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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 8
OBJECTIVES 9
METHODS 9
RESULTS 11
Figure 1. 13
Figure 2. 18
Figure 3. 20
Figure 4. 22
Figure 5. 24
Figure 6. 27
Figure 7. 30
Figure 8. 33
Figure 9. 34
Figure 10. 36
DISCUSSION 37
AUTHORS' CONCLUSIONS 39
ACKNOWLEDGEMENTS 39
REFERENCES 41
CHARACTERISTICS OF STUDIES 53
DATA AND ANALYSES 166
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) 169
Analysis 1.2. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 2: Live birth; type of antioxidant 171
Analysis 1.3. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 3: Live birth; indications for subfertility 173
Analysis 1.4. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 4: Live birth; IVF/ICSI 174
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) 175
Analysis 1.6. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 6: Clinical pregnancy; type of antioxidant 177
Analysis 1.7. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 7: Clinical pregnancy; indications for subfertility 180
Analysis 1.8. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 8: Clinical pregnancy; IVF/ICSI 182
Analysis 1.9. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 9: Adverse events ... 183
Analysis 2.1. Comparison 2: Head-to-head antioxidants, Outcome 1: Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments) 186
Analysis 2.2. Comparison 2: Head-to-head antioxidants, Outcome 2: Live Birth; indications for subfertility 187
Analysis 2.3. Comparison 2: Head-to-head antioxidants, Outcome 3: Live Birth; IVF/ICSI 187
Analysis 2.4. Comparison 2: Head-to-head antioxidants, Outcome 4: Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments) 188
Analysis 2.5. Comparison 2: Head-to-head antioxidants, Outcome 5: Clinical pregnancy; indications for subfertility 188
Analysis 2.6. Comparison 2: Head-to-head antioxidants, Outcome 6: Clinical pregnancy; IVF/ICSI 189
Analysis 2.7. Comparison 2: Head-to-head antioxidants, Outcome 7: Adverse events 190
ADDITIONAL TABLES 191
APPENDICES 191
WHAT'S NEW 199

HISTORY 199
CONTRIBUTIONS OF AUTHORS 200
DECLARATIONS OF INTEREST 200
SOURCES OF SUPPORT 200
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 200
INDEX TERMS 201

[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 may affect up to a quarter of all couples planning a child. It is estimated that for 40% to 50% of couples, subfertility may result from factors affecting women. Antioxidants are thought to reduce the oxidative stress brought on by these conditions. Currently, limited evidence suggests that antioxidants improve fertility, and trials have explored this area with varied results. This review assesses the evidence for the effectiveness of different antioxidants in female subfertility.

Objectives

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

Search methods

We searched the following databases (from their inception to September 2019), with no language or date restriction: Cochrane Gynaecology and Fertility Group (CGFG) specialised register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL and AMED. We checked reference lists of relevant studies and searched the trial registers.

Selection criteria

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

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The primary review outcome was live birth; secondary outcomes included clinical pregnancy rates and adverse events.

Main results

We included 63 trials involving 7760 women. Investigators compared oral antioxidants, including: combinations of antioxidants, *N*-acetylcysteine, melatonin, L-arginine, myo-inositol, carnitine, selenium, vitamin E, vitamin B complex, vitamin C, vitamin D+calcium, CoQ10, and omega-3-polyunsaturated fatty acids versus placebo, no treatment/standard treatment or another antioxidant. Only 27 of the 63 included trials reported funding sources.

Due to the very low-quality of the evidence we are uncertain whether antioxidants improve live birth rate compared with placebo or no treatment/standard treatment (odds ratio (OR) 1.81, 95% confidence interval (CI) 1.36 to 2.43; P < 0.001, I^2 = 29%; 13 RCTs, 1227 women). This suggests that among subfertile women with an expected live birth rate of 19%, the rate among women using antioxidants would be between 24% and 36%.

Low-quality evidence suggests that antioxidants may improve clinical pregnancy rate compared with placebo or no treatment/standard treatment (OR 1.65, 95% CI 1.43 to 1.89; P < 0.001, I^2 = 63%; 35 RCTs, 5165 women). This suggests that among subfertile women with an expected clinical pregnancy rate of 19%, the rate among women using antioxidants would be between 25% and 30%. Heterogeneity was moderately high.

