with miscarriage, multiple pregnancy or ectopic pregnancy when compared with placebo or no treatment/standard treatment. Evidence for miscarriage and multiple pregnancy was considered to be of 'low' quality (Summary of findings for the main comparison). Meta-analysis was not possible in the area of adverse effects of gastrointestinal disturbances, as one of the two trials that reported this reported no events in the treatment or control groups.

Effectiveness of antioxidants versus antioxidants- head to head

Only one trial reported on live birth; therefore, pooling was not possible.

Two trials reported on clinical pregnancy rate; however, pooling could not be performed in the subgroups of 'type of antioxidant' or 'indications for subfertility' as only one trial was included in each group. Antioxidant 'a' was associated with an increased clinical pregnancy rate compared with antioxidant 'b' in women undergoing IVF/ICSI. However, these trials were very small, including only 149 women in total. Moreover, antioxidant 'a' and antioxidant 'b' were different in each trial.

No apparent evidence suggested harm when antioxidant 'a' was compared with antioxidant 'b' in the reported adverse event of miscarriage. However, only two trials (149 women) reported this.

Effectiveness of pentoxifylline versus placebo/no treatment

Only one trial reported on live birth; therefore, pooling was not possible. Pentoxifylline was found to be associated with an increased clinical pregnancy rate; however, there were only three trials reporting on this outcome, two reported on pentoxifylline and one reported on pentoxifylline plus vitamin E. No association was found between pentoxifylline and clinical pregnancy rate in women with endometriosis and there was no apparent evidence to suggest that pentoxifylline was associated with miscarriage.

Overall completeness and applicability of evidence

Of the 28 trials included in this review, 21 provided data on clinical pregnancy, but only four trials reported on live birth. Miscarriage, harmful events and costs of the included trials generally were not well reported. A total of 15 reported on miscarriage, five reported on multiple pregnancy and two trials discussed gastrointestinal disturbances and ectopic pregnancy. The trials were generally quite small, and heterogeneity between the trials was moderately high overall.

We tried to assess which type of antioxidant might have a beneficial effect on the outcomes of interest in this review; however, only three trials at most could be pooled in this subgroup. Data on the effectiveness of antioxidants for women with different indications for subfertility were limited, as again only a maximum of three trials could be pooled. Within the subgroup of women undergoing IVF/ICSI, we pooled seven trials in the antioxidant versus placebo or no treatment/standard treatment comparison, and the meta-analysis showed no evidence of effects of antioxidants for this group of women.

The indications for subfertility within the trials were representative of the general subfertile population. However, only seven of the included trials were specific to one indication for subfertility (three for PCOS, three for unexplained subfertility and one for tubal subfertility), and when pooling was possible within these indications, we had to take into account that the women were also receiving different types of antioxidants and differing adjunct interventions such as laparoscopic ovarian drilling, timed intercourse or IVF/ICSI; therefore it was difficult to show any benefit or harm from antioxidants for a particular indication of subfertil-

ity.

Only two trials, each using different antioxidants, were included in the head-to-head analysis. No conclusions could be reached about benefits or harms in this comparison.

In the pentoxifylline versus placebo/no treatment comparison there was evidence of association with clinical pregnancy; however, as this agent is a medicine and has actions above and beyond the reactive oxygen species-scavenging capabilities of antioxidants it is difficult to say that this result is due to the antioxidant action of the drug.

Quality of the evidence

Overall the risk of bias within the evidence (because of methodological limitations) was moderately high (see Figure 2; Figure 3 and Characteristics of included studies). Not all trials described the sequence generation or allocation concealment methods, and most trials randomly assigned only small numbers of women.

The funnel plot for clinical pregnancy (Figure 4) was nearly symmetrical, which suggested that the high number of small studies was not having an overly positive effect on the overall results.

The quality of the evidence according to the summary of findings table (Summary of findings for the main comparison) ranged from 'very low' to 'low', and heterogeneity in the many of the analyses was quite high; three of the main analyses had low heterogeneity with an I^2 of 0%, however; the heterogeneity for the live birth outcome in the antioxidant versus placebo/no treatment comparison was 75% and for clinical pregnancy, for this comparison, the I^2 statistic was 55%.

This high risk of bias in the included trials is also described in other antioxidant reviews (Showell 2011; Lu 2012) and seems to be common in this area of complementary medicine.

Potential biases in the review process

There may have been some potential for bias in the review process, as there were some changes to the protocol. These included additions and deletions to inclusion/exclusion criteria and to the subgroup analyses. Please see Differences between protocol and review. None of these changes were made as a result of the findings of included studies, but rather they were made to improve the structure of the review.

Agreements and disagreements with other studies or reviews

The results of our review were in agreement with those of other published reviews. Sekhon 2010 concluded that, despite numerous advances made in this area, there is a need for further investigation using randomised controlled trials within a larger population to determine efficacy and safety of these supplements. A Cochrane review 'Pentoxifylline versus medical therapies for subfertile women with endometriosis' (Lu 2012) stated that evidence was still insufficient to support the use of pentoxifylline in the management of premenopausal women with endometriosis in terms of subfertility and relief of pain outcomes. Another Cochrane review 'Antioxidants for male subfertility' (Showell 2011) found a small significant effect in favour of antioxidants for pregnancy and live birth and no apparent association with any reported adverse events; however, there were too few similar trials to provide conclusive evidence.

A systematic review (Thomson 2012) looked at vitamin D for PCOS. This review reported, "there is some but limited evidence for the beneficial effects of vitamin D supplementation on menstrual dysfunction" but concluded that "current evidence is limited and additional randomised controlled trials are required."

Another systematic review concentrating on women with PCOS was prepared by Unfer 2012. This review looked specifically at the effects of myo-inositol for PCOS, and the review authors concluded that myo-inositol provided a beneficial effect for PCOS, this was "mainly based on improving insulin sensitivity of target tissues, resulting in a positive effect on the reproductive axis..." The meta-analysis in this review did not reveal an effect of myo-inositol. Only three studies were included for this intervention, and one was a head-to-head trial.

Two Cochrane reviews (Bjelakovic 2008; Bjelakovic 2012;) reported an increased risk of mortality associated with the use of supplemental antioxidants. Bjelakovic 2012 found this association with beta-carotene and possibly vitamin E and vitamin A; however, not with vitamin C or selenium. The review included healthy participants and participants with various stable diseases. The Cochrane review Bjelakovic 2008 reported on the use of antioxidants (beta-carotene, vitamin A, vitamin C and vitamin E) to prevent gastrointestinal cancers and found that there may be an increased risk of mortality for those participants taking these antioxidants. The review authors found that selenium may have preventative effects on gastrointestinal cancers.

AUTHORS' CONCLUSIONS

Implications for practice

In this review, there was no evidence that taking an antioxidant may provide benefit for subfertile women; however, there did not appear to be any evidence of obvious adverse effects. At this time, there is no evidence to recommend supplemental oral antioxidants for subfertile women.

Implications for research

Further appropriately powered and well-designed randomised placebo-controlled trials are needed to assess any evidence for benefits and/or harms of supplemental antioxidants for subfertile women. New trials should state a priori that they are going to

report and follow up on the outcomes of live birth, clinical or ongoing pregnancy and adverse events.

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The Cochrane Menstrual Disorders and Subfertility Group.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aboulfoutouh 2011

Methods	Randomised controlled trial.
Participants	Infertile women attending a fertility clinic undergoing IVF/ICSI (N = 218)
Interventions	Combined antioxidants (Octatron- zinc, selenium, molybdenum, bioflavonoids, biotin and vitamins A, E and C) one capsule twice a day (n = 105) versus no treatment (n = 99).
Outcomes	Clinical pregnancy rate. Number of oocytes retrieved. Number of Mll oocytes. Number of embryos obtained. Total units of follicle-stimulating hormone (FSH) used. Miscarriage. Multiple pregnancy.
Notes	Conference abstract plus further data from author. 14 women lost to follow-up- seven from each arm. Email and letter sent to authors 09.08.12 asking about types of antioxidants used and Intention to treat in the pregnancy outcome. Authors replied with data information. Full paper about to be submitted to Human Reproduction. Participants were followed up to clinical pregnancy; therefore no live birth data are provided No power calculation or funding reported. Trial held in Egypt.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a computer-generated list.
Allocation concealment (selection bias)	Unclear risk	"Closed opaque envelopes".
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding as the control is no treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Seven women lost from each arm after randomisation, and reasons for loss not given
Selective reporting (reporting bias)	High risk	Conference abstract.

Agrawal 2012

Methods	A prospective randomised trial. Third party randomisation by Research and Development Unit at the Royal Free Hospital
Participants	Women attending a teaching hospital fertility clinic undergoing ovulation induction for timed intercourse (N = 58). Age 32.2 years (range 19 to 40) Inclusion criteria: anovulatory infertility, at least 12 months of unexplained infertility, PCOS, hypothyroidism or minimal endometriosis Exclusion criteria: women whose partners had semen abnormalities and those who had been on multivitamins (except folate) 6 weeks before recruitment Women with tubal disease, moderate and severe endometriosis, medical disorders or haemoglobinopathies; smokers, those with excessive alcohol intake or BMI < 19 or > 34 kg/m_2.
Interventions	Multiple micronutrients (MMN): one tablet per day until completion of study (three treatment cycles). Women who became pregnant could continue if they wished. (n = 30) These micronutrients consist of thiamine, riboflavin, niacin B3, vitamins B6 and B12, folate, vitamins C, A and D, calcium, phosphorus, magnesium, sodium, potassium, chloride, iron, zinc, copper, selenium, iodine, vitamin E, vitamin K, L-arginine, inositol, *N*-acetyl-cysteine, biotin, pantothenic acid versus folic acid (n = 28). Women underwent ovulation induction with clomiphene citrate or human menopausal gonadotropin approximately 4 weeks after starting MMN or folic acid and continued until end of study, which was three cycles even if pregnancy was attained
Outcomes	Clinical pregnancy. Ongoing pregnancy. Miscarriage. Ectopic pregnancy.
Notes	Two women did not complete the study- one from each group. Reasons given: One woman in the control group stopped because she wanted to take the micronutrients, and one in the treatment group stopped because of nausea Trial is self-funded. Recruited between Febuary and August 2009. Location: London UK. Informed consent. Ethical approval. Sample size power calculation performed. Intention to treat performed. Author stated in an email received 13.02.12 that the trial was not funded Emailed author 12.01.12 regarding whether the women had IUI or timed intercourse. Author replied on 07.02.12 saying that all women underwent timed intercourse, not IUI. This email also gave adverse event data (miscarriage and ectopic pregnancy data) for the first cycle. Dr Agrawal is also currently recruiting for a new trial Emailed author on 09.08.12 asking about any live birth data. Author replied saying that live birth data were unavailable
Risk of bias	

Agrawal 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Third party randomization ... was carried out through the research and development department of the University College London and the Royal Free Hospitals using stratification..." "Participants were randomly allocated". Email sent 12.01.12 asking for methods of randomisation. Author replied 13.02.12 saying, "the subjects were randomised into 2 groups through computer randomisation"
Allocation concealment (selection bias)	Low risk	"Third party randomisation and allocation concealment was carried out through the research and development department of the University College London and the Royal Free Hospitals using stratification and numbered envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Women, caregivers and investigators were blinded to the treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat was performed and explanations given for the two dropouts (one from each group)
Selective reporting (reporting bias)	Unclear risk	Live birth not reported. Outcomes stated in the text are reported

Alborzi 2007

Methods	Randomised placebo-controlled trial.
Participants	Women with infertility (N = 88). Mean age 29 years in the treatment group and 28 years in the control group Inclusion criteria: Infertility for at least 12 months with endometriosis (different stages) was diagnosed by laparoscopy Exclusion criteria: women with other infertility factors including tubal obstruction
Interventions	Pentoxifylline 400 mg twice a day for 12 months (n = 43) versus placebo (n = 45). Duration: 12 months.
Outcomes	Cumulative pregnancy rate. Recurrence of endometriosis.

Notes	Study approved by the Shiraz University of Medical Sciences Institutional Review Board Trial conducted in Shiraz, Iran, from January 2002 to December 2003 One-year follow-up. Attempted to contact the author regarding clinical pregnancy rate and live birth 12.02.13

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"They were assigned into 1 of 2 groups by simple randomisation. An independent pharmacist generated the allocation and assigned the patients to their groups. To do so, he gave each patient a number on the basis of the order of her being referred to him. For example, the first patient was enlisted as number 1 and the second as number 2 and so on. He then assigned patients with odd numbers into one group and patients with even numbers into another. He decided which one should be the control group by flipping a coin" There is a query as to whether this trial is adequately randomised. It could be seen as block randomisation (cluster) or as alternate (in which case this study would have been excluded). After discussion with the statistician, it was decided to include this study because of the double-blind concealment- if double-blinding was truly successful and nobody involved in recruitment affected the sequence, then it is a third party concealed allocation system that is protecting against selection bias despite the lack of proper randomisation
Allocation concealment (selection bias)	High risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded: "During this period, neither the clinicians nor the patients knew who received the medication and who received the placebo. The only person who knew this was the pharmacist"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.
Selective reporting (reporting bias)	Unclear risk	Both outcomes stated in methods and reported on. Live birth not reported

Aleyasin 2009

Methods	Randomised clinical trial.
Participants	"Infertile women undergoing standardised controlled ovarian hyperstimulation for ICSI-ZIFT [zygote intrafallopian transfer" (N = 112) Table 1 p. 177 mentions cause of infertility to be male in 51 of 112 Participants were aged from 20 to 39 years, with no previous history of IVF or ZIFT failure. Infertility duration was from 1 to 20 years Exclusion criteria: hypothalamic amenorrhoea, drug reactions, endometriosis and fibroids
Interventions	Pentoxifylline 400 mg and vitamin E 400 mg twice a day (n = 56). Administered for two cycles before ICSI-ZIFT versus no treatment (n = 56). Duration: two cycles.
Outcomes	Term delivery. Clinical pregnancy rate confirmed by beta human chorionic gonadotropin (hCG) at 14 days after embryo transfer and transvaginal ultrasound 14 days following this Miscarriage rate. Multiple pregnancy.
Notes	Conducted in one centre in Tehran, Iran; ethical approval gained and written consents obtained Trial was carried out between April 2006 and April 2007. For sensitivity analysis performed because more than half (41/56) of women had male subfertile partners or because both partners had fertility problems

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number tables were used.
Allocation concealment (selection bias)	Low risk	Sealed opaque sequentially numbered envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Comparison group received no treatment. Authors stated "study not blinded" (p. 176)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.
Selective reporting (reporting bias)	High risk	Live birth reported as 'term delivery'. Cause of Infertility is male in 51 of 112 participants (see Table 1 p. 177), although this is not mentioned in the text, where it says that the participants were 112 infertile women

Badawy 2006

Methods	Prospective randomised double-blind controlled trial.
Participants	Women attending a fertility outpatient clinic for management of unexplained fertility problems (N = 804) Mn age in the treatment group 27 years and in the control 28 years Inclusion criteria: All women had at least one year of marriage without conception, unexplained subfertility and normal ovulating cycles; tubes were patent Exclusion criteria: any known reason for subfertility. Timed intercourse.
Interventions	*N*-acetyl-cysteine (1200 mg/d orally) plus clomiphene citrate 50 mg two times a day for five days, starting on day two of the cycle (n = 404) versus placebo plus clomiphene citrate 50 mg two times/d (n = 400). Duration of treatment: 1 cycle. Timed intercourse. No loss to follow-up.
Outcomes	Number and size of follicles. Hormonal profiles. Endometrial thickness. Pregnancy. Miscarriage. Multiple pregnancy.
Notes	Conducted in one centre in Mansoura, Egypt. Ethical approval and informed consents obtained Trial ran from October 2003 to April 2005. Contacted author 13.02.13 regarding methods of randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description of sequence generation apart from: "Patients were allocated randomly to either the trial group"
Allocation concealment (selection bias)	Low risk	Sealed, opaque, sequentially numbered, identical envelopes were used
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, investigators, outcome assessor and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.

Badawy 2006 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Outcomes stated in the text- multiple pregnancy and miscarriage- reported on, although not initially stated as outcomes of interest
Other bias	Unclear risk	Duration of follow-up not described.

Balasch 1997

Methods	Prospective randomised controlled trial. Pilot study.
Participants	Infertile women with asymptomatic minimal or mild endometriosis (N = 60) Mean ages 31.2 (±3.8) in treatment arm and 32.4 (±3.1) in control group Inclusion criteria: at least 12 months of primary infertility, no previous pelvic surgery, minimal or mild endometriosis confirmed by laparoscopy Exclusion criteria: any previous pelvic surgery, pelvic disorders such as adhesions and tubal obstructions, in addition to endometriosis
Interventions	Pentoxifylline 400 mg twice a day for 12 months (n = 30) versus placebo (n = 30).
Outcomes	Pregnancy rates confirmed by ultrasound. Miscarriage rate.
Notes	One dropout from the treatment group and three from the control group- all due to refusal to start treatment after randomisation. Number reported is 56. Intention to treat is used for meta-analysis Trial held from November 1993 to December 1995. Single-centre study conducted in Spain. 12-Month duration and 12-month follow-up. During this time, participants received treatment for infertility problems (i.e. male problems, ovulatory problems, cervical mucus abnormalities, IUI, ovulation induction) Ethical approval and all consents obtained. An earlier study of Creus 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process that was using a computer random number generator
Allocation concealment (selection bias)	Unclear risk	Allocation described as being "designated". Authors contacted regarding this and confirmed concealment "computerised alloca-

Balasch 1997 (*Continued*)

		tion"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Women are described as being blinded. Authors contacted regarding other blinded persons. They confirmed that participants were blinded, but investigators, outcome assessors and clinicians were not
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only a small number of dropouts- 4 participants lost; 1 in treatment, 3 in control. All explained- 1 due to refusal and 3 due to failure to continue taking the medication. No intention to treat carried out
Selective reporting (reporting bias)	Unclear risk	Pregnancy rates were stated as the outcome of interest in the methods section of the paper. However, miscarriage rates were given in the results and were not mentioned in the methods. One patient in each study group became pregnant, then miscarried, then became pregnant again. The first two pregnancies were not included in the analysis. Live births not reported
Other bias	Unclear risk	Some women with other fertility issues apart from endometriosis were treated for these additional conditions (i.e. male factor (receiving bromocriptine), oligo-ovulation (receiving ovulation induction and some additional IUI) poor post-coital test, hyperprolactinaemia). Numbers of women in treatment and numbers of controls in each of these categories are given. However, these treatments may bias the results, as nearly double the control women in the additional treatment group received IUI compared with the treatment group Pilot study.