Overall 28 trials reported on various adverse events in the meta-analysis. The evidence suggests that the use of antioxidants makes no difference between the groups in rates of miscarriage (OR 1.13, 95% CI 0.82 to 1.55; P = 0.46, I^2 = 0%; 24 RCTs, 3229 women; low-quality evidence). There was also no evidence of a difference between the groups in rates of multiple pregnancy (OR 1.00, 95% CI 0.63 to 1.56; P = 0.99, I^2 = 0%; 9 RCTs, 1886 women; low-quality evidence). There was also no evidence of a difference between the groups in rates of gastrointestinal disturbances (OR 1.55, 95% CI 0.47 to 5.10; P = 0.47, I^2 = 0%; 3 RCTs, 343 women; low-quality evidence). Low-quality evidence showed that there was also no difference between the groups in rates of ectopic pregnancy (OR 1.40, 95% CI 0.27 to 7.20; P = 0.69, I^2 = 0%; 4 RCTs, 404 women).

In the antioxidant versus antioxidant comparison, low-quality evidence shows no difference in a lower dose of melatonin being associated with an increased live-birth rate compared with higher-dose melatonin (OR 0.94, 95% CI 0.41 to 2.15; P = 0.89, I^2 = 0%; 2 RCTs, 140 women). This suggests that among subfertile women with an expected live-birth rate of 24%, the rate among women using a lower dose of melatonin compared to a higher dose would be between 12% and 40%. Similarly with clinical pregnancy, there was no evidence of a difference between the groups in rates between a lower and a higher dose of melatonin (OR 0.94, 95% CI 0.41 to 2.15; P = 0.89, I^2 = 0%; 2 RCTs, 140 women).

Three trials reported on miscarriage in the antioxidant versus antioxidant comparison (two used doses of melatonin and one compared N-acetylcysteine versus L-carnitine). There were no miscarriages in either melatonin trial. Multiple pregnancy and gastrointestinal disturbances were not reported, and ectopic pregnancy was reported by only one trial, with no events. The study comparing N-acetylcysteine with L-carnitine did not report live birth rate. Very low-quality evidence shows no evidence of a difference in clinical pregnancy (OR 0.81, 95% CI 0.33 to 2.00; 1 RCT, 164 women; low-quality evidence). Low quality evidence shows no difference in miscarriage (OR 1.54, 95% CI 0.42 to 5.67; 1 RCT, 164 women; low-quality evidence). The study did not report multiple pregnancy, gastrointestinal disturbances or ectopic pregnancy.

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

Authors' conclusions

In this review, there was low- to very low-quality evidence to show that taking an antioxidant may benefit subfertile women. Overall, there is no evidence of increased risk of miscarriage, multiple births, gastrointestinal effects or ectopic pregnancies, but evidence was of very low quality. At this time, there is limited evidence in support of supplemental oral antioxidants for subfertile women.

PLAIN LANGUAGE SUMMARY

Vitamins and minerals for subfertility in women

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

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

Search date:
The evidence is current to September 2019.

Study characteristics:
The review includes 63 randomised controlled trials that compare antioxidants with placebo or with no treatment/standard treatment, or with another antioxidant, in a total of 7760 women.

Funding sources:

Funding sources were reported by only 27 of the 63 included trials.

Key results:
We are uncertain whether the use of antioxidants will increase live births, as the evidence was of very low quality. Based on our results, we would expect that out of 100 subfertile women not taking antioxidants, 20 would have a baby, compared with between 24 and 36 women per 100 who would have a baby if taking antioxidants. Low-quality evidence suggests that antioxidants may be associated with increased clinical pregnancy rates. Adverse effects were poorly reported, but the use of antioxidants did not appear to lead to more miscarriages, multiple births, digestive effects or ectopic pregnancies.

Low-quality evidence suggests that there is no difference in live birth or clinical pregnancy rates when comparing a lower dose of melatonin to a higher dose. Here we would expect that out of 100 subfertile women not taking low-dose melatonin, 24 would have a baby, compared with between 12 and 40 women per 100 who would have a baby if taking higher-dose melatonin.

Three trials reported on miscarriage in the antioxidant versus antioxidant comparison (two used doses of melatonin and one compared N-acetylcysteine versus L-carnitine). There were no miscarriages in either melatonin trial. Multiple pregnancy and gastrointestinal disturbances were not reported, and ectopic pregnancy was reported by only one trial, with no events.

The study comparing N-acetylcysteine with L-carnitine did not report live birth rate. Very low-quality evidence shows no evidence of a difference in clinical pregnancy. Low quality evidence shows no difference in miscarriage. The study did not report multiple pregnancy, gastrointestinal disturbances or ectopic pregnancy.