Batioglu 2012

Methods	Randomised controlled trial.
Participants	Women with primary infertility between 20 and 40 years undergoing IVF (N = 85) Inclusion criteria: regular menstruation, no hormonal or nonhormonal drug therapy for less than 3 months and no systemic illness Exclusion criteria: serious endometriosis, serious male factor (azoospermia) hypogonadism with an FSH level less than 13. Also participants with cycles cancelled were excluded

Batioglu 2012 (*Continued*)

Interventions	Melatonin 3 mg (n = 40) versus no treatment (n = 45).
Outcomes	Primary outcome: number of morphologically mature oocytes retrieved (Mll oocytes) Secondary outcome: fertilisation rate, embryo quality and pregnancy rate
Notes	No information on miscarriage numbers. Funding sources not mentioned. Clinical pregnancy data (not chemical) used in the meta-analysis Trial held in Turkey.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation computer assisted 1:1.
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Embyologist was the only person blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat used. No dropouts were reported.
Selective reporting (reporting bias)	Unclear risk	Unclear why chemical pregnancy numbers are lower than clinical pregnancy numbers. Live births not reported

Battaglia 2002

Methods	Randomised controlled trial.
Participants	Women attending Modena University Infertility Clinic (N = 37) Mean age (mean ± SD) 33.8 ± 3.1 years (range 28 to 37 years), mean duration of infertility 6.8 ± 3.8 (range 4 to 12 years) Inclusion criteria: All participants were selected from among women who suffered from tubal infertility. They had regular menstrual cycles (28 ± 4 days), and their partners were fertile according to World Health Organization standards Exclusion criteria: participants with intercurrent illness, body mass index (BMI = weight (kg)/height^2 (m^2)) > 30, endometriosis, ovarian functional cyst, PCOS, unilateral ovarian resection or ovariectomy, participants who took regular exercise, heavy smokers (> 10 cigarettes/d), those with hypertension (systolic blood pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg) and women who had received hormonal treatments in the 4 months before the first IVF attempt

Battaglia 2002 (*Continued*)

Interventions	L-arginine 4 grams 4 times per day (n = 18) versus placebo (n = 19). Both groups were undergoing IVF with long gonadotropin-releasing hormone (GnRH) agonist protocol and pure FSH Duration: 10, 12 days.
Outcomes	Clinical pregnancy rates. Side effects. Follicular number and diameter. Endometrial thickness. Live birth.
Notes	Consent and ethical approval were obtained, and the trial was conducted in Modena, Italy 32 participants completed the trial, with five dropouts due to poor response. Author was emailed 16.08.12 and 12.02.13 with request for the number of live births for each group. Author replied on 14.02.13, providing data for live birth and miscarriage

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random number table".
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed envelopes using "opening sequentially numbered sealed envelopes containing treatment allocation"
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigtors, participants and outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	37 women were enrolled; however, investigators did state, "All 34 patients completed the trial". Numbers given for dropouts from each group. Authors contacted regarding this ITT not used. Five were said to be cancelled because of "poor response"
Selective reporting (reporting bias)	Low risk	Key outcomes reported, including live birth.
Other bias	Low risk	

Cicek 2012

Methods	Randomised controlled trial.
Participants	Women with a diagnosis of unexplained infertility undergoing ovulation induction and intrauterine insemination (N = 107) Inclusion criteria: no ovulatory problems, normal hysterosalpingography and laparoscopy. Normal semen sample Exclusion criteria: endometriosis, hypertension, diabetes, uterine myoma, ovarian cyst, excessive alcohol, caffeine, chronic illness and smoking
Interventions	Vitamin E (n = 53) 400 IU/d from 3rd to 5th day of the menstrual cycle until the hCG injection versus no treatment (n = 50). 4 women were lost to follow-up as the result of incorrect dose consumption (n = 3) and cycle cancellation (n = 1). Intention to treat not used in the trial
Outcomes	Primary outcome: ongoing pregnancy rate. Secondary outcomes: biochemical and clinical pregnancy rate, number of follicles, endometrium thickness, implantation rate
Notes	Study was conducted between June 2011 and December 2011 in Turkey Sample size calculated. Ethics approved and written consent obtained. Funding not reported, but authors say they have no conflict of interest Emailed author 09.08.12 regarding the number of women lost from treatment and/or control group. Data added. Will perform sensitivity analysis for quality if we do not hear back from the author regarding intention to treat

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned according to a randomisation table.
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded as the control was no treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons and numbers for attrition were given but unclear whether from treatment or control groups. Intention to treat not used
Selective reporting (reporting bias)	Unclear risk	Nil known.

Ciotta 2011

Methods	Randomised controlled trial.
Participants	Women with PCOS attending a fertility clinic- Gynecological Endocrinology Clinics and Human Reproduction Pathophysiology Centre (N = 34) Inclusion criteria: women with PCOS younger than 40 years. Exclusion criteria: concomitant endocrine and metabolic pathologies, such as hypothyroidism, hyperthyroidism, diabetes mellitus, androgen-secreting cancers, adrenal hyperplasia, Cushing's syndrome Women received IVF or ICSI after evaluation of sperm analysis
Interventions	Myo-inisitol 2 g + folic acid 200 µg twice a day (n = 16) versus folic acid 200 µg twice a day (n = 18). Treatment was given over 3 months.
Outcomes	Number of follicles. Number of oocytes retrieved. Number of embryos transferred. Embryo quality. Study states that there was "no difference in the total number of biochemical pregnancies detected", but no data were provided. Author replied, giving the data for chemical pregnancies and stating that no adverse events were reported
Notes	Trial held in Catania, Italy. Contacted authors 21.11.11 via letter and email regarding pregnancy data, allocation concealment and who was blinded. Author responded 28.11.11. Emailed the author 05.02.12 requesting data on clinical pregnancies and whether the sealed envelopes were numbered Funding, ethics approval and power calculation not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to a randomisation table, patients were divided into two groups"
Allocation concealment (selection bias)	Unclear risk	Author states that allocation was in "white sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"the investigation was performed in a double-blind design". Author states, "clinicians and patients were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No women were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Live births not reported.

Creus 2008

Methods	Randomised controlled trial.
Participants	Infertile women with mild to moderate endometriosis (N = 104) post laparoscopic surgery Inclusion criteria: at least 12 months with asymptomatic primary infertility, regular menstruation, aged between 23 and 37 years with normal BMI. Patients with other infertility factors were included if those factors were correctable and were non-contributory Exclusion criteria: patients with other pelvic disorders such as adhesions and tubal obstructions in addition to endometriosis
Interventions	Pentoxifylline 400 mg 2/d (n = 51) versus placebo (n = 53). Other procedures given post laparoscopy included biopsies, tubal dye perfusion and destruction of endometriotic implants by cautery Treatment was started with the first menses after laparoscopic surgery; then participants were observed for 6 months. During this time, participants with other infertility factors were treated (i.e. male problems or ovulatory defects). Treatments included IUI and/or ovulation induction. Not all participants were treated or received the same treatment, thus the potential for bias
Outcomes	Pregnancy. Miscarriage.
Notes	Six women dropped out: 4 from the treatment group and 2 from the control group. Reasons explained. No intention to treat. Trial held in Barcelona, Spain Work supported in part by the Comissionat per Universitat i Recerca-Generalitat de Catalunya Authors were also involved in Balasch 1997. Author emailed 23.11.11 regarding live birth data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list generated using the method of simple randomisation"
Allocation concealment (selection bias)	Low risk	"Concealment of treatment allocation was achieved with the use of sealed opaque envelopes, each containing a unique study number and prepared independently by a secretary"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Trial was blind- not stated whether single, double or triple- "randomised controlled blind trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small numbers of dropouts and reasons explained, no intention to treat

Creus 2008 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Live births not reported.
Other bias	Unclear risk	Some women with other fertility issues apart from endometriosis were treated for these additional conditions (i.e. male factor (receiving bromocriptine), oligo-ovulation (receiving ovulation induction and some additional IUI), poor post-coital test, hyperprolactinaemia). Numbers of women in treatment and control in each of these categories are given. However, treatments may bias the results, as nearly double the control women in the additional treatment group received IUI compared with the treatment group

Eryilmaz 2011

Methods	Randomised single-centre controlled clinical trial.
Participants	Women undergoing IVF with sleep disturbances (N = 63) from 24 to 38 years in age Inclusion criteria: unexplained infertility, no ovulatory problems, normal hysterosalpingogram or laparoscopy and normal semen sample Exclusion criteria: chronic drug usage, history of more than one fertilisation failure, hypertension, diabetes, uterine myoma, ovarian cyst and smoking
Interventions	Melatonin 3 mg taken at 22:00 to 23:00 (n = 30) from 3rd to 5th day of the menstrual cycle until the hCG injection versus no treatment (n = 30).
Outcomes	Primary outcome: oocyte quality. Secondary outcomes: fertilisation failure rate, number of follicles, number of oocytes retrieved, number of Mll oocytes, fertilisation rate, number of embryos transferred, embryo quality, implantation rate and clinical pregnancy rate
Notes	Trial held in Turkey. Ethics approved, written informed consent gained. Authors declare no conflicts of interest Power calculation performed. Emailed author 09.08.12 regarding which group or groups lost the three women. Data added. Tried to contact the author again regarding live birth data 05.02.12. Author replied on 07.02.13, saying that the 3 dropouts were from the treatment group, and that no allocation concealment was performed and no live birth data were available because participants were mainly from rural sites

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Eryilmaz 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Participants were randomly assigned according to a randomisation table
Allocation concealment (selection bias)	High risk	No allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding as control is no treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts explained.
Selective reporting (reporting bias)	Unclear risk	Live births not reported.

Firouzabadi 2012

Methods	Randomised controlled trial.
Participants	Infertile women with PCOS (N = 100). Age range 20 to 40 years. Natural conception.
Interventions	Calcium 1000 mg + vitamin D plus metformin 1500 mg (50) versus metformin (50). Treatment was given over 6 months.
Outcomes	Menstrual regularity. Number of follicles. BMI. Chemical pregnancy.
Notes	Trial ran for 2 years. Trial held in Iran. Tried to contact author 13.02.13 regarding allocation concealment, blinding and clinical pregnancy rates

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random number table".
Allocation concealment (selection bias)	Unclear risk	Not described.

Firouzabadi 2012 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Unclear risk	Only biochemical pregnancies reported.

Gerli 2007

Methods	Double-blind randomised trial.
Participants	Women with oligomenorrhoea or amenorrhoea and PCOS were recruited from gynaecology, endocrine and fertility clinics. Women were younger than 35 years of age (N = 92) "Infertility was an ailment in only half of the patients in each group. There was no difference in the proportions of infertile women with the groups" Exclsion criteria: hyperprolactinaemia, hormone treatment, abnormal thyroid function, congenital adrenal hyperplasia
Interventions	Myo-inositol 2 g twice/d plus folic acid 400 μg (n = 45) versus placebo (folic acid 400 μg) (n = 47). Duration: 16 weeks.
Outcomes	Ovulation frequency. Hormonal levels. Pregnancy.
Notes	Authors contacted (May 2010) to request any pregnancy outcomes considered and to ask whether the authors of the paper have the individual data on which women in each group were infertile. No reply as of 12.06.13 "Ethical committee approval was obtained before the study, and written informed consent was given by each patient" Trial carried out in Italy. Power calculation carried out. High dropouts- more than 30% in the treatment group. Included but data not used, as half the participants did not want to conceive. Study is included on the basis that half the participants were from a subfertility clinic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was effected in a double blind fashion; patients received either MYO combined with folic acid (Inofolic®) or only folic acid as placebo, ac-

Gerli 2007 (*Continued*)

		cording to the code provided by computer-generated randomization."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as "double-blind fashion".
Incomplete outcome data (attrition bias) All outcomes	High risk	"The high dropout rate in the myo-inositol arm (more than 30%) is notable"
Selective reporting (reporting bias)	High risk	Only half the participants declared before the study that they wanted to conceive. No intention to treat for the pregnancy outcome. One miscarriage was reported but no details of whether this occurred in the treatment or the control group. Miscarriage not prestated as an outcome of interest. Live births not reported

Griesinger 2002

Methods	A prospective, randomised, placebo-controlled, group comparative, double-blind study
Participants	Subfertile women having first IVF cycle aged < 40 years with mean age of 31.73 (± 4.4 SD) years (N = 620) 10% described as male factor infertility, and associated data were not presented separately Inclusion criteria: tubal, idiopathic and male infertility were included Exclusion criteria: patients with repeated IVF cycles and patients with renal or gastrointestinal disease
Interventions	Ascorbic acid 1 g per day (n = 172) versus ascorbic acid 5 g per day (n = 153) versus ascorbic acid 10 g per day (n = 136) versus placebo (n = 158). Duration one cycle.
Outcomes	Clinical pregnancy rate confirmed by fetal heartbeat at eight weeks per embryo transfer Implantation rate per embryo transfer.
Notes	1 person lost to follow-up- no explanation. Tried to contact author 10% of women had partners with male infertility. Trial conducted in two clinics in Budapest, Hungary (n = 237) and Vienna, Austria (n = 383) No power calculation performed.

Griesinger 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"This prospective randomised double-blind study". Method not described
Allocation concealment (selection bias)	Low risk	By an independent pharmacy in Vienna "prepared and coded by number"
Blinding (performance bias and detection bias) All outcomes	Low risk	Women and clinicians were blinded: "double-blind study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	One set of participant data noted as missing but not explained; authors contacted regarding this
Selective reporting (reporting bias)	Unclear risk	Live births not reported.
Other bias	Unclear risk	Pregnancies were confirmed at eight weeks with no further follow-up; authors contacted regarding this. No reply as of 12.06.13 No clarity regarding the number of treatment cycles involved in this study Ethics approval not gained as "a study on vitamin supplementation is not subject to IRB approval". Consent forms were signed

Kim 2006

Methods	Randomised controlled trial.
Participants	Infertile women aged 25 to 39 years with PCOS undergoing IVF (N = 58)
Interventions	*N*-acetyl-cysteine for 13 to 15 weeks 400 mg twice daily (n = unknown) versus placebo (n = unknown). Duration 13 to 15 weeks.
Outcomes	Insulin sensitivity, endocrine levels, ovarian stimulation, number and size of follicles, number of retrieved oocytes, number and quality of embryos transferred, pregnancy rate, miscarriage and ovarian hyperstimulation syndrome rates
Notes	Conference abstract only. Trial held in Korea. The authors contacted to request pregnancy outcome data and study protocol to appraise

Kim 2006 (*Continued*)

	risk of bias elements. No reply as of 14.09.11

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients randomly assigned..." No description of method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	High risk	Conference abstract only.

Kim 2010

Methods	Prospective randomised controlled study.
Participants	Infertile women with a history of unexplained total fertilisation failure undergoing ICSI (N = 98). Ages not given Inclusion criteria: unknown. Exclusion criteria: unknown.
Interventions	Omega-3-polyunsaturated fatty acids (o-3 PUFAs) 1000 mg/d (n = unknown) versus unknown control (n = unknown).
Outcomes	Total recombinant human (rh)FSH dose and days required. Numbers of oocytes retrieved. Number of oocytes fertilised. Embryo quality. Embryo implantation. Clinical pregnancy rate.
Notes	Conference abstract only. Trial held in Korea. Authors emailed 22.11.11 regarding risk of bias, pregnancy data per woman, numbers in intervention and control groups and inclusion/exclusion criteria

Risk of bias

Kim 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospective randomised controlled study" - no explanation given
Allocation concealment (selection bias)	Unclear risk	No explanation given.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No explanation given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No explanation given.
Selective reporting (reporting bias)	Unclear risk	No explanation given.
Other bias	High risk	No explanation given. Conference abstract.

Lisi 2012

Methods	Randomised open-label, multicentre pilot study.
Participants	Infertile women undergoing IVF/ICSI (N = 100). Exclusion criteria: women with PCOS, with any endocrine or metabolic disease, taking any hormonal treatment, with BMI > 30 kg/m^2
Interventions	Myo-inositiol 4000 mg + folic acid 400 µg (n = 50) versus folic acid 400 µg (n = 50). Duration of treatment 3 months, duration of trial 12 months.
Outcomes	Length of stimulation. Total quantity of gonadotropins required. Number of oocytes retrieved. Implantation rate. Clinical pregnancy.
Notes	Center for Reproductive Medicine Research, Clinica Villa Mafalda, Rome, Italy Emailed author 13.02.13 regarding randomisation, allocation concealment and live birth data. Professor Lisi replied, clarifying these questions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomisation in a computer-generated sequence" is written in the paper

		and in further correspondence from the author ..."About randomization, a computer software generated 100 numbers from 1 to 10,000, and the numbers were stored in sealed envelopes and opened on the day of preparation and explanation of the stimulation protocol to patients. Patients with odd number were assigned to folic acid, myo-inositol and rhFSH; patients with even number were assigned to folic acid and rFSH". Unsure whether this may be quasi-randomised. Further information has been sought from the author. Author replied, "The envelope outside had 100 numbers in order and opened in that order; numbers outside were different from numbers inside"
Allocation concealment (selection bias)	Low risk	Envelopes were numbered sequentially and were opaque.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label, although outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Unclear risk	Live births not reported.

Mier-Cabrera 2008

Methods	Randomised controlled trial.
Participants	Infertile women with peritoneal endometriosis stage 1 or 2 diagnosed by laparoscopy (N = 36). All participants had fulguration of endometrial implants Inclusion criteria: women between 25 and 35 years old who had been diagnosed as having peritoneal endometriosis on exploratory laparoscopy, with fertile male partner Exclusion criteria: women who reported having used nutritional supplements during the previous year; who had pelvic inflammatory disease or autoimmune, endocrine or metabolic disorders; or who did not accept to participate or missed a medical visit
Interventions	Vitamins C and E (343 mg and 84 mg) in a bar form (n = 18) versus placebo (n = 18). Duration of trial was 6 months. Follow-up for up to 9 months after the trial.

Outcomes	Live birth. Pregnancy (no explanation of whether pregnancies were clinical or ongoing) MDA, LOOH levels (oxidative stress markers) obtained during the exploratory laparoscopy
Notes	Consent signed. Ethics was approved. The study was conducted at the National Institute of Perinatology "Isidro Espinosa de los Reyes" in Mexico City Funding given as a grant from Consejo Nacional de Ciencia Tecnologia Mexico Power calculation done. Tried to contact author. Contacted author again 12.02.13 to ask about clinical pregnancy and live birth

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reference was made to the use of 'randomisation codes', and investigators stated, "Thirty-six participants were randomly assigned". Authors contacted regarding this
Allocation concealment (selection bias)	High risk	Not stated in the paper. Authors contacted regarding this. The response was, "women were randomly allocated depending on the colour of a ball they took out from a container", so some doubt exists regarding allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Women were blinded. The bars were "identical-looking and tasting bars". Authors contacted regarding this and confirmed that investigators, outcome assessors and clinicians were blinded also. "Randomization codes were unlocked at the end of the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two women in the treatment arm dropped out 'for personal reasons'. ITT not applied
Selective reporting (reporting bias)	High risk	Investigators stated they would collect live birth rates but reported only pregnancy rates
Other bias	Unclear risk	Nil known.

Nasr 2010

Methods	Randomised, double-blind, placebo-controlled pilot study.
Participants	Women undergoing unilateral laparoscopic ovarian drilling (LOD) for clomiphene-resistant PCOS (N = 60) Aged 18 to 38 years with at least two years of infertility due to anovulation, patent fallopian tubes, normal semen analysis Exclusion criteria included no hormonal treatment for three months before enrolment and any contraindications to anaesthesia or laparoscopy
Interventions	*N*-acetyl-cysteine (n = 30) 1.2 g/d for five days, starting at day three of the cycle (immediately after LOD) for 12 consecutive cycles versus placebo (n = 30). Both groups also had LOD. Follow-up by cycle monitoring and timed intercourse for a year. No women were lost to follow-up
Outcomes	Priamry outcome: pregnancy. Secondary outcomes: ovulation, number of follicles, endometrial thickness, pregnancy, miscarriage, multiple pregnancies, ongoing pregnancy, number of preterm deliveries, live birth
Notes	Trial took place in Egypt between January 2005 and June 2007 Ethics obtained. Informed written consent.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomised double-blind placebo-controlled pilot study", "computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. "The placebo sachets were specially manufactured to look identical to the NAC sachets". "Throughout the study, access to the randomisation code was available only to the pharmacist and was not available to the treating gynaecologist or patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No women lost to follow-up.
Selective reporting (reporting bias)	Low risk	No outcomes not reported.

Nasr 2010 (*Continued*)

Other bias	Unclear risk	Pilot study.

Ozkaya 2011

Methods	Randomised trial.
Participants	Women undergoing IVF (N = 56) aged 22 to 43 years. Inclusion criteria: non-smokers, free from major illness including hypertension, all interested in becoming pregnant Exclusion criteria: myoma, adenomyosis, congenital abnormality, ovarian tumours, hormone or long-term medication use
Interventions	Multi-vitamin/mineral tablet (containing vitamins A, B, C, D, E and H, calcium, folic acid, nicotinic acid, iron, magnesium, phosphor copper, manganese and zinc) (n = 26) versus placebo (candy) (n = 30) for 45 days.
Outcomes	Follicular fluid.
Notes	Turkey. Three groups were used in the study. The first group consisted of aged matched controls; therefore these data were not used in this review. The second and third groups were randomly assigned Author emailed on 01.08.12 to ask for any data on pregnancy, live birth or adverse events. Author replied on 13.08.12. No outcomes appropriate to this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised by a computer-generated list.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding (performance bias and detection bias) All outcomes	High risk	Placebo used was candy.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None mentioned.
Selective reporting (reporting bias)	Unclear risk	Nil known.

Papaleo 2009

Methods	Randomised controlled trial.
Participants	Infertile women with PCOS undergoing ovulation induction for ICSI (N = 60) Inclusion criteria: women aged < 40 years with PCOS, indicated by oligomenorrhoea (six or fewer menstrual cycles during a period of 1 year), hyperandrogenism (hirsutism, acne or alopecia) or hyperandrogenaemia (elevated levels of total or free T) and typical features of ovaries on ultrasound scan. All women had been treated at the IVF clinic for longer than 12 months Exclusion criteria: other medical conditions causing ovulatory disorders such as hyperinsulinaemia, hyperprolactinaemia, androgen excess such as adrenal hyperplasia or Cushing's syndrome Age (years) treatment 36.2 ± 2.4; non-treatment 35.4 ± 2.5. Duration of infertility (months) treatment 46.1 ± 18.5, non-treatment 37.7 ± 9.6
Interventions	Myo-inositol 2 g twice a day plus folic acid 400 µg (n = 30) versus folic acid 400 µg (n = 30). Duration: for one cycle of ICSI. Treatment starting on the day of GnRH administration
Outcomes	Number of mature oocytes retrieved. Embryo quality. Pregnancy. Implantation rates. Total number of days of FSH stimulation. Total dose of gonadotropin administered. Estrogen levels. Fertilisation rate. Number of retrieved oocytes. Embryo cleavage rate. Live births. Miscarriage rates. Cancellation rate. Incidence of moderate or severe ovarian hyperstimulation syndrome
Notes	The Institutional Review Board approved the protocol, and all participants gave written informed consent before entering into the trial Source of funding not stated. Power calculation performed. Authors contacted. Trial conducted in Italy. Authors could not supply live birth data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised according to "computerised allocation". Authors have since confirmed this

Papaleo 2009 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"Computerised allocation".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Authors confirmed in correspondence that participants and investigators were not blinded; however, outcome assessors and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.
Selective reporting (reporting bias)	High risk	Data on live birth were not reported in the paper, even though it was listed as an outcome
Other bias	Unclear risk	Unknown.

Rashidi 2009

Methods	Randomised clinical trial.
Participants	Infertile women with PCOS (N = 60). Inclusion criteria: oligomenorrhoea/amenorrhoea, hyperandrogenism, polycystic ovaries on transvaginal ultrasound Exclusion criteria: women with systemic disease, coexisting male factor infertility or abnormal hysterosalpingography. Natural conception
Interventions	Calcium 1000 mg + vitamin D 400 IU (n = 20) versus calcium 1000 mg + vitamin D 400 IU + metformin 1500 mg (n = 20) versus metformin 1500 mg (n = 20).
Outcomes	Follicular response. Frequency of menstrual cycle. Chemical pregnancy. Clinical pregnancy.
Notes	Trial lasted 3 months with a 3-month follow-up. Trial held in Iran. Tried to contact authors regarding allocation concealment and blinding 13.02.13

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were divided into three groups with the use of a random number table
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment.

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts from the trial.
Selective reporting (reporting bias)	Unclear risk	Reported only chemical pregnancy.

Rizk 2005

Methods	Placebo-controlled, double-blind, randomised trial.
Participants	Women diagnosed with clomiphene citrate- resistant PCOS (N = 150) aged 18 to 39 years, undergoing therapy for infertility. Timed intercourse Inclusion criteria: clomiphene citrate- resistant, at least one patent tube, adequate semen analysis according to World Health Organization (WHO) guidelines, no hormonal treatment Exclusion criteria: hormonal treatment within 2 months of the study, no participants had taken medication to affect carbohydrate metabolism, hyperprolactinaemia, hypercorticism or thyroid dysfunction
Interventions	*N*-acetyl-cysteine (NAC) 1.2 g/d plus clomiphene citrate (CC) for five days, starting at day three of the cycle for one cycle (n = 75) versus placebo plus clomiphene citrate (n = 75).
Outcomes	Ovulation rate. Ongoing pregnancy rate. Number of follicles of 18 mm. Hormone levels. Endometrial thickness. Ovarian hyperstimulation syndrome (OHSS). Multiple gestations.
Notes	Single-centre university-based hospital and private infertility practice in Eygpt Trial conducted from March 2002 to November 2003. Informed consent. No mention of funding source. Data for miscarriage and multiple pregnancy not in meta-analysis, as they appear to skew data because of the fact that there were no pregnancies or live birth events in the control group, therefore no miscarriages. The intervention appears worse in terms of miscarriage when it is simply due to the intervention group having pregnancy and live birth. Emailed author 07.09.12 regarding the pregnancy rate in the control group and asking for live birth data. Author replied on 10.09.12, confirming that there were no pregnancies in the control group and no live birth data

Risk of bias

Rizk 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to receive CC and either NAC or placebo". Method not described
Allocation concealment (selection bias)	Unclear risk	"Allocation was done by a third party (nurse)". "Using sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The NAC and placebo were supplied in identical sachets. The patients and the physician monitoring the cycles were blinded to the identity of each medication"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported.
Selective reporting (reporting bias)	Unclear risk	Outcomes described in the methods section were reported on in the results section. Miscarriage and OHSS are not stated as outcomes in the methods section but are reported in the results. A total of 16 pregnancies occurred in the treatment group and 0 in the control group

Rizzo 2010

Methods	A prospective, randomised clinical trial.
Participants	Women with low oocyte quality detected in previous IVF cycles (N = 65). Aged 35 to 42 years IVF.
Interventions	Myo-inositol 2 g plus folic acid 200 mg plus melatonin 3 mg two times per day (n = 32) versus myo-inositol 2 g plus folic acid 200 mg two times per day (n = 33) Administered continuously from the day of GnRH administration
Outcomes	Embryo quality. Pregnancy rate, biochemical and clinical. Total number of oocytes retrieved (immature and mature oocytes) Fertilisation rate per number of retrieved oocytes and embryo cleavage rate Miscarriage.
Notes	Setting: Messina, Italy. All participants gave written informed consent for the procedure, and the study was approved by the local ethics committee. Source of funding unclear
Risk of bias	

Rizzo 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised: "According to a randomisation table, patients were assigned to receive either 2 g..."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	Data given for all outcomes reported in the text. Live birth data not reported

Salehpour 2009

Methods	Randomised, controlled, double-blind trial.
Participants	Women with PCOS attending IVF clinic (N = 46). Exclusion criteria: infertility factors apart from anovulation, other pathologies, hormone consumption for less than 2 months before enrolment Mn age 27 in treatment group and 28 in control group.
Interventions	*N*-acetyl-cysteine 200 mg three times per day (n = 23) versus placebo (n = 23). Seven women lost to follow up. Reasons described were intolerance to the smell of medications and blood samples inappropriate for the study Treatment 6 weeks' duration. Follow-up 6 weeks.
Outcomes	Ovulation. Weight. Endocrine. Metabolic and hormonal factors.
Notes	Trial carried out in Teheran, Iran, from February 2007 and February 2008 Informed consent. Power calculation. Ethics approved. Funding source stated, "research is supported by Shahid Beheshti Medical University"
Risk of bias	

Salehpour 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"In order to minimise the effects of confounding factors through a randomised method". Method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Medication was provided to patients by a midwife. Both patient and physician were blinded to the type of treatment regimen"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14 dropouts- seven from each arm, reasons generally described but not for each woman
Selective reporting (reporting bias)	Unclear risk	All outcomes described in the text were reported on. Live birth data not reported
Other bias	Unclear risk	Unknown.

Unfer 2011

Methods	Prospective randomised trial.
Participants	Euglycemic (normal levels of serum glucose) women with PCOS undergoing ovulation induction for ICSI (N = 84) Inclusion criteria: women who have attended IVF department for longer than 12 months, younger than 40 years, diagnosed with PCOS according to the Rotterdam criteria Exclusion criteria: patients with hyperglycaemia and/or insulin resistance
Interventions	Myo-inositol 2 g (n = 43) versus d-chiro-inositol 0.6 g (member of vitamin B family) (n = 41) Twice a day for 8 weeks.
Outcomes	Total number of oocytes. Number of mature oocytes. Embryo quality. Pregnancy- divided into biochemical and clinical pregnancies. Miscarriage.
Notes	Trial held in Messina, Italy. Funding source not mentioned. Emailed and posted letter to Dr Unfer 28.11.11, requesting information on risk of bias. A colleague of the author, Gianfranco Carlomagno [gianfranco.carlomagno@agunco.it], replied 05.12.11 with risk of bias information and offering to find data on live birth. Emailed back asking for live birth data 12.12.11. Emailed again 10.08.12 asking about live birth data. Author replied 16.08.12. Live birth data added to the analysis

Unfer 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to receive..." In email correspondence, author replied, "The randomisation was computer based"
Allocation concealment (selection bias)	Unclear risk	In email correspondence, author replied, "the treatments were provided in opaque envelopes identified by A or B"
Blinding (performance bias and detection bias) All outcomes	Low risk	In email correspondence, author replied, "both patients and clinicians were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All losses were accounted for- 4 women in the control group had cancelled cycles and nil in the treatment group
Selective reporting (reporting bias)	Low risk	Key outcomes reported, including live birth.
Other bias	Low risk	

Westphal 2006

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Infertile women (N = 93). Inclusion criteria: women aged 24 to 42 years, unsuccessfully trying to conceive for 6 to 36 months Exclusion criteria: any woman taking any pharmacological treatment for infertility for 2 months before commencement of the trial
Interventions	Fertility blend- capsules containing chaste berry, green tea amino acid, L-arginine, vitamins E, B6 and B12 and folate, iron, magnesium, zinc and selenium. Three capsules per day for three menstrual cycles (n = 53) versus placebo (n = 40). Duration of treatment: three menstrual cycles, then women received an additional 3 months of open-label fertility blend after completion of the study, with monitoring only of pregnancy and side effects Duration of trial: 4 months.
Outcomes	Basal body temperature changes. Length of menstrual cycle. Pregnancy rates. Side effects.

	Mid-luteal phase progesterone levels. Miscarriage.
Notes	No power calculation performed. Institutional review board approval was obtained for the trial Conducted in the USA. Funding stated- David Sen Lin Foundation. No loss to follow-up. 14 pregnant in treatment group in first 3 months, then 17 in 6 months, but the second 3 months was unblinded; therefore, only first 3 months' data used. Not all women in the trial received the extra 3 months of treatment or placebo Miscarriage and side effect data cannot be used as they include data from the later 3 months Tried to contact author 25/11/09 with email, mail and fax, with no reply. Tried to contact author again regarding live birth

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; mechanism not stated. "Fértilty Blend5 (FB), administered in a randomised, double-blind, placebo-controlled fashion"
Allocation concealment (selection bias)	Unclear risk	Mechanism not stated. Authors contacted May 2010 regarding this
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as being double-blinded, no explicit explanation. Authors contacted regarding this
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts.
Selective reporting (reporting bias)	High risk	Data on miscarriage and side effects cannot be used in analysis, as these data were combined with the extra open-label 3-month data. Not all women received treatment or placebo in this phase. Miscarriage not stated as an outcome in the methods section but reported in the results. All other outcomes that were discussed in the methods section were reported on in the results section. Live birth data not given

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aksoy 2010	Not a randomised study.
Al-Omari 2003	Non-randomised trial. "Forty-two infertile PCOS were divided into three groups"
Ardabili 2012	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Baillargeon 2004	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Bonakdaran 2012	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Cheang 2008	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Ciotta 2012	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Costantino 2009	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Crha 2003	Not an RCT. "patients for the supplemented and control sets were selected by the case-control method according to their age and smoking or non-smoking habits."
Elgindy 2008	Participants were fertile women with infertile male partners. Conference proceeding of Elgindy 2010
Elgindy 2010	Participants were fertile women with infertile male partners
Elnashar 2005	This is a conference abstract of the included trial Elnashar 2007.
Elnashar 2007	Interventions *N*-acetyl-cysteine versus metformin.
Farzadi 2006	The intervention versus control used in this trial was metformin versus placebo
Genazzani 2008	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is incorrect for inclusion in this review
Hashim 2010	Interventions *N*-acetyl-cysteine plus clomiphene citrate versus metformin plus clomiphene citrate
Henmi 2003	Described as randomised, but authors confirmed the process of allocation as "alternative treatments". Additionally, 28 of 46 in the placebo arm withdrew because of travel difficulties and movement out of the study area. No withdrawals from the treatment arm were reported. There was no Intention to treat

(*Continued*)

Hernndez-Yero 2012	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Iuorno 2002	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Kamencic 2008	This trial included women with endometriosis, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Kilicdag 2005	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Le Donne 2012	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Moosavifar 2010	Participants were not subfertile women; they were partners of subfertile men
Nazzaro 2011	Not randomised. Attempted to contact authors regarding sequence allocation via email 10.11.11
Nestler 1999	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Nestler 2001	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Nichols 2010	Lead investigator confirmed (May 2010). Stated that the trial was abandoned before recruitment because of lack of funding
Nordio 2012	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Oner 2011	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Papaleo 2007	Not a randomised controlled trial.
Papaleo 2008	Interventions myo-inositol plus folic acid versus clomiphene citrate
Raffone 2010	Interventions myo-inositol plus folic acid versus metformin.
Rezk 2004	This was a conference abstract of the included trial Rizk 2005.
Santanam 2003	The population included here were women with endometriosis, and the trial aimed to show differences in inflammatory markers. These women were not attending a fertility clinic
Tamura 2008	A quasi-randomised trial. “Patients were divided into two groups”. Email sent asking about randomisation but undeliverable. Letter sent to University of Texas 12.01.12. Letter returned to sender 17.02.12

(*Continued*)

Thiel 2006	This trial included women with endometriosis, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review. A conference abstract of Kamencic 2008.
Twigt 2011	Participants were randomly assigned to different stimulation protocols and not to folic acid. All participants took folic acid
Vargas 2011	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review
Yoon 2010	This trial included women with PCOS, but they were not intending to become pregnant. Therefore, the population is not suitable for inclusion in this review

Characteristics of studies awaiting assessment *[ordered by study ID]*

Beigi 2012

Methods	RCT using block randomisation method.
Participants	Subfertile women with PCOS.
Interventions	Calcium- vitamin D plus clomiphene citrate versus placebo plus clomiphene citrate
Outcomes	Follicle size.
Notes	

Carlomagno 2012

Methods	Double-blind RCT.
Participants	Participants undergoing ICSI procedure.
Interventions	Myo-inositol (MI) versus placebo (folic acid).
Outcomes	Total dosage of rhFSH. Number of stimulation days. Fertilisation and cleavage rates. Embryo quality. Biochemical and clinical pregnancy rates.
Notes	Conference: 68th Annual Meeting of the American Society for Reproductive Medicine, ASRM 2012, San Diego, CA, United States. Conference start: 20121020 Conference end: 20121024

Choi 2012

Methods	Prospective, randomised controlled trial.
Participants	Infertile patients with PCOS undergoing IVF/ICSI.
Interventions	Calcium and vitamin D versus placebo.
Outcomes	Total dose. Numbers of oocytes. Quality of embryos. Clinical pregnancy rate. Miscarriage.
Notes	Conference: 68th Annual Meeting of the American Society for Reproductive Medicine, ASRM 2012, San Diego, CA, United States. Conference start: 20121020 Conference end: 20121024

Rosalbino 2012

Methods	RCT.
Participants	Women with PCOS.
Interventions	D-chiro-inositol versus placebo and different doses of d-chiro-inositol
Outcomes	Total rhFSH units. Number of oocytes. Quality of embryos.
Notes	

Salehpour 2012

Methods	Placebo-controlled double-blind randomised clinical trial.
Participants	PCOS infertile patients.
Interventions	*N*-acetyl-cysteine as an adjuvant to clomiphene citrate.
Outcomes	Number of follicles. Ovulation. Pregnancy rates. Adverse effects- OHSS.
Notes	

Salem 2012

Methods	Randomised controlled study.
Participants	Clomiphene-resistant PCO infertile female undergoing induction of ovulation
Interventions	L-Carnitine 3 g plus 100 mg clomiphene citrate vs 150 mg of clomiphene citrate
Outcomes	Ovulation. Pregnancy.
Notes	Conference 28th Annual Meeting of European Society of Human Reproduction and Embryology (ESHRE), Turkey, 1-4 July. Record number 14424

Schachter 2007

Methods	Randomised controlled study
Participants	Women with insulin resistant PCOS
Interventions	These 102 patients were randomized before treatment, and after giving informed consent, assigned to one of four groups by opening sealed envelopes containing computer generated random assignation numbers. Group one (control) underwent infertility treatment only. Group-two underwent fertility treatment plus metformin, group three infertility treatment plus vitamin B, group 4 infertility treatment plus metformin plus vitamin B
Outcomes	Homocysteine levels Cumulative pregnancy rate
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

Agrawal 2012a

Trial name or title	Unknown.
Methods	Randomised controlled trial.
Participants	Subfertile women.
Interventions	Multiple micronutrients (MMN).
Outcomes	Unknown.
Starting date	2011.
Contact information	Dr. Rina Agrawal [rinaagrawal@aol.com].

Agrawal 2012a (*Continued*)

Notes	Email received regarding this trial 07.02.12.