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

Summary of findings 1. Antioxidant(s) compared to placebo or no treatment/standard treatment for female subfertility

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

Patient or population: women with subfertility
Setting: Infertility clinics
Intervention: Antioxidant(s)
Comparison: placebo or no treatment/standard treatment

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Quality of the evidence (GRADE)	What happens
		Without antioxidant(s)	With antioxidant(s)	Difference		
Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments) № of participants: 1227 (13 RCTs)	OR 1.81 (1.36 to 2.43)	19.0%	29.8% (24.2 to 36.3)	10.8% more (5.2 more to 17.3 more)	⊕⊖⊖⊖ VERY LOW[a,b,c]	We are uncertain whether antioxidants improve live birth rate compared with placebo or no treatment/standard treatment.
Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments) № of participants: 5165 (35 RCTs)	OR 1.65 (1.43 to 1.89)	18.8%	27.6% (24.8 to 30.4)	8.8% more (6.1 more to 11.6 more)	⊕⊕⊖⊖ LOW[a,d]	Antioxidant(s) may improve clinical pregnancy rate, compared with placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments).
Adverse events - Miscarriage № of participants: 3229 (24 RCTs)	OR 1.13 (0.82 to 1.55)	4.8%	5.4% (4 to 7.3)	0.6% more (0.8 fewer to 2.5 more)	⊕⊕⊖⊖ LOW[a,c]	Antioxidant(s) may result in little to no difference in adverse events - Miscarriage
Adverse events - Multiple pregnancy № of participants: 1886 (9 RCTs)	OR 1.00 (0.63 to 1.56)	4.3%	4.3% (2.7 to 6.5)	0.0% fewer (1.6 fewer to 2.2 more)	⊕⊕⊖⊖ LOW[a,c]	Antioxidant(s) may result in little to no difference in adverse events - Multiple pregnancy
Adverse events - Gastrointestinal disturbances № of participants: 343 (3 RCTs)	OR 1.55 (0.47 to 5.10)	2.4%	3.7% (1.2 to 11.2)	1.3% more (1.2 fewer to 8.8 more)	⊕⊕⊖⊖ LOW[a,c]	Antioxidant(s) may result in little to no difference in adverse events - Gastrointestinal disturbances
Adverse events - Ectopic pregnancy № of participants: 404	OR 1.40	0.6%	0.9%	0.3% more	⊕⊕⊖⊖ LOW[a,c]	Antioxidant(s) may result in little to no difference in adverse events - Ectopic pregnancy

(4 RCTs)	(0.27 to 7.20)	(0.2 to 4.3)	(0.4 fewer to 3.7 more)	

*__The risk in the intervention group__ (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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to serious risk of bias. The no-treatment group increases risk due to the lack of blinding.
[b]Downgraded one level; overall the heterogeneity is low (0%), but in the placebo subgroup the heterogeneity statistic is 60% and some trials are showing potential benefit of the intervention while others are showing benefit of the placebo.
[c]Downgraded one level as the event rate is low (< 400).
[d]Downgraded one level as the heterogeneity statistic (63%) is considered to represent moderate to substantive heterogeneity.

Summary of findings 2. Head-to-head antioxidants for female subfertility

Head-to-head antioxidants for female subfertility

Patient or population: women with subfertility
Setting: Infertility clinics
Intervention: Head-to-head antioxidants
Comparison: Other antioxidant

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Quality of the evidence (GRADE)	What happens
		With one antioxidant	With another antioxidant	Difference		
Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments) - Melatonin lower dose versus melatonin higher dose № of participants: 140 (2 RCTs)	OR 0.94 (0.41 to 2.15)	24.0%	22.9% (11.5 to 40.4)	1.1% fewer (12.5 fewer to 16.4 more)	⊕⊕⊖⊖ LOW[a,b]	There was no clear evidence of a difference between the lower and higher doses of melatonin

Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments) - *N*-acetylcysteine versus *L*-carnitine № of participants: 164 (1 RCT)	OR 0.81 (0.33 to 2.00)	14.6%	12.2% (5.4 to 25.5)	2.4% fewer (9.2 fewer to 10.9 more)	⊕⊖⊖⊖ VERY LOW[c,d]	There was no clear evidence of a difference between *N*-acetylcysteine versus *L*-carnitine
Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments) - Melatonin lower dose versus melatonin higher dose № of participants: 140 (2 RCTs)	OR 0.94 (0.41 to 2.15)	24.0%	22.9% (11.5 to 40.4)	1.1% fewer (12.5 fewer to 16.4 more)	⊕⊕⊖⊖ LOW[a,b]	There was no clear evidence of a difference between the lower and higher doses of melatonin
Adverse events - Miscarriage № of participants: 304 (3 RCTs)	OR 1.54 (0.42 to 5.67)	3.0%	4.6% (1.3 to 15.1)	1.6 more (1.7 fewer to 12.1 more)	⊕⊕⊖⊖ LOW[a,b]	There were no miscarriages in either melatonin study (140 women) There was no clear evidence of a difference between *N*-acetylcysteine versus *L*-carnitine (164 women)
Adverse events - Multiple pregnancy	There were no trials reporting multiple pregnancy					
Adverse events - Gastrointestinal disturbances	There were no trials reporting gastrointestinal disturbances					
Adverse events - Ectopic pregnancy Melatonin lower dose versus melatonin higher dose № of participants: 120 (1 RCT)	Not estimable, there were no ectopic pregnancies in either group				⊕⊖⊖⊖ VERY LOW [3 4]	There was no clear evidence of a difference between the lower and higher doses of melatonin

*__The risk in the intervention group__ (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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level as there are only two trials in this analysis and one is small.
[b]Downgraded one level as event rate is low (< 400).
[c]Downgraded two levels as one study can not represent possible subfertile populations.

[d]Downgraded two levels as only one study, event rate low and small number of participants

BACKGROUND

Description of the condition

A couple that has tried to conceive for a year or longer without success is considered to be subfertile (Practice Committee of ARSM 2020) or less fertile than a typical couple. The World Health Organization (WHO) (Zegers-Hochschild 2009) defines infertility as the "failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse". Levels of infertility in 2010 were similar to those in 1990 in most of the world, apart from declines in Sub-Saharan Africa and in South Asia (Mascarenhas 2012). Thirty to forty per cent of cases of subfertility are due to causes in women (WHO). 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 (Boivin 2007; Hart 2003). Nine per cent of men and 11% of women of reproductive age are thought to experience infertility (Chandra 2013)

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

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

Description of the intervention

Antioxidants are biological and chemical compounds that reduce oxidative damage, the imbalance between creation of reactive oxygen species and the body's ability to detoxify. 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*-acetylcysteine; 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 omega-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 a 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).

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 can then 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 ROSs within the ovary and the endometrium may have physiological and pathological implications for women when they try to conceive. Oxidative stress (OS) is a result of an imbalance between the amount of ROS and the quantity of natural antioxidants present within the body, and results in overwhelming the body's natural defence mechanism. ROS can attack lipids, proteins DNA and affect metabolic pathways (chemical transformations in the cells) (Agarwal 2012). Natural antioxidants present in the body include catalase, glutathione peroxidase, superoxide dismutase and glutathione reductase, vitamins C and E, 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 (Agarwal 2012; Ruder 2008). Other lifestyle factors such as diet, disease, pollution, stress and allergies also contribute to increased levels of free radicals (Agarwal 2012).

The global vitamin and supplement market has grown exponentially and has been reported in 2016 as being worth over USD 140 billion, and projected to reach USD 230 billion by 2027 (Global Supplement Report 2019; Global Supplement report 2016; Reportlinker.com 2010). In the UK there has been a 13.8% growth in vitamin and supplement manufacturing from 2015 to 2020. In 2009 sales of vitamins and dietary supplements in the UK "totalled £674.6 million, a growth of about 16% over the previous five years, with the two biggest-selling areas being multivitamins (GBP 138.6 million) and fish oils (GBP 139.1 million)" (NHS News 2011). Vitamins and supplements are dispensed through various retail outlets, including health-food shops, online retailers, health centres, fitness clubs, supermarkets and pharmacies.

In an effort to enhance fertility, couples are increasingly resorting to ART; however, these techniques do not cure the causes of subfertility, but rather overcome some of its barriers. Adjunctive 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 ovary syndrome (PCOS) and potentially unexplained subfertility (Agarwal 2012; 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 (immature egg cell), 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 particularly benefit women with PCOS in lowering hyperandrogenism (androgen excess) (Thomson 2012). Myo-inositol helps ovarian function and decreases hyperandrogenism and insulin resistance (Nestler 1998); L-arginine improves endometrial blood flow (Takasaki 2009); *N*-acetylcysteine is needed for fertile cervical mucus and ovulation (Badawy 2007); and PUFAs influence prostaglandin (lipid compounds with hormone-like effects) synthesis and steroidogenesis (creation of steroid hormones), 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

There is currently limited evidence on whether antioxidants improve fertility, and ongoing trials in this area show varied results. This review assesses the effectiveness of different antioxidants and different dosages. This is an update of a review first published in 2013 (Showell 2013) and updated in 2017 (Showell 2017).