Bentov 2010

Trial name or title	The Effect of Co-Enzyme Q10 Together With Fertility Drugs on Pregnancy Outcome of In Vitro Fertilization (CoQ10-IVF)
Methods	Study type: interventional randomised, parallel-assignment, double-blind (participant, caregiver, investigator)
Participants	35 years to 43 years. Inclusion criteria: • Age 35 to 43 years at the time of enrolment. • Diagnosis of primary infertility. Exclusion criteria: • Body mass index (BMI) > 38 kg/m^2. • Early follicular phase (days 2 to 4) serum FSH level > 20 mIU/mL. • Abnormal uterine cavity, as evidenced by sonohysterography or hysterosalpingography. • Current use of any systemic steroid medication or any infertility treatment within 3 months of study enrolment. • Any contraindication to being pregnant and carrying a pregnancy to term. • Contraindication to the use of CoQ10, Superfact, Puregon, hCG, Estrace and Progesterone suppositories. • Any ovarian or abdominal abnormality that may interfere with adequate TVS evaluation. • Absence of one or two ovaries. • Clinically relevant systemic disease (e.g. insulin-dependent diabetes, adrenal dysfunction, organic intracranial lesion, PCOS, hyperprolactinaemia, hypothalamic tumour) or serious illness (neoplasia). • History (within past 12 months) or current abuse of alcohol or drugs. • Administration of any investigational drugs within 3 months before study enrolment. • Any medical condition that may interfere with the absorption, distribution, metabolism or excretion of study drugs, gastrointestinal diseases, malabsorption syndromes and liver dysfunction. • Unexplained gynaecological bleeding. • Ejaculated sperm is not sufficient for ICSI. • Participant not able to communicate adequately with investigators and to comply with the requirements of the entire study. • Abnormal COH screening of blood done for both partners, including prolactin, thyroid-stimulating hormone, HIV serology, hepatitis B and C serology, rubella group and screen and syphilis serology, before participation in study. • Unwillingness to give written informed consent. Previous entry into this study or simultaneous participation in another clinical trial. • Concurrent use of any of the following drugs: ○ Daunorubicin, doxorubicin, blood pressure medications, warfarin, timolol, atorvastatin, cerivastatin, lovastatin, pravastatin, simvastatin gemfibrozil, tricyclic antidepressant medications (including amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline and trimipramine), multi-vitamins or any vitamin supplementation, except folic acid.
Interventions	Coenzyme Q10 versus placebo.

Bentov 2010 (*Continued*)

Outcomes	• Primary outcome measure will be the number and percentage of euploid eggs per retrieval. • Secondary outcome measures will include ovarian response, embryo quality, cumulative pregnancy rate/retrieval, cumulative live birth rate/retrieval and CoQ10 activity in saliva and follicular fluid by arNOX assay.
Starting date	11.01.10.
Contact information	Contact: Yaakov H. Bentov, Dr The Toronto Center for Advanced Reproductive Technology Toronto, Ontario, Canada, M5S 2X9 ph 416-972-0110 bentov@lunenfeld.ca; or Robert F. Casper, Dr 416-972-0777 RFCasper@aol.com
Notes	ClinicalTrials.gov identifier: NCT01048385.

Lindqvist 2009

Trial name or title	Vitamin D During In Vitro Fertilization (IVF)- A Prospective Randomized Trial Delivery
Methods	Randomised double-blind trial.
Participants	Target sample size: 1000 women older than 18 years of age initiating IVF treatment in Sweden
Interventions	Dietary supplementation: ergocalciferol (vitamin D), either high 100,000 U once or low-dose 500 U once
Outcomes	Biochemical pregnancy, live birth, take-home baby rate, OHSS and pregnancy complication rate (pregnancy, hypertension, SGA, diabetes)
Starting date	November 2009.
Contact information	Pelle G. Lindqvist Karolinska University Hospital Huddinge ClinicalTrials.gov identifier NCT01019785.
Notes	http://clinicaltrials.gov/ct2/show/NCT01019785?term=NCT01019785&rank=1

Mahdian 2012

Trial name or title	Impact of Calcium- Vitamin D Supplementation on Ovulation in Polycystic Ovary Syndrome
Methods	Randomisation: randomised. Blinding: double-blind. Placebo: used
Participants	Abnormal menstrual cycles (oligomenorrhoea or amenorrhoea); sonographically confirmed polycystic ovary; hyperandrogenism
Interventions	Intervention 1: In control group, participants do not receive routine administration of calcium-D combinations. Intervention 2: In intervention group, supplementary tablets of 1000 mg calcium combined with 400 IU vitamin D is administered (orally) twice a day for 3 months
Outcomes	Pregnancy. Timepoint: 2 and 12 weeks. Method of measurement: Sonography and Biochemistry Laboratory
Starting date	2012-01-21.
Contact information	Azadeh Mahdian Department of Obstetrics and Gynecology, Vali-e- Asr Hospital, Imam Khomeini Hospital Complex, Keshavarz Blv Tehran Iran, Islamic Republic of mahdian@razi.tums.ac.ir
Notes	

Mane 2012

Trial name or title	Nutritional Supplement for Women With Polycystic Ovary Syndrome or Subfertilty
Methods	Randomised, parallel-group, placebo-controlled trial. Method of generating randomisation sequence: computer-generated randomisation Method of allocation concealment: pre-numbered or coded identical Containers blinding and masking: participant- and investigator-blinded
Participants	Inclusion criteria: young women between 18 and 38 years of age with PCOS Presence of any two of the following parameters: (Roterdam criteria 2003) • Oligomenorrhoea and/or anovulation; and • Hyperandrogenism (clinical and/or biochemical) (Ferriman-Gallwey score > 8); biological (luteinising hormone (LH)/FSH ratio > 2). OR • Subfertile females; • Sexually active and male partner with potential to produce a child; • Polycystic ovaries with exclusion of other etiologies; • Women with normal uterine cavity; • Participants with impaired glucose tolerance or insulin resistance; and • Normal physical activity confirmed by physical and clinical examination, and routine laboratory tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), haematology, routine urinalysis and measurement of oral temperature and vital signs.

Mane 2012 (*Continued*)

Interventions	Intervention 1: multiple micro-nutrients supplementation: one Formula A tablet + one Formula B tablet together after main meal twice a day for 4 months. Ingredients Formula A: *N*-acetyl L-cysteine, elemental magnesium, zinc, iron, manganese, copper, selenium, iodine, chromium. Ingredients Formula B: inositol, vitamin C, para-amino-benzoic acid, vitamin E acetate, L-arginine, d-chiro-inositol, vitamin B complex. Control intervention 1: placebo tablets for Formula A: one tablet after main meal twice a day for 4 months. Control intervention 2: placebo tablets for Formula B: one tablet after main meal twice a day for 4 months
Outcomes	Improvement in overall status of PCOS or infertility. • Timepoint: days 30, 60, 90 and 120. Improvement in different parameters defining the status of PCOS or infertility like hormonal levels, insulin resistance, weight and safety of the therapy • Timepoint: days 30, 60, 90 and 120.
Starting date	31-08-2012.
Contact information	Dr Yashwant Mane Dr Yashwant Mane Atharva Infertilty and Test Tube Baby Center Jagir Complex Dwarka, Nasik, India 422011 Nashik, MAHARASHTRA India ph 02532598953 email drysmane7473@yahoo.co.in
Notes	

Mohammadbeigi 2011

Trial name or title	Effect of Calcium- Vitamin D in Efficacy of Induction-Ovulation in Infertile Women With Polycystic Ovary Syndrome
Methods	Randomised. Blinding: double-blind. Placebo: used. Assignment: parallel. Purpose: treatment.
Participants	Inclusion criteria: primary or secondary infertility due to PCOS Exclusion criteria: proven endocrine disease.
Interventions	Intervention 1: daily dose of 50 mg clomiphene tablet with 400 U vitamin D3 and 1000 mg calcium. Intervention 2: control group: daily dose of 50 mg clomiphene tablet with placebo

Mohammadbeigi 2011 (*Continued*)

Outcomes	Follicle size: • Timepoint: 60 days after the beginning of the study; • Method of measurement: sonography.
Starting date	22.05.2010.
Contact information	Robabeh Mohammadbeigi Address: Besat Hospital, Keshavarz Ave Sanandaj Iran, Islamic Republic of Telephone: 00989123106438 Email: robabe.mohammadbeigi@muk.ac.ir Affiliation: Kurdistan University of Medical Sciences
Notes	Funding: Kurdistan University of Medical Sciences.

Ortega 2013

Trial name or title	Effect of Resveratrol on Metabolic Parameters and Oocyte Quality in PCOS Patients (RES-IVF)
Methods	Randomised.
Participants	Women with PCOS.
Interventions	Resveratrol versus placebo.
Outcomes	Implantation. Pregnancy rates.
Starting date	February 2013.
Contact information	Israel Ortega, Medical doctor 91 180 2900 israel.ortega@ivi.es
Notes	Not yet recruiting. Madrid.

Pasha 2011

Trial name or title	The Effect of Calcium- Vitamin D and Metformin on Polycystic Ovarian Syndrome
Methods	Randomised. Blinding: single-blind. Assignment: parallel.
Participants	Age 18 to 35 years. PCOS. Condition 2: female infertility associated with anovulation.

Pasha 2011 (*Continued*)

	Inclusion criteria: • Reproductive age range 18 to 35 years; and • According to the Rotterdam criteria, the presence of two of the three following characteristics was required for inclusion in the study: ○ Oligomenorrhoea/amenorrhoea; ○ Chemical or clinical findings of hyperandrogenism; or ○ Polycystic ovaries on transvaginal sonography. Exclusion criteria: Patients with systemic diseases such as Cushing's syndrome, hyperparathyroidism or hyperprolactinaemia, androgen-secreting tumours, history of abdominal/pelvic surgery, coexisting male factor infertility, or abnormal hysterosalpingography were excluded from the study
Interventions	Intervention 1: Metformin 1500 mg/d for three months. Intervention 2: Calcium (1000 m) + vitamin D 400 IU for three months Intervention 3: Calcium (1000 m) + vitamin D 400 IU + metformin 1500 mg/d for three months
Outcomes	Calcium and vitamin D: • Timepoint: after three months; • Method of measurement: laboratory. Follicular growth: • Timepoint: after three months; • Method of measurement: ultrasound. Regulating menstruation: • Timepoint: after three months; • Method of measurement: 35-21 day intervals with standard. Pregnancy rate: • Timepoint: after three months; • Method of measurement: ultrasound.
Starting date	23.09.2010.
Contact information	Nargess Gholizadeh Pasha Address: Fatemehzahra Fertility & Reproductive Health Research Center Noshirvani Street 4719173716 Babol Iran, Islamic Republic of Telephone: 00981112274881 Email: ngh_pa@yahoo.com Affiliation: Fatemehzahra Fertility & Reproductive Health Research Center
Notes	IRCT201009131760N9 http://apps.who.int/trialsearch/Trial.aspx?TrialID=IRCT201009131760N9 http://www.irct.ir/searchresult.php?id=1760&number=9

Pourghassem 2010

Trial name or title	Effect of Vitamin D3 Supplementation on Polycystic Ovarian Syndrome
Methods	Randomised. Blinding: double-blind. Placebo: used.

Pourghassem 2010 (*Continued*)

	Assignment: parallel. Purpose: treatment.
Participants	Inclusion criteria: PCOS, diagnosis of PCOS based on Rotterdam criteria (presence of two of the three following characteristics): • Oligomenorrhoea/amenorrhoea; • Chemical or clinical finding of hyperandrogenism; and • Polycystic appearance of ovary; Voluntary consent for participation in the study, age of 16 to 40 years Gender: female. Exclusion criteria: other common causes of hyperandrogenaemia and/or anovulation; hyperprolactinaemia; congenital adrenal hyperplasia; Cushing's syndrome; virilising ovarian or adrenal tumours; diabetes mellitus; heart, kidney and liver dysfunction; use of vitamin D or calcium supplement, metformin or insulin-sensitising drugs; corticosteroids or anticonvulsants during last 2 months or during the study; smoking; alcohol abuse; breast-feeding and pregnancy Age minimum: 18 years. Age maximum: 40 years.
Interventions	Intervention 1: 50,000 IU vitamin D3 every 20 days for 60 days Intervention 2: control group: placebo every 20 days for 60 days
Outcomes	Improvement in glycaemic parameters: • Timepoint: 60 days; • Method of measurement: serum level of blood sugar and fasting Insulin. Lipid profile and high-sensitivity C-reactive protein (hs-CRP): • Timepoint: 60 days; • Method of measurement: serum level of high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TG), apolipoprotein A (ApoA)1, hs-CRP. Serum level of 25(OH)-D and parathyroid hormone: • Timepoint: 60 days; • Method of measurement: serum level of 25(OH)-D and parathyroid hormone. Anthropometric indicators (body mass index (BMI)): • Timepoint: 60 days; • Method of measurement: Body weight without shoes with calibrated scale and standing height without shoes are measured. BMI was calculated with this equation: W (kg)/H $(m)^2$. Dietary regime: • Timepoint: 60 days; • Method of measurement: 3 days, 24-hour dietary recall.
Starting date	2010-04-19.
Contact information	Name: Bahram Pourghassem Address: Health and Nutrition Faculty of Tabriz Tabriz Iran, Islamic Republic of Telephone: 00984113357580 Email: pourghassemb@tbzmed.ac.ir & bahrampg@yahoo.com Affiliation: Health and Nutrition Faculty, Tabriz University of Medical Sciences

Pourghassem 2010 (*Continued*)

Notes	

Unfer 2010

Trial name or title	Improving Oocyte Retrieval Using a Combined Therapy of Recombinant Follicle-Stimulating Hormone (rFSH) and Inositol and Melatonin
Methods	Randomised double-blinded (participant, investigator) controlled trial
Participants	Women 18 years to 39 years undergoing assisted reproductive techniques (ART) because of male infertility BMI 18 to 30 kg/m^2. Fewer than 3 prior oocyte retrievals. No fertility problems.
Interventions	Recombinant FSH: 225 IU rFSH. Drug: recombinant FSH (rFSH) 225 IU. Experimental: recombinant FSH inositol melatonin. 225 IU rFSH, 4 g inositol and 3 mg melatonin dietary supplement: rFSH + inositol + melatonin 225 IU rFSH, 4 g inositol, 3 mg melatonin.
Outcomes	Primary: total number of oocytes, number of clinical pregnancies, live birth rate
Starting date	December 2010.
Contact information	Vittorio Unfer, MD +39 0640500835 vunfer@gmail.com Gianfranco Carlomagno, PhD gianfranco.carlomagno@gmail.com University of Modena and Reggio Emilia Recruiting Reggio Emilia, Italy, 42100 Contact: Giovanni Battista La Sala, MD +39 0522 296464 giovanni.lasala@asmn.re.it Principal investigator: Giovanni Battista La Sala, MD Research Center for Reproductive Medicine Villa Mafalda Recruiting Roma, Italy, 00199
Notes	May not become an included study because all women are fertile, but they have subfertile male partners ClinicalTrials.gov Identifier: NCT01267604. Recruiting. Trial found on clinicaltrials.gov on 07.08.12.

Unfer 2011a

Trial name or title	Role of Myo-inositol and D-chiro-inositol on Oocyte Quality.
Methods	Allocation: randomised. Endpoint classification: efficacy study. Intervention model: parallel assignment. Masking: double-blind (participant, investigator).
Participants	Inclusion criteria: • Women undergoing IVF treatments; • Body mass index < 28; • FSH < 10 IU/L; • Normal uterine cavity, anatomy and functions.
Interventions	Dietary supplement: d-chiro-inositol. Dietary supplement: myo-inositol.
Outcomes	Number of grade 1 embryos. Number of morphologically mature oocytes. Total international units (IU) of recombinant FSH administered
Starting date	September 2011.
Contact information	Gianfranco Carlomagno, PhD AGUNCO Obstetrics and Gynecology Centre Vittorio Unfer, MD AGUNCO Obstetrics and Gynecology Centre Franco Lisi, MD Research Center for Reproductive Medicine
Notes	? same trial as Carlomagno G, Montanino OM, Roseff SJ, Unfer V. Myo-inositol: ovarian stimulation and IVF outcomes. Fertility and Sterility 2012;98(Suppl 1):S74-S75. Abstract no: O-251. Currently in 'Studies awaiting classification'.

Youssef 2011

Trial name or title	Can Antioxidant Supplementation Improve ICSI/IVF Outcomes in Women Undergoing IVF/ICSI Treatment Cycles? Randomised Controlled Study. NTR2816
Methods	Randomised: yes. Masking: none. Control: not applicable. Group: parallel. Type: 2 or more arms, randomised.
Participants	Inclusion criteria: • Female age 18 to 45 years; • Menstrual cycles between 25 and 34 days;

	• Absence of uterine abnormalities; and • Has an indication for IVF/ICSI. Exclusion criteria: poor sperm quality with counts less than 1 million or azoospermia
Interventions	At the start of downregulation treatment or previous cycle preceding the IVF cycle, participants will be randomly assigned into two groups. The antioxidant group (study group) will receive oral antioxidant medication (Octatron) 2 tablets/d up to the pregnancy test: • Ovarian stimulation will be initiated with HP-FSH (HP FSH; Fostimon; IBSA, Egypt) from cycle day 2 or 3 and continued until the day of ovulation induction. A fixed dose of HP-FSH will be used, 225 IU to 300 IU per day for the first 5 days, according to age, body mass index, basal FSH level and antral follicle count. After 5 days, doses will be adjusted according to ovarian response; • Different downregulation protocols will be used daily mid-luteal long GnRH protocol, 1 mg, SC, Decapeptyl (Ferring) or flexible GnRH antagonist ganirelix (Cetrotide 0.25 mg; Organon) is initiated and continued up to and including the day of ovulation induction; and • When at least two follicles reach a size of 18 mm, both groups will receive hCG (10,000 IU SC) for final oocyte maturation, followed by OPU 34 to 36 hours later.
Outcomes	Number of retrieved oocytes. Number of mature oocytes. Number of embryos obtained. Implantation rate. Biochemical and clinical pregnancy rates. Duration of stimulation. Amount of FSH and number of adverse events.
Starting date	01.03.11.
Contact information	Mohamed A.F Youssef Post Office Box 109, Dept. Obstetrics and Gynaecology, Kasr-Alainy Hospitals, Faculty of Medicine-Cairo University, Elmalek Al Saleh 11559 Cairo Egypt ph +20 2148088826 mmfatah@yahoo.com / m.a.youssef@amc.uva.nl
Notes	Main trial ID NTR2816 http://apps.who.int/trialsearch/Trial.aspx?TrialID=NTR2816 Recruiting. Same trial as included in conference abstract Aboulfoutouh 2011.