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 (O'Reilly 2014; 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 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 are included, but we used only first-phase data 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.
- Trials enrolling women exclusively with any vitamin deficiency.

Types of interventions

Inclusion criteria

- 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).

On clinical advice, we analysed 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 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.

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: if live birth data were unavailable and the trial reported ongoing pregnancy, we reported ongoing pregnancy as live birth (footnoted in the forest plot). We defined live birth as delivery of a live fetus after 20 completed weeks of gestation, and ongoing pregnancy as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed with ultrasound.

Secondary outcomes

- Clinical pregnancy rate per woman (as confirmed by the identification of a gestational sac on ultrasound at seven or more weeks' gestation).
- Any adverse effects reported by the trial. We subgrouped these events 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 event rates. We used both indexed and free-text terms, and applied no language or date restrictions.

Electronic searches

We searched the following databases:

- The Cochrane Gynaecology and Fertility Group's (CGFG) specialised register of controlled trials; searched 12 September 2019, PROCITE platform (Appendix 1);
- CENTRAL, via the Cochrane Register of Studies Online (CRSO); searched 12 September 2019, Web platform (Appendix 2);
- MEDLINE; searched from 1946 to 12 September 2019, OVID platform (Appendix 3);
- Embase; searched from 1980 to 12 September 2019, OVID platform (Appendix 4);
- PsycINFO; searched from 1806 to 12 September 2019, OVID platform (Appendix 5);
- AMED (Allied and Complementary Medicine); searched from 1985 to 12 September 2019, OVID platform (Appendix 6);
- CINAHL; searched from 1961 to 12 September 2019, EBSCO platform (Appendix 7).

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* (Chapter 6, 6.4.11; Lefebvre 2011). We combined the Embase searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/what-we-do/methodology/search-filters/).

Searching other resources

(last searched September 2019):

- International trial registers: the ClinicalTrials database, a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home) and the World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx);
- 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;
- 'Grey' literature (unpublished and unindexed), through the openGREY database (www.opengrey.eu/); (Appendix 8).

We also contacted known experts and personal contacts for information on any unpublished materials, and we checked the citation lists of appropriate papers 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 2019).

Selection of studies

Two review authors (MGS and RM-P) independently reviewed titles and abstracts of trials for eligibility. We obtained the full texts of trials that we considered for inclusion. We sought further information from the authors of trials that did not contain sufficient information to make a decision about eligibility. We resolved any disagreements by reference to a third review author. We documented the selection process with a PRISMA flow chart.

Data extraction and management

Two review authors (MGS and RM-P) 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.

We designed the data extraction forms to extract information on study characteristics and outcomes. We have included this information and present 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 2019). If any information on trial methodology or any trial data were missing, we contacted the study authors 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

We assessed the included studies for risks of bias using the Cochrane 'Risk of bias' 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 review authors (MGS and RM-P) assessed the included studies according to these six criteria, resolving any disagreements by discussion with a third review author. We sought published protocols.

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

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

We expressed the dichotomous data for live birth, pregnancy rate, miscarriage and adverse events as Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (95% CIs).

Unit of analysis issues

We analysed the outcomes of live birth, pregnancy and adverse events per woman randomly assigned, counting multiple births 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, i.e. to include in the analyses all women randomly assigned to each group and to analyse all women in the group to which they were assigned, 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. We assessed statistical heterogeneity according to the guidelines set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019). We examined heterogeneity between the results of different trials by visually examining 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 50% or higher, we assumed high heterogeneity, and conducted a sensitivity analysis. 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 (Page 2019).

Data synthesis

We conducted statistical analysis of the data using Review Manager 5 (RevMan 2014). We considered pregnancy outcomes to be positive, and higher numbers of pregnancy rates to be a benefit. We considered the outcomes of miscarriage and adverse events to be negative effects, and higher numbers harmful.

We combined data from primary studies 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.

We displayed increases in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse events), graphically in meta-analyses to the right of the centre line, and decreases in the odds of a particular outcome to the left of the centre line.

The aim was to define analyses that were comprehensive and mutually exclusive, so that we could slot all eligible study results into one stratum only. We specified comparisons 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, we pooled intervention groups versus the control group.

If individuals had been randomly re-assigned after failed cycles, we did not pool the data in a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses:

- Type of control, placebo or no treatment;
- 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);
- Trials that enrolled women who were also undergoing IVF or ICSI.

Sensitivity analysis

We conducted sensitivity analyses on the primary outcomes if we detected a high degree of heterogeneity (where the I^2 statistic was 50% or more), excluding studies:

- with a high risk of bias, or
- that used antioxidants plus a fertility drug (a co-intervention) versus placebo plus a fertility drug

We also conducted a sensitivity analysis on the choice of using a fixed-effect model by using a random-effects model.

Overall quality of the body of evidence: 'Summary of findings' tables

We produced a 'Summary of findings' table, using GRADEpro GDT software (GRADEpro GDT 2015) and Cochrane methods (Schünemann 2019) for the main review comparison (Antioxidant(s) compared to placebo or no treatment/standard treatment). This table evaluates the overall quality of the body of evidence for the main review outcomes (live birth, clinical pregnancy and adverse events), using GRADE criteria (study limitations: risk of bias, consistency of effect, imprecision, indirectness and publication bias). We have included an additional 'Summary of findings' table for the main review outcomes for the head-to-head comparison, evaluating those trials that look at one antioxidant versus another antioxidant. Two review authors, working independently, made judgements about evidence quality ('high', 'moderate', 'low' or 'very low').

Summary of findings and assessment of the certainty of the evidence

RESULTS

Description of studies

Results of the search

2013 version of the review

The search retrieved 2127 abstracts and titles, which we screened to identify trials that met our inclusion criteria. We retrieved the full texts of 67 trials for appraisal. Only one study (Bonakdaran 2012) was not published in English, with the full text in Persian; however, the English abstract contained enough information to show that

it did not meet the inclusion criteria, and we therefore excluded it. Of the 67 studies assessed, we included 28 and excluded 39. A repeat search in April 2013 revealed seven studies (Carlomagno 2012; Choi 2012; Mohammadbeigi 2012; Rosalbino 2012; Salehpour 2012; Schachter 2007; Salem 2012) that we placed into the 'Awaiting classification' section of the review. We found 12 ongoing trials in searches of the clinical trial registers.

2017 Update

We assessed 926 abstracts (after 222 duplicates were removed) for inclusion from the title and abstract found in a search dated from April 2013 to September 2016. We assessed 39 of these papers in full text. One study was published in Persian (Mohammadbeigi 2012) and required translation (see Acknowledgements). We excluded 15 articles (14 studies) of the 39, and included 24 (23 studies). Of the latter, six were from the seven trials placed in 'Awaiting classification' in the original review, while Salem 2012 was excluded due to inappropriate intervention and control. For the 2017 update, four of the 12 previously ongoing trials are now included (Bentov 2014; Mohammadbeigi 2012; Unfer 2011; Youssef 2015). The conference abstract of the included study Aboulfoutouh 2011 in the original review became a secondary reference of Youssef 2015 in the update, and Rezk 2004, formerly an excluded study, is now included as a secondary reference of Rizk 2005. Pourghassem 2010 was found to be the same trial as the excluded Ardabili 2012. We excluded Pasha 2011 due to an ineligible population. We added two trials (NCT03023514; NCT02058212) after the search in September 2016, so eight trials were now ongoing (Fernando 2014; NCT01019785; NCT03023514; NCT02058212; IRCT201112148408N1; CTRI/2012/08/002943; NCT01782911; NCT01267604).