DATA AND ANALYSES

Comparison 1. Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	2	97	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.19, 8.26]
1.1 Placebo	2	97	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.19, 8.26]
2 Live birth; type of antioxidant	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 N-acetyl-cysteine	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.87 [1.05, 7.84]
2.2 L-arginine	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.10, 2.00]
3 Live birth; indications for subfertility	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Polycystic ovary syndrome	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.87 [1.05, 7.84]
3.2 Tubal subfertility	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.10, 2.00]
4 Live birth; IVF/ICSI	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.10, 2.00]
5 Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	13	2441	Odds Ratio (M-H, Random, 95% CI)	1.30 [0.92, 1.85]
5.1 Placebo	6	1763	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.69, 2.61]
5.2 No treatment/standard treatment	7	678	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.98, 1.92]
6 Clinical pregnancy; type of antioxidant	13		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 N-acetyl-cysteine	3	1014	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.80, 1.53]
6.2 Combined antioxidants	3	369	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [1.07, 2.58]
6.3 Melatonin	2	145	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.65, 2.60]
6.4 Vitamin E	1	103	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.50, 4.00]
6.5 Ascorbic acid	1	619	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.49, 1.14]
6.6 L-arginine	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.10, 2.00]
6.7 Myo-inositol plus folic acid	2	154	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.60, 2.48]
7 Clinical pregnancy; indications for subfertility	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Polycystic ovary syndrome	3	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.40 [1.84, 6.29]
7.2 Unexplained	3	967	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.59, 1.14]
7.3 Tubal subfertility	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.10, 2.00]
7.4 Varying indications	5	1073	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.85, 1.52]
8 Clinical pregnancy; IVF/ICSI	7	1173	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.74, 1.27]
9 Adverse events	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Miscarriage	8	1456	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.57, 1.36]
9.2 Multiple pregnancy	2	1022	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.41, 1.21]

9.3 Gastrointestinal disturbances	1	93	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.14 [0.29, 15.99]
9.4 Ectopic pregnancy	1	58	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.91 [0.14, 349.18]

Comparison 2. Head to head antioxidants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments)	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.44 [1.27, 9.34]
1.1 Myo-Inositol versus d-chiro-inositol	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.44 [1.27, 9.34]
2 Live birth; indications for subfertility	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Polycystic ovary syndrome	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.44 [1.27, 9.34]
3 Live birth; IVF/ICSI	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.44 [1.27, 9.34]
4 Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Myo-Inositol versus d-chiro-inositol	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.44 [1.27, 9.34]
4.2 Myo-inositol plus folic acid plus melatonin versus myo-inositol plus folic acid	1	65	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.65, 5.25]
5 Clinical pregnancy; indications for subfertility	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Polycystic ovary syndrome	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.44 [1.27, 9.34]
5.2 Poor responders	1	65	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.65, 5.25]
6 Clinical pregnancy; IVF/ICSI	2	149	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.56 [1.24, 5.26]
7 Adverse events	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Miscarriage	2	149	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.35, 4.04]

Comparison 3. Pentoxifylline versus placebo or no treatment/standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]
1.1 No treatment/standard treatment	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]

2 Live birth; type of antioxidant	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]
2.1 Pentoxifylline plus vitamin E	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]
3 Live birth; indications for subfertility	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]
3.1 Varying indications	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]
4 Live birth; IVF/ICSI	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.68, 3.44]
5 Clinical pregnancy; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.19, 3.44]
5.1 Placebo	2	164	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.95, 4.33]
5.2 No treatment	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [0.97, 4.25]
6 Clinical pregnancy; type of antioxidant	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Pentoxifylline	2	164	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.95, 4.33]
6.2 Pentoxifylline plus vitamin E	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [0.97, 4.25]
7 Clinical pregnancy; indications for subfertility	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Endometriosis	2	164	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.95, 4.33]
7.2 Varying indications	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [0.97, 4.25]
8 Clinical pregnancy; IVF/ICSI	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [0.97, 4.25]
9 Adverse events	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Miscarriage	3	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.46, 4.05]
9.2 Multiple pregnancy	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.20, 3.06]
9.3 Ectopic pregnancy	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [0.20, 19.35]

Analysis 1.1. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 1 Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 1 Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)

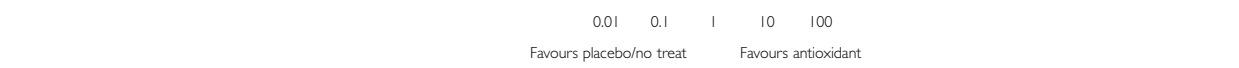
Study or subgroup	Favours antioxidant n/N	Placebo/No treatment n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Placebo					
Battaglia 2002 (1)	3/18	6/19		45.3 %	0.43 [0.09, 2.09]
Nasr 2010 (2)	20/30	12/30		54.7 %	3.00 [1.05, 8.60]
Total (95% CI)	**48**	**49**		**100.0 %**	**1.25 [0.19, 8.26]**

Total events: 23 (Favours antioxidant), 18 (Placebo/No treatment)

Heterogeneity: $Tau^2 = 1.41$; $Chi^2 = 4.02$, df = 1 (P = 0.04); $I^2 = 75\%$

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable



(1) Women are also undergoing IVF/ICSI

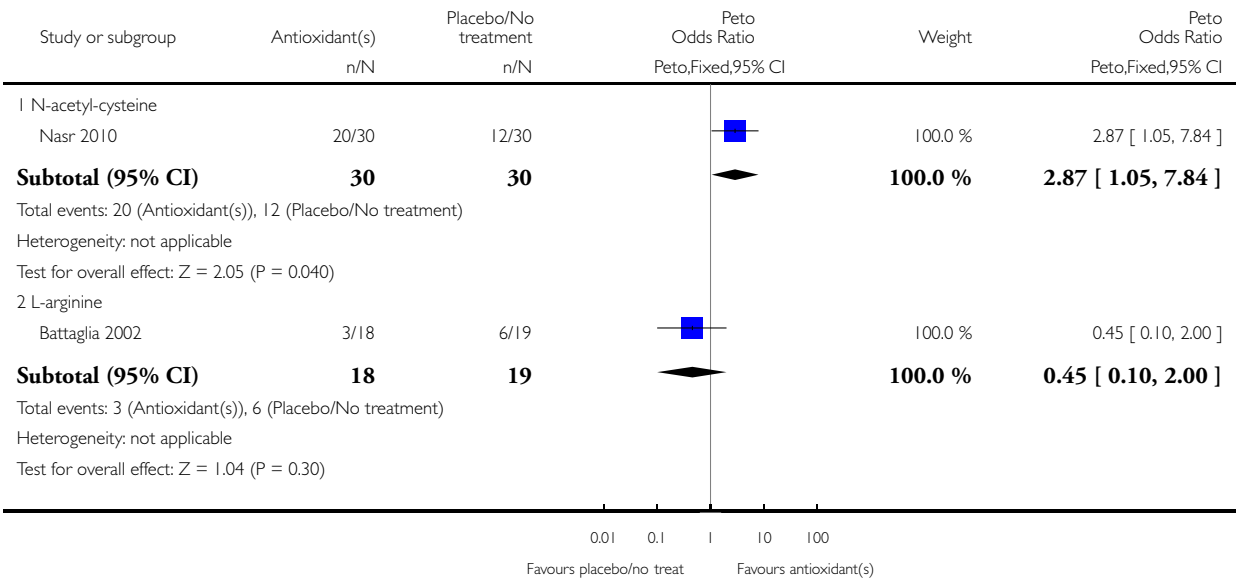
(2) Women are also undergoing laparoscopic ovarian drilling

Analysis 1.2. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 2 Live birth; type of antioxidant.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 2 Live birth; type of antioxidant



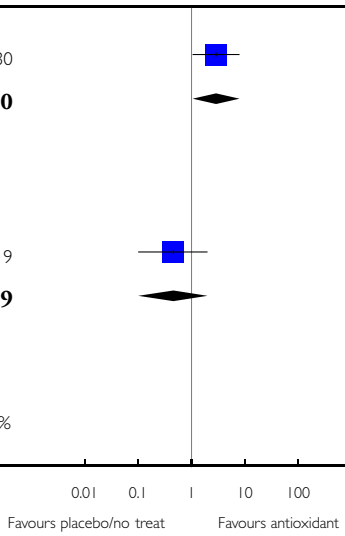
Analysis 1.3. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 3 Live birth; indications for subfertility.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 3 Live birth; indications for subfertility

Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Polycystic ovary syndrome					
Nasr 2010	20/30	12/30		100.0 %	2.87 [1.05, 7.84]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**2.87 [1.05, 7.84]**
Total events: 20 (Antioxidant(s)), 12 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.040)					
2 Tubal subfertility					
Battaglia 2002	3/18	6/19		100.0 %	0.45 [0.10, 2.00]
Subtotal (95% CI)	**18**	**19**		**100.0 %**	**0.45 [0.10, 2.00]**
Total events: 3 (Antioxidant(s)), 6 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Test for subgroup differences: Chi^2 = 4.06, df = 1 (P = 0.04), I^2 =75%					



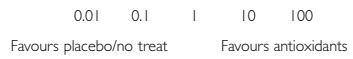
Analysis 1.4. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 4 Live birth; IVF/ICSI.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 4 Live birth; IVF/ICSI

Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Battaglia 2002	3/18	6/19		100.0 %	0.45 [0.10, 2.00]
Total (95% CI)	**18**	**19**		**100.0 %**	**0.45 [0.10, 2.00]**
Total events: 3 (Antioxidant(s)), 6 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
Test for subgroup differences: Not applicable					



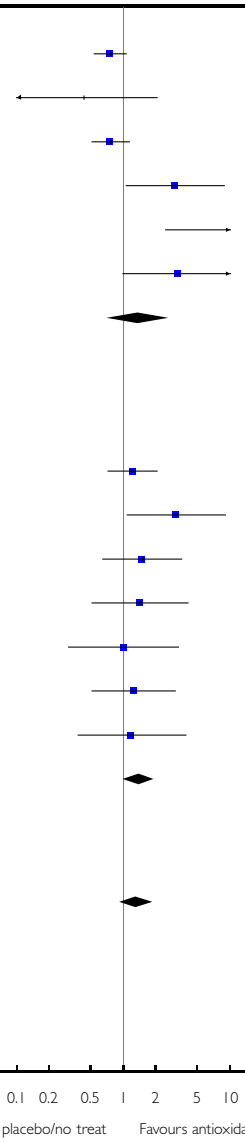
Analysis 1.5. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 5 Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 5 Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)

Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Placebo					
Badawy 2006 (1)	63/404	79/400		14.6 %	0.75 [0.52, 1.08]
Battaglia 2002	3/18	6/19		3.9 %	0.43 [0.09, 2.09]
Griesinger 2002 (2)	104/461	44/158		14.0 %	0.75 [0.50, 1.14]
Nasr 2010	21/30	13/30		6.7 %	3.05 [1.05, 8.84]
Rizk 2005 (3)	16/75	0/75		1.4 %	41.87 [2.46, 712.37]
Westphal 2006 (4)	14/53	4/40		5.7 %	3.23 [0.97, 10.73]
Subtotal (95% CI)	**1041**	**722**		**46.3 %**	**1.34 [0.69, 2.61]**
Total events: 221 (Antioxidant(s)), 146 (Placebo/No treatment)					
Heterogeneity: Tau^2 = 0.40; Chi^2 = 19.79, df = 5 (P = 0.001); I^2 =75%					
Test for overall effect: Z = 0.86 (P = 0.39)					
2 No treatment/standard treatment					
Aboulfoutouh 2011	43/112	36/106		12.1 %	1.21 [0.70, 2.11]
Agrawal 2012 (5)	20/30	11/28		6.6 %	3.09 [1.06, 9.04]
Batioglu 2012	20/40	18/45		8.5 %	1.50 [0.63, 3.55]
Cicek 2012	10/53	7/50		6.8 %	1.43 [0.50, 4.10]
Eryilmaz 2011	7/30	7/30		5.8 %	1.00 [0.30, 3.31]
Lisi 2012	14/47	12/47		8.1 %	1.24 [0.50, 3.06]
Papaleo 2009	8/30	7/30		5.9 %	1.19 [0.37, 3.85]
Subtotal (95% CI)	**342**	**336**		**53.7 %**	**1.37 [0.98, 1.92]**
Total events: 122 (Antioxidant(s)), 98 (Placebo/No treatment)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.81, df = 6 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 1.87 (P = 0.062)					
Total (95% CI)	**1383**	**1058**		**100.0 %**	**1.30 [0.92, 1.85]**
Total events: 343 (Antioxidant(s)), 244 (Placebo/No treatment)					
Heterogeneity: Tau^2 = 0.19; Chi^2 = 26.46, df = 12 (P = 0.01); I^2 =55%					
Test for overall effect: Z = 1.48 (P = 0.14)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%					



(1) The treatment and control in Badawy 2006 was N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate

(2) Griesinger 2002: The three active arms versus placebo of this trial have been pooled.

(3) The treatment and control in Rizk 2005 was N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate

(4) Women are conceiving naturally and the combined antioxidants included chaste berry, green tea extracts, L-arginine, Vitamins - E, B6, B12, folate, iron, magnesium, zinc and selenium

(5) Agrawal 2012, Lisi 2012 and Papaleo 2009 all use folic acid 400 mcg (standard care) as control

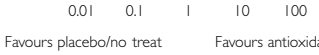
Analysis 1.6. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 6 Clinical pregnancy; type of antioxidant.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 6 Clinical pregnancy; type of antioxidant

Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 N-acetyl-cysteine					
Badawy 2006 (1)	63/404	79/400		79.9 %	0.75 [0.52, 1.08]
Nasr 2010	21/30	13/30		10.2 %	2.91 [1.06, 8.01]
Rizk 2005 (2)	16/75	0/75		9.8 %	9.24 [3.29, 25.98]
Subtotal (95% CI)	**509**	**505**		**100.0 %**	**1.10 [0.80, 1.53]**
Total events: 100 (Antioxidant(s)), 92 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 24.08, df = 2 (P<0.00001); I^2 =92%					
Test for overall effect: Z = 0.60 (P = 0.55)					
2 Combined antioxidants					
Aboulfoutouh 2011	43/112	36/106		63.5 %	1.21 [0.70, 2.10]
Agrawal 2012	20/30	11/28		18.4 %	2.95 [1.06, 8.21]
Westphal 2006 (3)	14/53	4/40		18.1 %	2.83 [1.01, 7.96]
Subtotal (95% CI)	**195**	**174**		**100.0 %**	**1.66 [1.07, 2.58]**
Total events: 77 (Antioxidant(s)), 51 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 3.50, df = 2 (P = 0.17); I^2 =43%					
Test for overall effect: Z = 2.27 (P = 0.023)					
3 Melatonin					
Batioglu 2012	20/40	18/45		66.0 %	1.49 [0.64, 3.50]



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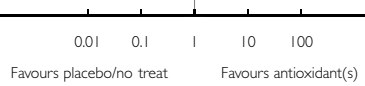
Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Eryilmaz 2011	7/30	7/30		34.0 %	1.00 [0.31, 3.28]
Subtotal (95% CI)	**70**	**75**		**100.0 %**	**1.30 [0.65, 2.60]**
Total events: 27 (Antioxidant(s)), 25 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.75 (P = 0.45)					
4 Vitamin E					
Cicek 2012	10/53	7/50		100.0 %	1.42 [0.50, 4.00]
Subtotal (95% CI)	**53**	**50**		**100.0 %**	**1.42 [0.50, 4.00]**
Total events: 10 (Antioxidant(s)), 7 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
5 Ascorbic acid					
Griesinger 2002 (4)	104/461	44/158		100.0 %	0.75 [0.49, 1.14]
Subtotal (95% CI)	**461**	**158**		**100.0 %**	**0.75 [0.49, 1.14]**
Total events: 104 (Antioxidant(s)), 44 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
6 L-arginine					
Battaglia 2002	3/18	6/19		100.0 %	0.45 [0.10, 2.00]
Subtotal (95% CI)	**18**	**19**		**100.0 %**	**0.45 [0.10, 2.00]**
Total events: 3 (Antioxidant(s)), 6 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
7 Myo-inositol plus folic acid					
Lisi 2012	14/47	12/47		62.4 %	1.23 [0.50, 3.03]
Papaleo 2009	8/30	7/30		37.6 %	1.19 [0.37, 3.80]
Subtotal (95% CI)	**77**	**77**		**100.0 %**	**1.22 [0.60, 2.48]**
Total events: 22 (Antioxidant(s)), 19 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 0.54 (P = 0.59)					
Test for subgroup differences: Chi^2 = 8.46, df = 6 (P = 0.21), I^2 =29%					



(1) The treatment and control in Badawy 2006 was N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate

(2) The treatment and control in Rizk 2005 was N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate

(3) Combined antioxidants included chaste berry, green tea extracts, L-arginine, Vitamins - E, B6, B12, folate, iron, magnesium, zinc and selenium

(4) Griesinger 2002: The three active arms versus placebo of this trial have been pooled.

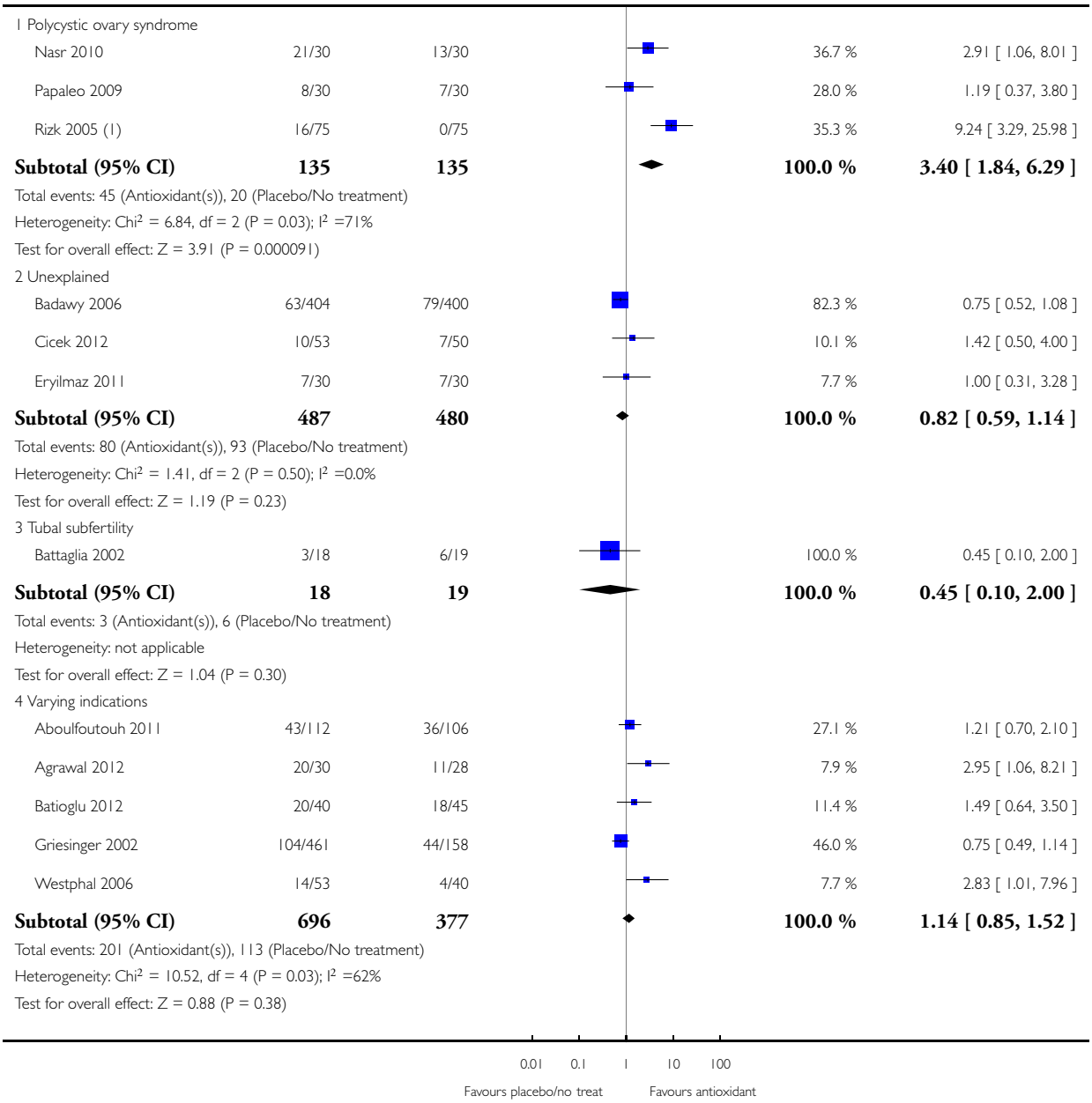
Analysis 1.7. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 7 Clinical pregnancy; indications for subfertility.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 7 Clinical pregnancy; indications for subfertility

Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Polycystic ovary syndrome					
Nasr 2010	21/30	13/30		36.7 %	2.91 [1.06, 8.01]
Papaleo 2009	8/30	7/30		28.0 %	1.19 [0.37, 3.80]
Rizk 2005 (1)	16/75	0/75		35.3 %	9.24 [3.29, 25.98]
Subtotal (95% CI)	**135**	**135**		**100.0 %**	**3.40 [1.84, 6.29]**
Total events: 45 (Antioxidant(s)), 20 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 6.84, df = 2 (P = 0.03); I^2 =71%					
Test for overall effect: Z = 3.91 (P = 0.000091)					
2 Unexplained					
Badawy 2006	63/404	79/400		82.3 %	0.75 [0.52, 1.08]
Cicek 2012	10/53	7/50		10.1 %	1.42 [0.50, 4.00]
Eryilmaz 2011	7/30	7/30		7.7 %	1.00 [0.31, 3.28]
Subtotal (95% CI)	**487**	**480**		**100.0 %**	**0.82 [0.59, 1.14]**
Total events: 80 (Antioxidant(s)), 93 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 1.41, df = 2 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 1.19 (P = 0.23)					
3 Tubal subfertility					
Battaglia 2002	3/18	6/19		100.0 %	0.45 [0.10, 2.00]
Subtotal (95% CI)	**18**	**19**		**100.0 %**	**0.45 [0.10, 2.00]**
Total events: 3 (Antioxidant(s)), 6 (Placebo/No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
4 Varying indications					
Aboulfoutouh 2011	43/112	36/106		27.1 %	1.21 [0.70, 2.10]
Agrawal 2012	20/30	11/28		7.9 %	2.95 [1.06, 8.21]
Batioglu 2012	20/40	18/45		11.4 %	1.49 [0.64, 3.50]
Griesinger 2002	104/461	44/158		46.0 %	0.75 [0.49, 1.14]
Westphal 2006	14/53	4/40		7.7 %	2.83 [1.01, 7.96]
Subtotal (95% CI)	**696**	**377**		**100.0 %**	**1.14 [0.85, 1.52]**
Total events: 201 (Antioxidant(s)), 113 (Placebo/No treatment)					
Heterogeneity: Chi^2 = 10.52, df = 4 (P = 0.03); I^2 =62%					
Test for overall effect: Z = 0.88 (P = 0.38)					



(1) The treatment and control in Rizk 2005 was N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate

Analysis 1.8. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 8 Clinical pregnancy; IVF/ICSI.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 8 Clinical pregnancy; IVF/ICSI

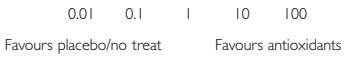
Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Aboulfoutouh 2011	43/112	36/106		24.6 %	1.21 [0.70, 2.10]
Batioglu 2012	20/40	18/45		10.3 %	1.49 [0.64, 3.50]
Battaglia 2002	3/18	6/19		3.4 %	0.45 [0.10, 2.00]
Eryilmaz 2011	7/30	7/30		5.3 %	1.00 [0.31, 3.28]
Griesinger 2002 (1)	104/461	44/158		41.7 %	0.75 [0.49, 1.14]
Lisi 2012	14/47	12/47		9.2 %	1.23 [0.50, 3.03]
Papaleo 2009	8/30	7/30		5.6 %	1.19 [0.37, 3.80]
Total (95% CI)	**738**	**435**		**100.0 %**	**0.97 [0.74, 1.27]**

Total events: 199 (Antioxidant(s)), 130 (Placebo/No treatment)

Heterogeneity: Chi^2 = 4.45, df = 6 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable



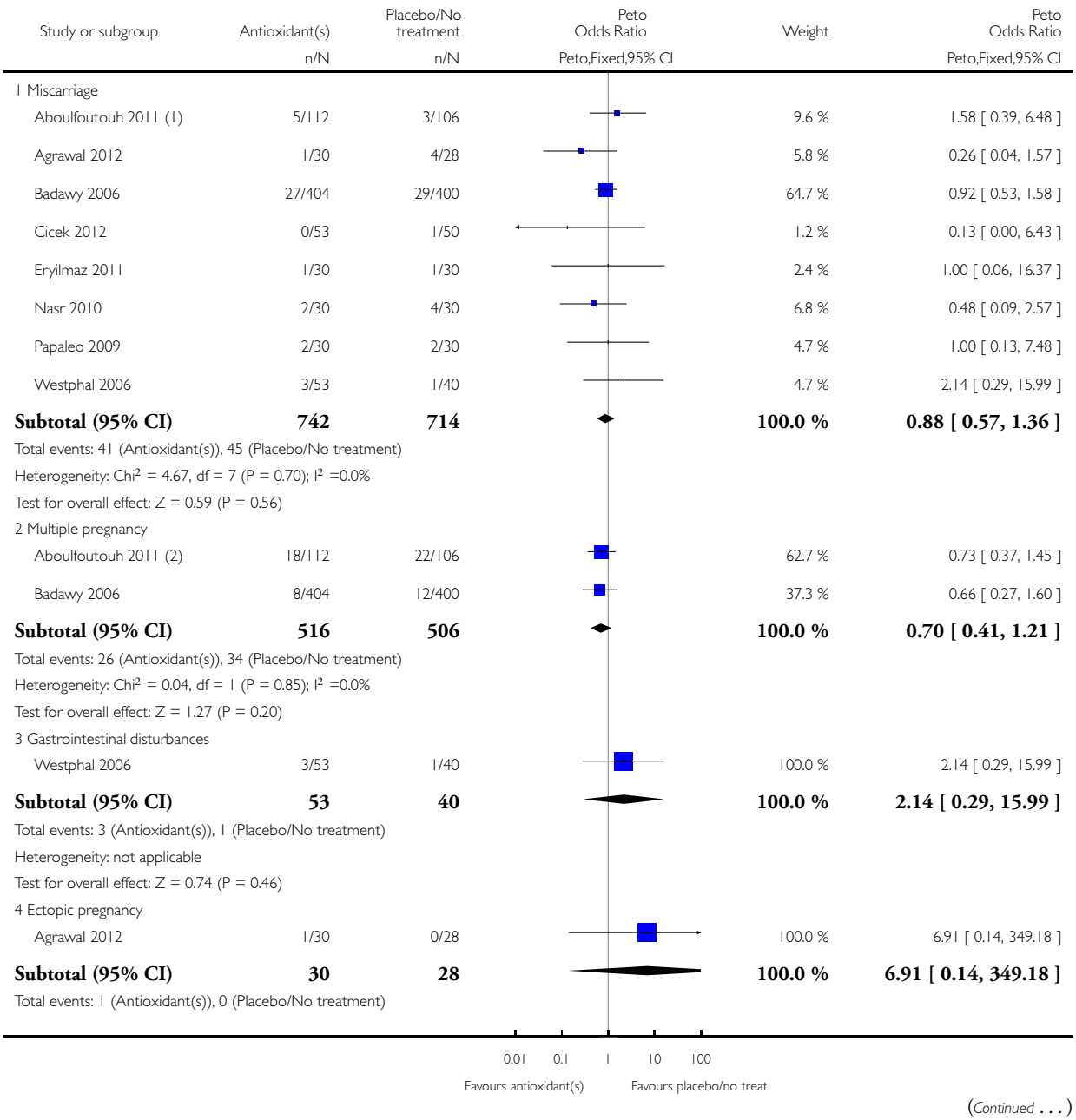
(1) Griesinger 2002: three active arms of this trial have been pooled versus placebo

Analysis 1.9. Comparison 1 Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 9 Adverse events.

Review: Antioxidants for female subfertility

Comparison: 1 Antioxidant(s) versus placebo or no treatment/standard treatment

Outcome: 9 Adverse events



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Study or subgroup	Antioxidant(s) n/N	Placebo/No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: Chi² = 2.39, df = 3 (P = 0.50), I² =0.0%					

(1) Rizk 2005 also reported on miscarriage (2 miscarriages in the treatment group (n=75) and 0 in the control (n=75)) but data not pooled as no pregnancies in the control group

(2) Rizk 2005 also reported on multiple pregnancy (5 multiples in the treatment group (n=75) and 0 in the control (n=75)) but data not pooled as no pregnancies in the control group

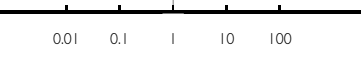
Analysis 2.1. Comparison 2 Head to head antioxidants, Outcome 1 Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments).

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 1 Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments)

Study or subgroup	Antioxidant a n/N	Antioxidant b n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Myo-Inositol versus d-chiro-inositol					
Unfer 2011 (1)	15/43	5/41		100.0 %	3.44 [1.27, 9.34]
Total (95% CI)	**43**	**41**		**100.0 %**	**3.44 [1.27, 9.34]**
Total events: 15 (Antioxidant a), 5 (Antioxidant b)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.43 (P = 0.015)					
Test for subgroup differences: Not applicable					



(1) Women are undergiong IVF/ICSI

Analysis 2.2. Comparison 2 Head to head antioxidants, Outcome 2 Live birth; indications for subfertility.

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 2 Live birth; indications for subfertility

Study or subgroup	Antioxidant a n/N	Antioxidant b n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Polycystic ovary syndrome					
Unfer 2011	15/43	5/41		100.0 %	3.44 [1.27, 9.34]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**3.44 [1.27, 9.34]**
Total events: 15 (Antioxidant a), 5 (Antioxidant b)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.43 (P = 0.015)					
Test for subgroup differences: Not applicable					

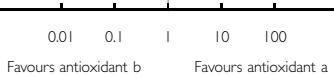
Analysis 2.3. Comparison 2 Head to head antioxidants, Outcome 3 Live birth; IVF/ICSI.

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 3 Live birth; IVF/ICSI

Study or subgroup	Antioxidant a n/N	Antioxidant b n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Unfer 2011	15/43	5/41		100.0 %	3.44 [1.27, 9.34]
Total (95% CI)	**43**	**41**		**100.0 %**	**3.44 [1.27, 9.34]**
Total events: 15 (Antioxidant a), 5 (Antioxidant b)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.43 (P = 0.015)					
Test for subgroup differences: Not applicable					

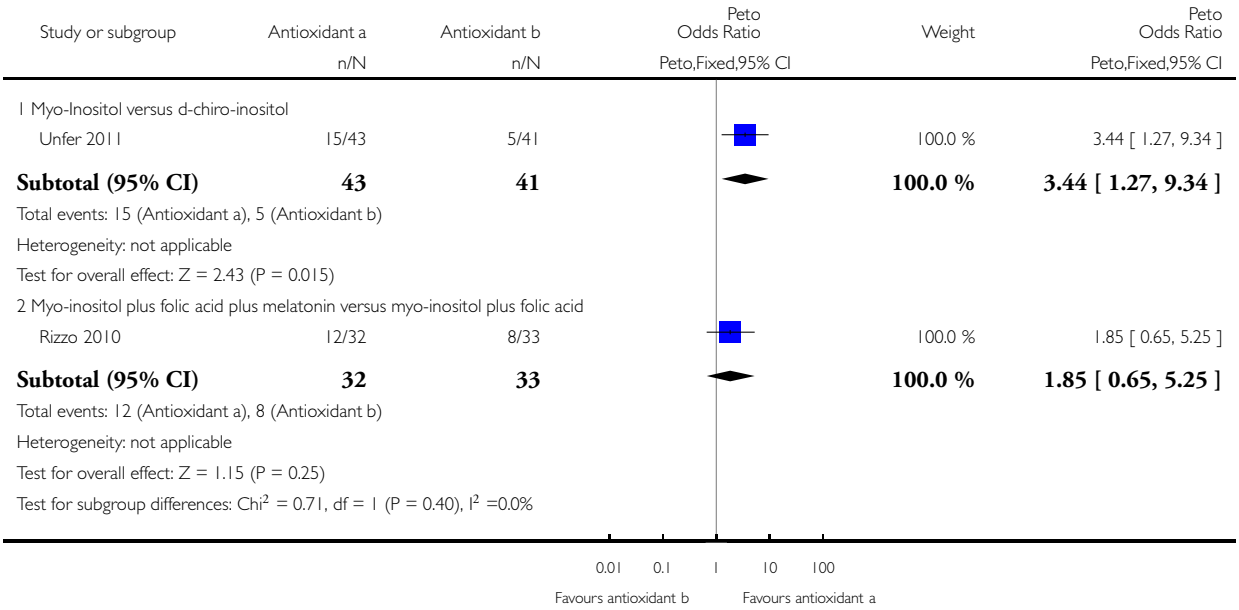


Analysis 2.4. Comparison 2 Head to head antioxidants, Outcome 4 Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments).

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 4 Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments)



Analysis 2.5. Comparison 2 Head to head antioxidants, Outcome 5 Clinical pregnancy; indications for subfertility.

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 5 Clinical pregnancy; indications for subfertility

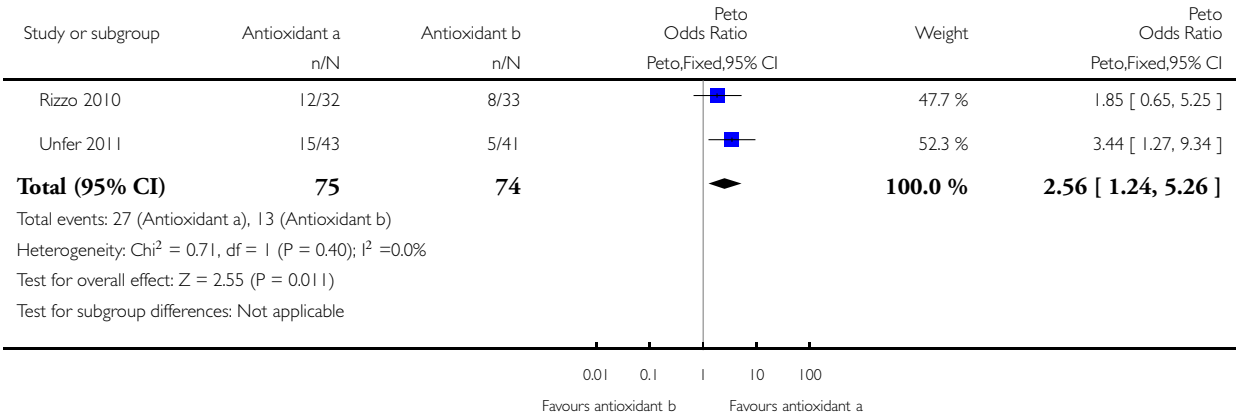
Study or subgroup	Antioxidant a n/N	Antioxidant b n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Polycystic ovary syndrome					
Unfer 2011	15/43	5/41		100.0 %	3.44 [1.27, 9.34]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**3.44 [1.27, 9.34]**
Total events: 15 (Antioxidant a), 5 (Antioxidant b)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.43 (P = 0.015)					
2 Poor responders					
Rizzo 2010	12/32	8/33		100.0 %	1.85 [0.65, 5.25]
Subtotal (95% CI)	**32**	**33**		**100.0 %**	**1.85 [0.65, 5.25]**
Total events: 12 (Antioxidant a), 8 (Antioxidant b)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Chi^2 = 0.71, df = 1 (P = 0.40), I^2 =0.0%					

Analysis 2.6. Comparison 2 Head to head antioxidants, Outcome 6 Clinical pregnancy; IVF/ICSI.

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 6 Clinical pregnancy; IVF/ICSI

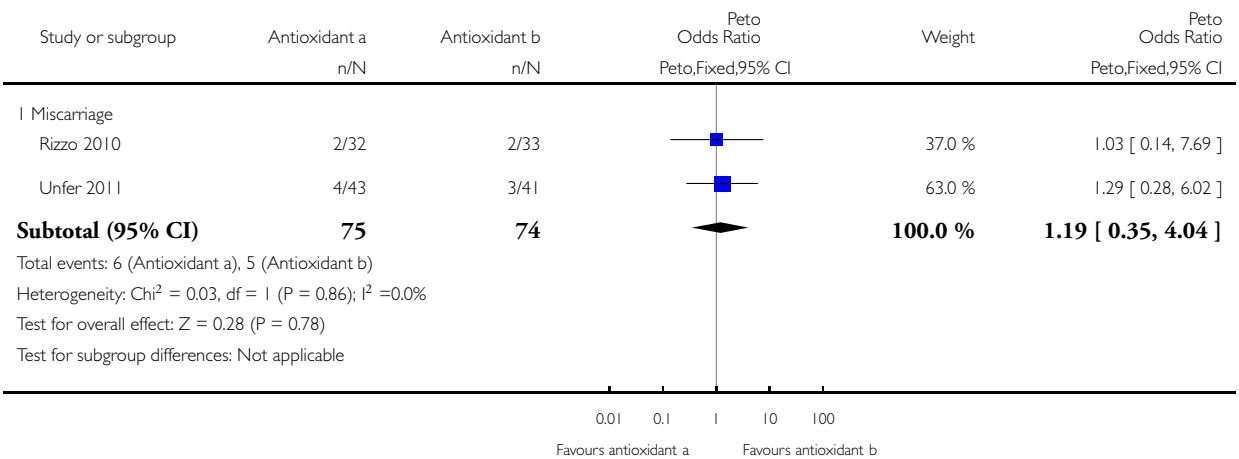


Analysis 2.7. Comparison 2 Head to head antioxidants, Outcome 7 Adverse events.