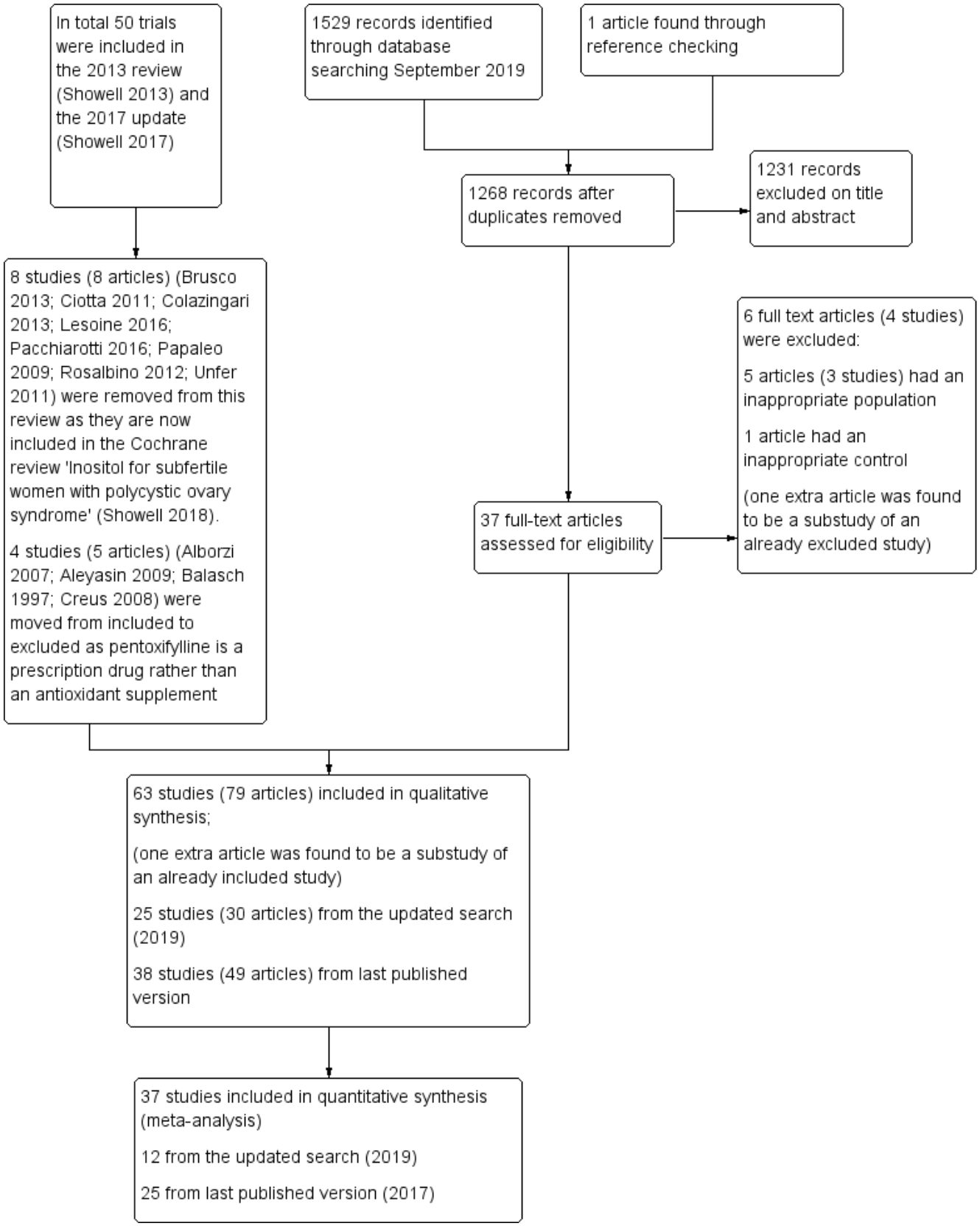
We included 23 trials in the 2017 update: Battaglia 1999; Bentov 2014; Brusco 2013; Carlomagno 2012; Cheraghi 2016; Choi 2012; Colazingari 2013; Daneshbodi 2013; Deeba 2015; El Refaeey 2014; Ismail 2014; Keikha 2010; Lesoine 2016; Maged 2015; Mohammadbeigi 2012; Pacchiarotti 2016; Panti Abubakar 2015; Polak de Fried 2013; Razavi 2015; Rosalbino 2012; Salehpour 2012; Schachter 2007; Valeri 2015.

Fifty trials were included in this updated review and 50 have been excluded.

2020 Update

For the 2020 update we assessed 1268 abstracts (after removing 262 duplicates), checking titles and abstracts for eligibility criteria. The articles were found in a search dated from 1st January 2013 to 12th September 2019. We retrieved 39 full-text papers for further eligibility criteria and from this we excluded six articles (four studies) and included 31 articles (25 studies); one of these (Schillaci 2012) was found through handsearching references (See the PRISMA flow chart (Figure 1). All papers were in English.

Figure 1. Study flow diagram.