Review: Antioxidants for female subfertility

Comparison: 2 Head to head antioxidants

Outcome: 7 Adverse events

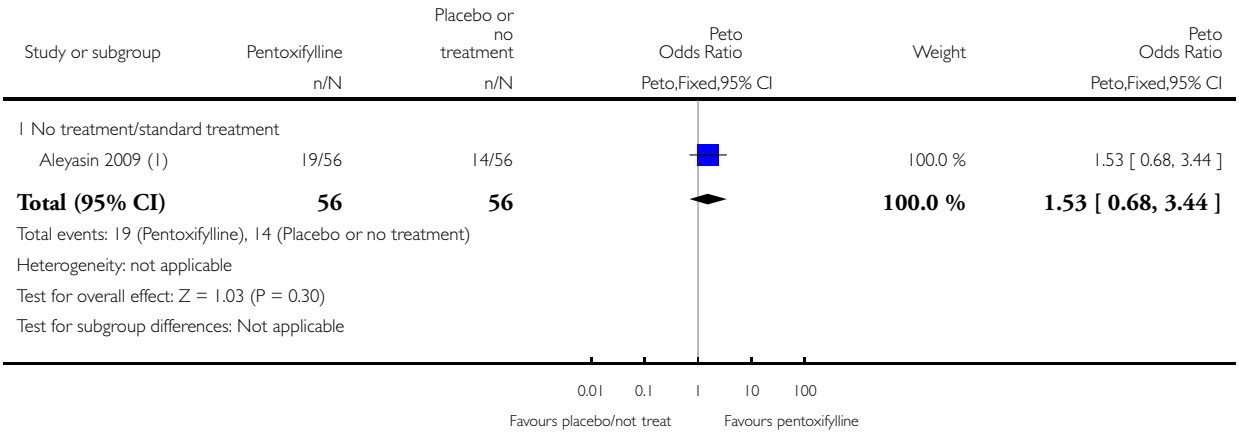


Analysis 3.1. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 1 Live birth; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 1 Live birth; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)



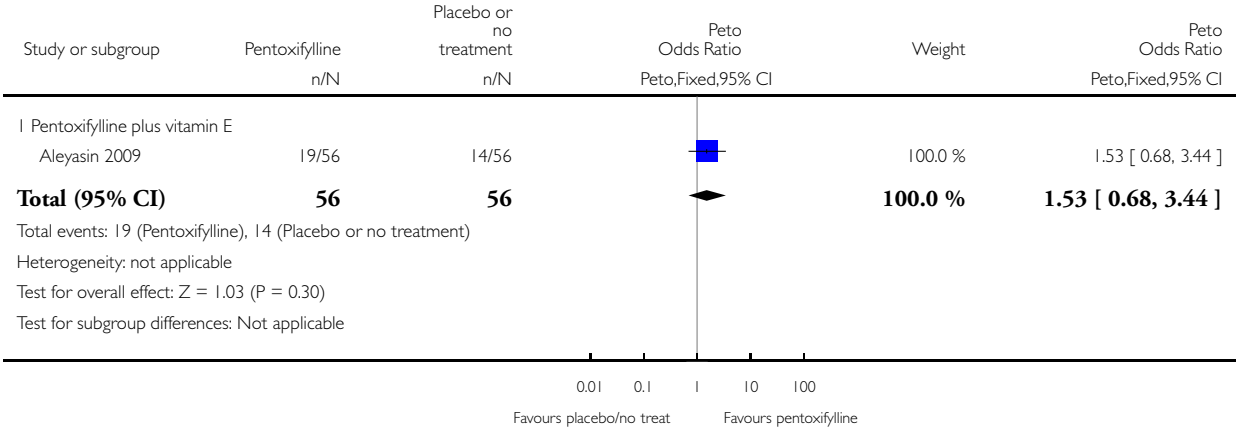
(1) Women are also undergoing IVF/ICSI

Analysis 3.2. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 2 Live birth; type of antioxidant.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 2 Live birth; type of antioxidant



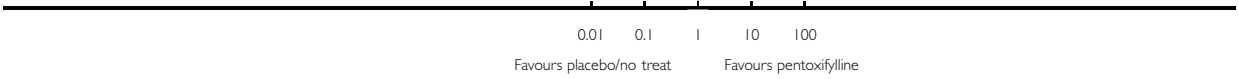
Analysis 3.3. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 3 Live birth; indications for subfertility.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 3 Live birth; indications for subfertility

Study or subgroup	Pentoxifylline n/N	Placebo or no treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Varying indications					
Aleyasin 2009 (1)	19/56	14/56		100.0 %	1.53 [0.68, 3.44]
Total (95% CI)	**56**	**56**		**100.0 %**	**1.53 [0.68, 3.44]**
Total events: 19 (Pentoxifylline), 14 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
Test for subgroup differences: Not applicable					



(1) Women are also undergoing IVF

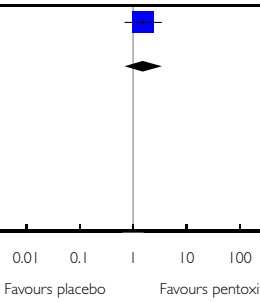
Analysis 3.4. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 4 Live birth; IVF/ICSI.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 4 Live birth; IVF/ICSI

Study or subgroup	Pentoxifylline n/N	Placebo or no treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Aleyasin 2009	19/56	14/56		100.0 %	1.53 [0.68, 3.44]
Total (95% CI)	**56**	**56**		**100.0 %**	**1.53 [0.68, 3.44]**
Total events: 19 (Pentoxifylline), 14 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
Test for subgroup differences: Not applicable					



Analysis 3.5. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 5 Clinical pregnancy; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 5 Clinical pregnancy; pentoxifylline vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)

Study or subgroup	Pentoxifylline n/N	Placebo or no treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Placebo					
Balasch 1997 (1)	9/30	5/30		19.9 %	2.08 [0.64, 6.82]
Creus 2008 (2)	12/51	7/53		28.6 %	1.98 [0.74, 5.34]
Subtotal (95% CI)	**81**	**83**		**48.5 %**	**2.02 [0.95, 4.33]**
Total events: 21 (Pentoxifylline), 12 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 1.82 (P = 0.069)					
2 No treatment					
Aleyasin 2009 (3)	32/56	22/56		51.5 %	2.03 [0.97, 4.25]
Subtotal (95% CI)	**56**	**56**		**51.5 %**	**2.03 [0.97, 4.25]**
Total events: 32 (Pentoxifylline), 22 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.88 (P = 0.060)					
Total (95% CI)	**137**	**139**		**100.0 %**	**2.03 [1.19, 3.44]**
Total events: 53 (Pentoxifylline), 34 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 0.00, df = 2 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 2.62 (P = 0.0089)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 =0.0%					

(1) Women are conceiving naturally

(2) Women are also undergoing laparoscopic ovarian drilling, IUI and induction of ovulation

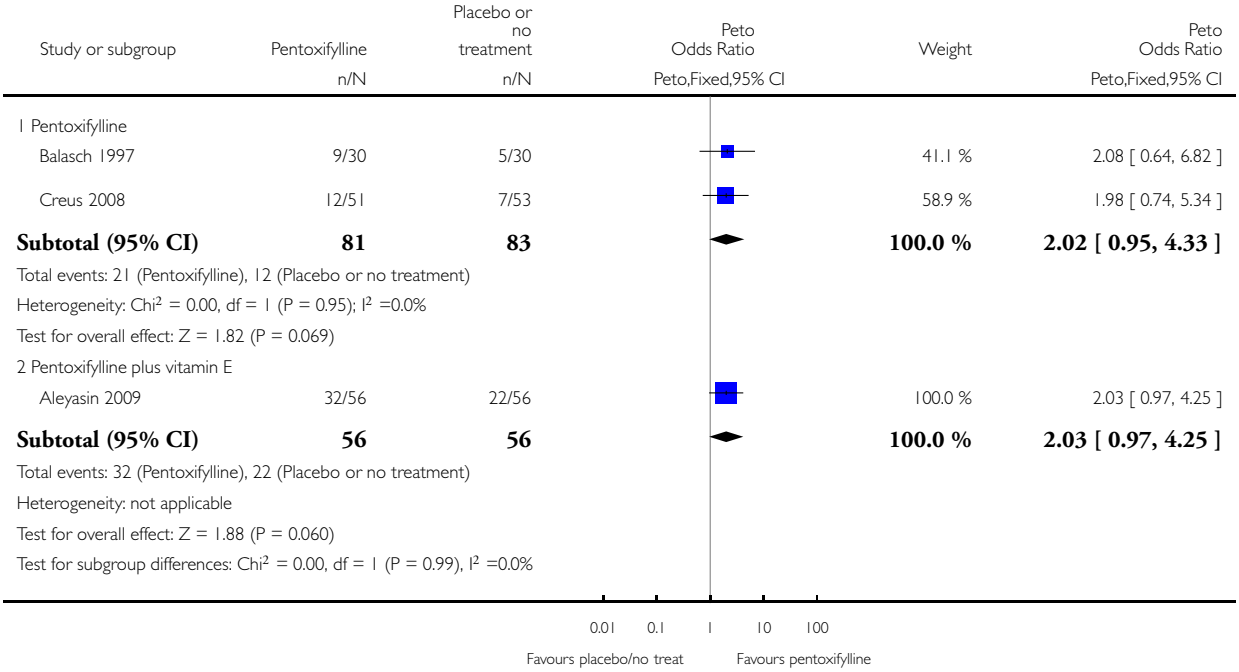
(3) Women are undergoing IVF

Analysis 3.6. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 6 Clinical pregnancy; type of antioxidant.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 6 Clinical pregnancy; type of antioxidant

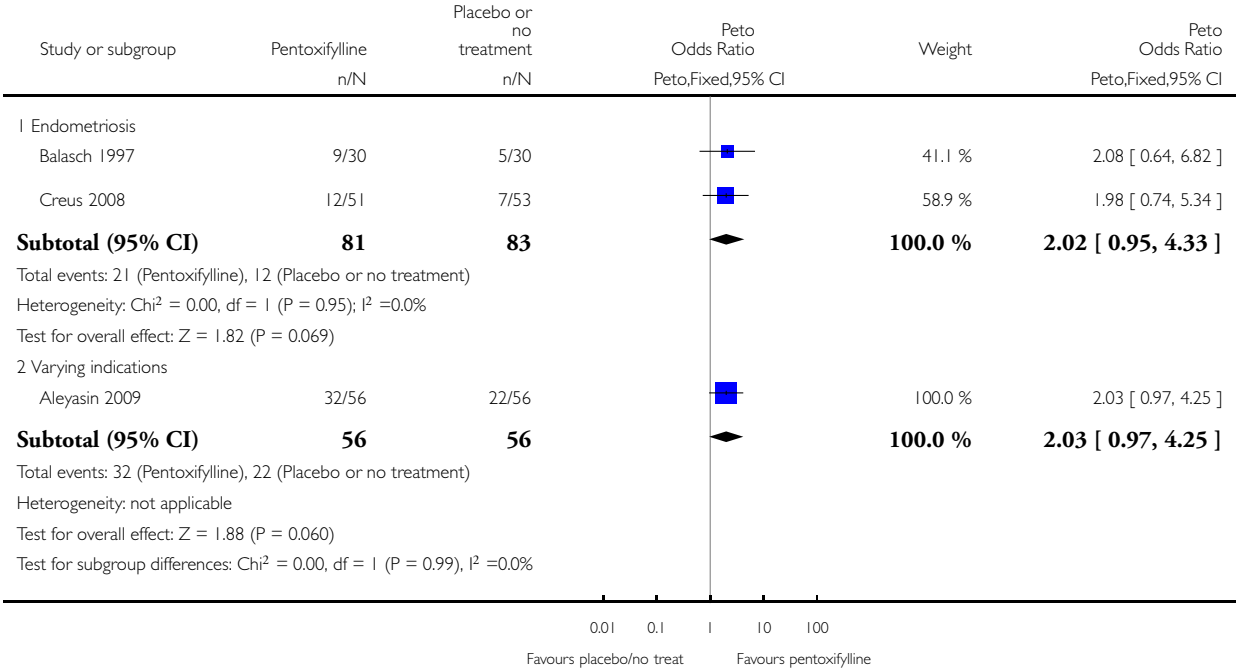


Analysis 3.7. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 7 Clinical pregnancy; indications for subfertility.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 7 Clinical pregnancy; indications for subfertility

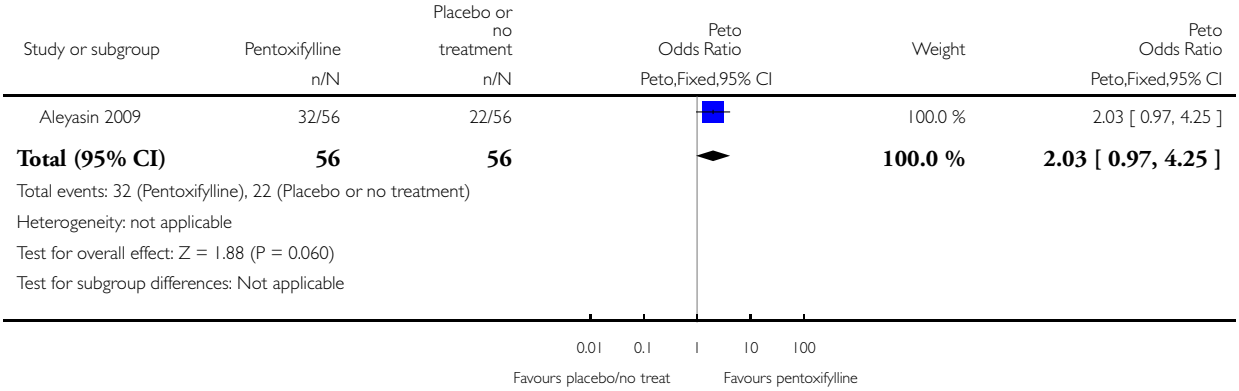


Analysis 3.8. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 8 Clinical pregnancy; IVF/ICSI.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 8 Clinical pregnancy; IVF/ICSI

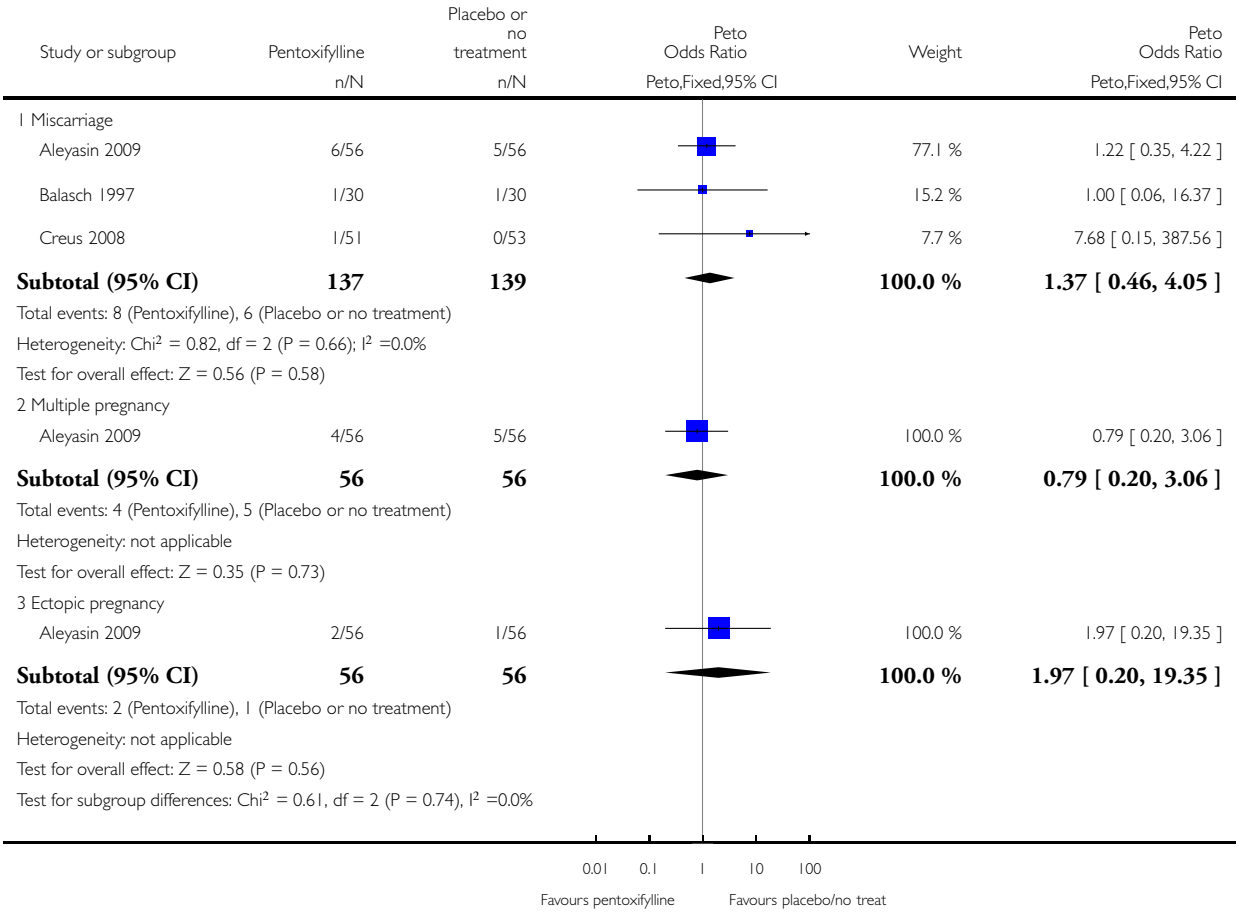


Analysis 3.9. Comparison 3 Pentoxifylline versus placebo or no treatment/standard care, Outcome 9 Adverse events.

Review: Antioxidants for female subfertility

Comparison: 3 Pentoxifylline versus placebo or no treatment/standard care

Outcome: 9 Adverse events



ADDITIONAL TABLES

Table 1. Gerli 2007- data not included in meta-analysis

Outcome	Data	Notes
Clinical pregnancy rate; myo-inositol + folic acid	4/23	Only 42 of the total 92 women enrolled in this trial declared a desire to become pregnant

Table 1. Gerli 2007- data not included in meta-analysis (*Continued*)

Clinical pregnancy rate; folic acid + placebo	1/19	
Miscarriage rate; myo-inositol + folic acid	Miscarriage reported but unknown from treatment or control	1 miscarriage occurred in the first trimester, but it is unknown from which group
Miscarriage rate; folic acid + placebo	Unknown	

Table 2. 'Biochemical' and 'pregnancy' data for those trials that did not specifically report 'clinical pregnancy'

Trial	Pregnancy in antioxidant group	Pregnancy in control group
Ciotta 2011	4/16 (myo-inositol + folic acid)	5/18 (folic acid)
Firouzabadi 2012	9/50 (metformin + calcium + vitamin D)	6/50 (metformin)
Alborzi 2007	17/43 (pentoxifylline)	16/45 (placebo)
Mier-Cabrera 2008	0/16 (vitamins C + E)	0/18 (placebo)

APPENDICES

Appendix 1. Menstrual Disorders and Subfertility key word search

Inception to 15.04.13
Keywords CONTAINS "antioxidants"or "antioxidant" or "antioxidant levels" or "vitamin" or "vitamin A" or "vitamin B" or "Vitamin-B-12" or "Vitamin-B-12-Therapeutic-Use" or "vitamin B6" or "vitamin C" or "Vitamin D" or "vitamin E" or "vitamins" or "selenium" or "folic acid" or "glutathione" or "Menevit anti-oxidant" or "carnitene" or "carnitine" or "ascorbic acid" or "zinc" or "fatty acids" or "oil" or "fish oils" or "plant extracts" or "tocopherol"or"ubiquinol "or"coenzyme Q10"or "multivitamins"or "N-acetyl cysteine"or "L-acetyl-carnitine"or"acetyl L-carnitine"or "acetylcysteine"or"pentoxifylline"or"alpha tocopherol"or"pycnogenol"or"Myo-inositol"or "inositol"or "melatonin" or Title CONTAINS "antioxidants" or "antioxidant"or"antioxidant levels" or "vitamin" or "vitamin A" or "vitamin B" or "Vitamin-B-12" or "Vitamin-B-12-Therapeutic-Use" or "vitamin B6" or "vitamin C" or "Vitamin D" or "vitamin E" or "vitamins" or "selenium" or "folic acid" or "glutathione" or "Menevit anti-oxidant" or "carnitene" or "carnitine" or "ascorbic acid" or "zinc"or "Myo-inositol"or "inositol"or "melatonin"
AND
Keywords CONTAINS "IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection" or "superovulation" or "superovulation induction" or "IUI" or "insemination, intrauterine " or "Intrauterine Insemination" or "ART" or "artificial insemination" or "assisted reproduction techniques" or "subfertility-Female" or "Polycystic Ovary Syndrome" or "PCOS" or "endometriosis"or "subfertility" or "unexplained and endometriosis related infertility" or"unexplained infertility" or"unexplained subfertility" or Title CONTAINS"IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection" or "superovulation" or "superovulation induction" or "IUI" or "insemination, intrauterine " or "Polycystic Ovary Syndrome" or "subfertility"

262 records found

Appendix 2. CENTRAL

Inception to 15.04.13
1 exp antioxidants/ or free radical scavengers/ (9281)
2 (antioxidant$ or radical scavengers).tw. (3411)
3 exp vitamins/ or exp ascorbic acid/ or exp dehydroascorbic acid/ or exp vitamin a/ or exp vitamin e/ or exp vitamin u/ or exp alpha-tocopherol/ or exp beta carotene/ or exp beta-tocopherol/ or exp gamma-tocopherol/ (10370)
4 vitamin$.tw. (8540)
5 exp Zinc/ (1038)
6 (zinc or selenium).tw. (2819)
7 exp Selenium/ (385)
8 exp Glutathione Peroxidase/ or exp folic acid/ (2185)
9 (Glutathione$ or folate).tw. (2144)
10 exp Ubiquinone/ (244)
11 (ubiquin$ or folic acid).tw. (1262)
12 coenzyme q10.tw. (225)
13 exp Carnitine/ (409)
14 (carnitine$ or carotenoid$).tw. (1083)
15 (astaxanthin$ or lycopene$).tw. (280)
16 multivitamin$.tw. (449)
17 (betacarotene$ or beta carotene$).tw. (1032)
18 ascorbic acid.tw. (816)
19 n-acetylcysteine.tw. (543)
20 exp Acetylcysteine/ (474)
21 alpha-tocopherol$.tw. (902)
22 exp Pentoxifylline/ (386)
23 Pentoxifylline$.tw. (642)
24 (fish adj2 oil$).tw. (1134)
25 omega$.tw. (1103)
26 exp fatty acids/ or exp fish oils/ or exp cod liver oil/ or exp fatty acids, omega-3/ or exp plant oils/ (14892)
27 fatty acid$.tw. (5704)
28 (plant adj4 oil$).tw. (52)
29 l-arginine$.tw. (853)
30 flavonoid$.tw. (275)
31 riboflavin$.tw. (265)
32 pycnogenol$.tw. (59)
33 lutein$.tw. (1540)
34 lipoic acid$.tw. (154)
35 exp Inositol/ (234)
36 (Inositol or myoinositol).tw. (193)
37 mesoinositol.tw. (0)
38 myo inositol.tw. (65)
39 n acetyl cysteine.tw. (82)
40 d chiro inositol.tw. (15)
41 melatonin.tw. (858)
42 or/1-41 (43448)
43 exp Infertility, Female/ (819)
44 female$ subfertil$.tw. (0)
45 female$ infertilit$.tw. (20)
46 subfertil$ women.tw. (13)
47 infertil$ women.tw. (326)

48 female$ fertility.tw. (3)
49 (in vitro fertilisation or intracytoplasmic sperm injection$).tw. (530)
50 intrauterine insemination$.tw. (399)
51 (ivf or icsi or iui).tw. (2495)
52 in vitro fertilization.tw. (1222)
53 ART.tw. (947)
54 Artificial reproduc$ technique$.tw. (0)
55 or/43-54 (4722)
56 42 and 55 (372)

Appendix 3. MEDLINE

Inception to 15.04.13
1 exp antioxidants/ or free radical scavengers/ (330361)
2 (antioxidant$ or radical scavengers).tw. (101777)
3 exp vitamins/ or exp ascorbic acid/ or exp dehydroascorbic acid/ or exp vitamin a/ or exp vitamin e/ or exp vitamin u/ or exp alpha-tocopherol/ or exp beta carotene/ or exp beta-tocopherol/ or exp gamma-tocopherol/ (264949)
4 vitamin$.tw. (139453)
5 exp Zinc/ (46748)
6 (zinc or selenium).tw. (92277)
7 exp Selenium/ (15844)
8 exp Glutathione Peroxidase/ or exp folic acid/ (41759)
9 (Glutathione$ or folate).tw. (102666)
10 exp Ubiquinone/ (6205)
11 (ubiquin$ or folic acid).tw. (19643)
12 coenzyme q10.tw. (1933)
13 exp Carnitine/ (7634)
14 (carnitine$ or carotenoid$).tw. (22030)
15 (astaxanthin$ or lycopene$).tw. (3855)
16 multivitamin$.tw. (2590)
17 (betacarotene$ or beta carotene$).tw. (8645)
18 ascorbic acid.tw. (22280)
19 n-acetylcysteine.tw. (7320)
20 exp Acetylcysteine/ (9543)
21 alpha-tocopherol$.tw. (11448)
22 exp Pentoxifylline/ (3622)
23 Pentoxifylline$.tw. (3534)
24 (fish adj2 oil$).tw. (7176)
25 omega$.tw. (29276)
26 exp fatty acids/ or exp fish oils/ or exp cod liver oil/ or exp fatty acids, omega-3/ or exp plant oils/ (379560)
27 fatty acid$.tw. (138058)
28 (plant adj4 oil$).tw. (1435)
29 l-arginine$.tw. (28928)
30 flavonoid$.tw. (18313)
31 riboflavin$.tw. (7206)
32 pycnogenol$.tw. (244)
33 lutein$.tw. (31314)
34 lipoic acid$.tw. (2734)
35 exp Inositol/ (20428)
36 (Inositol or myoinositol).tw. (30608)
37 mesoinositol.tw. (35)
38 myo inositol.tw. (4698)
39 n acetyl cysteine.tw. (1956)

40 d chiro inositol.tw. (122)
41 melatonin.tw. (16367)
42 or/1-41 (1239820)
43 exp Infertility, Female/ (22690)
44 female$ subfertil$.tw. (35)
45 female$ infertilit$.tw. (991)
46 subfertil$ women.tw. (198)
47 infertil$ women.tw. (3052)
48 female$ fertility.tw. (1268)
49 (in vitro fertilisation or intracytoplasmic sperm injection$).tw. (5857)
50 intrauterine insemination$.tw. (1711)
51 (ivf or icsi or iui).tw. (18797)
52 in vitro fertilization.tw. (14872)
53 ART.tw. (42946)
54 Artificial reproduc$ technique$.tw. (69)
55 or/43-54 (90627)
56 42 and 55 (4177)
57 randomized controlled trial.pt. (347097)
58 controlled clinical trial.pt. (85769)
59 randomized.ab. (265050)
60 placebo.tw. (147404)
61 clinical trials as topic.sh. (163996)
62 randomly.ab. (192945)
63 trial.ti. (113213)
64 (crossover or cross-over or cross over).tw. (56490)
65 or/57-64 (853363)
66 (animals not (humans and animals)).sh. (3711406)
67 65 not 66 (786854)
68 67 and 56 (463)

Appendix 4. EMBASE

Inception to 15.04.13
1 exp antioxidants/ or free radical scavengers/ (103607)
2 (antioxidant$ or radical scavengers).tw. (130000)
3 vitamin$.tw. (166429)
4 exp vitamin/ or exp ascorbic acid/ or exp carotenoid/ or exp tocopherol/ (432169)
5 exp Zinc/ (75273)
6 (zinc or selenium).tw. (106356)
7 exp Selenium/ (26722)
8 exp Glutathione Peroxidase/ or exp folic acid/ (62168)
9 (Glutathione$ or folate).tw. (116792)
10 exp Ubiquinone/ (6514)
11 (ubiquin$ or folic acid).tw. (22527)
12 coenzyme q10.tw. (3023)
13 exp Carnitine/ (10125)
14 (carnitine$ or carotenoid$).tw. (25360)
15 (astaxanthin$ or lycopene$).tw. (4669)
16 multivitamin$.tw. (3250)
17 (betacarotene$ or beta carotene$).tw. (11613)
18 ascorbic acid.tw. (25154)
19 n-acetylcysteine.tw. (8893)
20 exp acetylcysteine/ (22243)

21 n-acetyl-cysteine.tw. (2448)
22 alpha-tocopherol$.tw. (13936)
23 exp Pentoxifylline/ (10809)
24 Pentoxifylline$.tw. (4357)
25 (fish adj2 oil$).tw. (8913)
26 omega$.tw. (14166)
27 fatty acid$.tw. (154677)
28 exp edible oil/ or exp castor oil/ or exp cod liver oil/ or exp fish oil/ or exp lyprinol/ or exp olive oil/ or exp safflower oil/ or exp fatty acid/ or exp essential fatty acid/ or exp arachidonic acid/ or exp linoleic acid/ or exp linolenic acid/ or exp gamma linolenic acid/ or exp unsaturated fatty acid/ or exp omega 3 fatty acid/ or exp omega 6 fatty acid/ or exp polyunsaturated fatty acid/ (425301)
29 (plant adj4 oil$).tw. (2056)
30 l-arginine$.tw. (32378)
31 flavonoid$.tw. (26182)
32 riboflavin$.tw. (7713)
33 pycnogenol$.tw. (352)
34 lipoic acid$.tw. (3265)
35 exp inositol/ (8444)
36 (Inositol or myoinositol).tw. (34393)
37 mesoinositol.tw. (36)
38 myo inositol.tw. (5416)
39 melatonin.tw. (19303)
40 d chiro inositol.tw. (142)
41 or/1-40 (1344153)
42 exp Infertility, Female/ (34044)
43 (female$ adj2 subfertil$).tw. (94)
44 (female$ adj2 infertilit$).tw. (1554)
45 (subfertil$ adj2 women).tw. (348)
46 (infertil$ adj2 women).tw. (5126)
47 (female$ adj2 fertility).tw. (2010)
48 (vitro fertilisation or intracytoplasmic sperm injection$).tw. (7363)
49 (intrauterine adj3 insemination$).tw. (2295)
50 (ivf or icsi or iui).tw. (26704)
51 vitro fertilization.tw. (17633)
52 Artificial reproduc$ technique$.tw. (117)
53 exp artificial insemination/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ or exp intrauterine insemination/ (52724)
54 exp Superovulation/ (2032)
55 Superovulation.tw. (1744)
56 or/42-55 (91018)
57 Clinical Trial/ (876796)
58 Randomized Controlled Trial/ (340260)
59 exp randomization/ (61167)
60 Single Blind Procedure/ (17227)
61 Double Blind Procedure/ (114019)
62 Crossover Procedure/ (36637)
63 Placebo/ (216063)
64 Randomi?ed controlled trial$.tw. (85514)
65 Rct.tw. (11229)
66 random allocation.tw. (1227)
67 randomly allocated.tw. (18541)
68 allocated randomly.tw. (1874)
69 (allocated adj2 random).tw. (717)
70 Single blind$.tw. (13168)

71 Double blind$.tw. (135429)
72 ((treble or triple) adj blind$).tw. (310)
73 placebo$.tw. (187097)
74 prospective study/ (230049)
75 or/57-74 (1319736)
76 case study/ (19249)
77 case report.tw. (241847)
78 abstract report/ or letter/ (864231)
79 or/76-78 (1120296)
80 75 not 79 (1283559)
81 41 and 56 and 80 (785)

Appendix 5. CINAHL

Inception to 2010 OVID Platform
1 exp antioxidants/ or free radical scavengers/(3884)
2 (antioxidant$ or radical scavengers).tw.(2881)
3 exp vitamins/ or exp ascorbic acid/ or exp dehydroascorbic acid/ or exp vitamin a/ or exp vitamin e/ or exp vitamin u/ or exp alpha-tocopherol/ or exp beta carotene/ or exp beta-tocopherol/ or exp gamma-tocopherol/(12571)
4 vitamin$.tw.(7275)
5 exp Zinc/(1145)
6 (zinc or selenium).tw.(1670)
7 exp Selenium/(584)
8 exp Glutathione Peroxidase/ or exp folic acid/(2519)
9 (Glutathione$ or folate).tw.(1901)
10 exp Ubiquinone/(360)
11 (ubiquin$ or folic acid).tw.(1043)
12 coenzyme q10.tw.(164)
13 exp Carnitine/(294)
14 (carnitine$ or carotenoid$).tw.(641)
15 (astaxanthin$ or lycopene$).tw.(237)
16 exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp Insemination, Artificial, Homologous/(1013)
17 (in vitro fertilisation or intracytoplasmic sperm injection$).tw.(162)
18 (intrauterine adj3 insemination$).tw.((46)
19 (ivf or icsi or iui).tw.(360)
20 in-vitro fertilisation.tw.(99)
21 in vitro fertilization.tw.(306)
22 ART.tw.(5953)
23 Artificial reproduc$ technique$.tw.(1)
24 or/1-15(20136)
25 or/16-23(7140)
26 24 and 25(38)
27 exp clinical trials/(66862)
28 Clinical trial.pt.(35432)
29 (clinic$ adj trial$1).tw.*(15232)
30 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.(8971)
31 Randomi?ed control$ trial$.tw.(12969)
32 Random assignment/(19621)
33 Random$ allocat$.tw.(1370)
34 Placebo$.tw.(12376)
35 Placebos/(4758)
36 Quantitative studies/(4326)
37 Allocat$ random$.tw.(78)

38 or/27-37(91904)
39 38 and 26(8)
40 from 39 keep 1-8 (8)
CINAHL EBSCO Platform search 27.09.10 to 15.04.13

#	Query	Results
S18	S7 and S17	(205)
S17	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	(7142)
S16	TX timed intercourse	(13)
S15	TX IUI	(52)
S14	“”intrauterine insemination“” or (MM “Insemination, Artificial”)	(419)
S13	TX intracytoplasmic sperm injection*	(197)
S12	TX icsi	(186)
S11	(MM “Fertilization in Vitro”) OR “ivf”	(1443)
S10	TX Infertil*	(5861)
S9	TX subfertil*	(342)
S8	(MM “Infertility”)	(2886)
S7	S1 or S2 or S3 or S4 or S5 or S6	(57291)
S6	TX fatty acid*	(12539)
S5	(MH “Fatty Acids, Omega 3”) OR (MH “Fatty Acids, Unsaturated+”)	(12971)
S4	TX vitamin*	(26133)
S3	(MH “Vitamins+”)	(25710)
S2	TX antioxidant*	(12063)
S1	(MH “Antioxidants+”)	(9509)

Appendix 6. PSYCINFO

Inception to 15.04.13
1 exp Antioxidants/ (1289)
2 (antioxidant$ or radical scavengers).tw. (2536)
3 exp Vitamins/ (2994)
4 vitamin$.tw. (4313)
5 exp Zinc/ (472)
6 (zinc or selenium).tw. (1360)
7 (Glutathione$ or folate).tw. (1988)
8 (ubiquin$ or folic acid).tw. (508)
9 coenzyme q10.tw. (101)
10 (carnitine$ or carotenoid$).tw. (439)
11 multivitamin$.tw. (148)
12 (betacarotene$ or beta carotene$).tw. (45)
13 ascorbic acid.tw. (330)
14 n-acetylcysteine.tw. (141)
15 alpha-tocopherol$.tw. (58)
16 Pentoxifylline$.tw. (53)
17 (fish adj2 oil$).tw. (138)
18 omega$.tw. (909)
19 exp Fatty Acids/ (2614)
20 fatty acid$.tw. (2322)
21 l-arginine$.tw. (754)
22 or/1-21 (15067)
23 exp Infertility/ (1531)
24 female$ subfertil$.tw. (2)
25 female$ infertilit$.tw. (40)
26 subfertil$ women.tw. (2)
27 infertil$ women.tw. (187)
28 female$ fertility.tw. (95)
29 (vitro fertilisation or intracytoplasmic sperm injection$).tw. (92)
30 intrauterine insemination$.tw. (13)
31 (ivf or icsi or iui).tw. (353)
32 vitro fertilization.tw. (435)
33 Artificial reproduc$ technique$.tw. (6)
34 or/23-33 (2032)
35 22 and 34 (12)

Appendix 7. AMED

Inception to 15.04.13
1 exp Antioxidants/ or exp Free radicals/ (1454)
2 (antioxidant$ or radical scavengers).tw. (2082)
3 exp Vitamins/ or exp Dietary supplements/ (2999)
4 exp Ascorbic acid/ (252)
5 vitamin$.tw. (2113)
6 exp Zinc/ (100)
7 (zinc or selenium).tw. (421)
8 (Glutathione$ or folate).tw. (638)
9 exp Selenium/ (88)
10 (ubiquin$ or folic acid).tw. (149)
11 coenzyme q10.tw. (73)

12 exp Carnitine/ (16)
13 (carnitine$ or carotenoid$).tw. (171)
14 multivitamin$.tw. (54)
15 ascorbic acid.tw. (410)
16 n-acetylcysteine.tw. (26)
17 Acetylcysteine.tw. (27)
18 alpha-tocopherol$.tw. (80)
19 Pentoxifylline$.tw. (10)
20 (fish adj2 oil$).tw. (154)
21 omega$.tw. (211)
22 exp Fatty acids/ (432)
23 exp Fish oils/ (86)
24 fatty acid$.tw. (661)
25 (plant adj4 oil$).tw. (782)
26 l-arginine$.tw. (109)
27 flavonoid$.tw. (1049)
28 riboflavin$.tw. (20)
29 (Inositol or myoinositol).tw. (45)
30 pycnogenol$.tw. (16)
31 or/1-30 (7934)
32 exp Infertility female/ (150)
33 female$ subfertil$.tw. (0)
34 female$ infertilit$.tw. (18)
35 subfertil$ women.tw. (0)
36 infertil$ women.tw. (13)
37 female$ fertility.tw. (6)
38 (vitro fertilisation or intracytoplasmic sperm injection$).tw. (19)
39 intrauterine insemination$.tw. (5)
40 (ivf or icsi or iui).tw. (31)
41 in vitro fertilization.tw. (15)
42 Artificial reproduc$ technique$.tw. (0)
43 or/32-42 (186)
44 31 and 43 (4)

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 8, 2013

Date	Event	Description
22 April 2008	Amended	Converted to new review format.
9 August 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Marian Showell conducted the searches, assessed studies for inclusion, extracted data, analysed the data and wrote the review.

Julie Brown assisted with assessing the trials for inclusion, extracted the data, assisted with the data analysis and helped with writing of the review.

Jane Clarke initiated and conceptualised the review, extracted the initial pool of data and wrote the first draft of the review.

Roger Hart helped with the writing of the review and provided clinical advice.

DECLARATIONS OF INTEREST

None known. This review was not funded by any organisation.

SOURCES OF SUPPORT

Internal sources

- NZ GOVT MOH, New Zealand.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Two of the five protocol authors (Agarwal A, Gupta S) withdrew from involvement in the review.

The secondary outcome of stillbirth rate per woman has been removed.

The exclusion criterion 'Trials that exclusively reported on women who have previously had chemotherapy' has been removed as not clinically relevant to this review.

The inclusion criteria for participants were expanded to include women undergoing ART. Exclusion criteria now include trials that enrol exclusively fertile women attending a fertility clinic because of male partner infertility.

Exclusion criteria for interventions now include antioxidants versus fertility drugs alone as controls, as they are themselves active agents. They might include metformin or clomiphene citrate.

The review includes a subgroup analysis based on the type of subfertility problem, including women with PCOS, endometriosis, poor responders and tubal and unexplained subfertility, as well as a subgroup of women who are undergoing IVF or ICSI.

A separate comparison for pentoxifylline was created as there was a concern that this medicine does not have purely antioxidant capabilities.

The search strategy has been updated.

A Summary of findings table has been added.

Where we had data from multi-armed trials, the intervention arms were pooled versus the control arm. This differs from the protocol, where we said that we would divide the intervention arms. This was done with the advice of a statistician.

A decision was made with clinical advice that trials using folic acid (< 1 mg) as a control would be treated as assessing standard treatment and would be included in the 'no treatment' subgroup.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antioxidants [*administration & dosage]; Infertility, Female [*drug therapy]; Live Birth [epidemiology]; Oxidative Stress; Pregnancy Rate

MeSH check words

Female; Humans; Pregnancy