For the current update one ongoing trial, Fernando 2014 became an included study (Fernando 2018). In addition to the seven ongoing trials from the 2017 update (NCT01019785; NCT03023514; NCT02058212; IRCT201112148408N1; CTRI/2012/08/002943; NCT01782911; NCT01267604), we added 26 new ongoing trials: ChiCTR1800019772; ChiCTR-IPR-15006369; EUCTR2015-004233-27-IT; IRCT201009131760N9; IRCT201207156420N11; IRCT2012120311430N2; IRCT201306115942N2; IRCT20150831023831N2; IRCT201510266917N3; IRCT2016022821653N5; IRCT20160410027311N6; ISRCTN23488518; JPRN-UMIN000016992; NCT01659788; NCT01665547; NCT01896492; NCT02239107; NCT02993588; NCT03085030; NCT03117725; NCT03306745; NCT03396380; NCT03476564; NCT04019899; PACTR201902584533870; TCTR20171109001.

We include 25 new studies in this review update: Al-Alousi 2018; Behrouzi 2017; Caballero 2016; El Sharkwy 2019a; El Sharkwy 2019b; Espino 2019; Fernando 2018; Ghomian 2019; Hashemi 2017; Hefny 2018; Heidar 2019; Jahromi 2017; Jamilian 2018; Lu 2018; Mokhtari 2016; Mokhtari 2019; Mostajeran 2018; Rasekhjahromi 2018; Schillaci 2012; Sen Sharma 2017; Siavashani 2018; Taylor 2018; Tunon 2017; Xu 2018; Zadeh Modarres 2018.

Eight studies (Brusco 2013; Ciotta 2011; Colazingari 2013; Lesoine 2016; Pacchiarotti 2016; Papaleo 2009; Rosalbino 2012; Unfer 2011) were removed from the original review as they are now included in the Cochrane Review *Inositol for subfertile women with polycystic ovary syndrome* (Showell 2018).

Four pentoxifylline studies (Alborzi 2007; Aleyasin 2009; Balasch 1997; Creus 2008), were moved from the included category to excluded, as pentoxifylline is a prescription drug rather than an over-the-counter antioxidant supplement and therefore does not fit the inclusion criteria.

We now include 63 studies in this updated review (see Characteristics of included studies) and we exclude 58 (see Characteristics of excluded studies).

Included studies

Sixty-three studies met the criteria for inclusion. Twenty were based in Iran (Behrouzi 2017; Cheraghi 2016; Daneshbodi 2013; Ghomian 2019; Hashemi 2017; Heidar 2019; Jahromi 2017; Jamilian 2018; Keikha 2010; Mohammadbeigi 2012; Mokhtari 2016; Mokhtari 2019; Mostajeran 2018; Rasekhjahromi 2018; Rashidi 2009; Razavi 2015; Salehpour 2009; Salehpour 2012; Siavashani 2018; Zadeh Modarres 2018), 10 in Egypt (Badawy 2006; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Hefny 2018; Ismail 2014; Maged 2015; Rizk 2005; Nasr 2010; Youssef 2015). Eight were based in Italy (Battaglia 1999; Battaglia 2002; Carlomagno 2012; Gerli 2007; Lisi 2012; Rizzo 2010; Schillaci 2012; Valeri 2015), four in Turkey (Batioglu 2012; Cicek 2012; Eryilmaz 2011; Ozkaya 2011), three in Korea (Choi 2012; Kim 2006; Kim 2010), two in Spain (Espino 2019; Tunon 2017), in the USA (Taylor 2018; Westphal 2006), Argentina (Caballero 2016; Polak de Fried 2013) and China (Lu 2018; Xu 2018), and one each in the UK (Agrawal 2012), Hungary/Austria (Griesinger 2002), Mexico (Mier-Cabrera 2008), Canada (Bentov 2014), Bangladesh (Deeba 2015), Nigeria (Panti Abubakar 2015), Israel (Schachter 2007), Australia (Fernando 2018), Iraq (Al-Alousi 2018) and India (Sen Sharma 2017).

We tried to contact authors of all the included studies to obtain further details and clarification, but we could not obtain data for meta-analysis from 24 trials (Al-Alousi 2018; Caballero 2016; Carlomagno 2012; Choi 2012; Daneshbodi 2013; Deeba 2015; Ghomian 2019; Hashemi 2017; Hefny 2018; Heidar 2019; Jamilian 2018; Keikha 2010; Kim 2006; Kim 2010; Mohammadbeigi 2012; Mokhtari 2016; Ozkaya 2011; Rasekhjahromi 2018; Razavi 2015; Schillaci 2012; Siavashani 2018; Taylor 2018; Valeri 2015; Zadeh Modarres 2018), and one did not report on the outcomes included in this review (Salehpour 2009). In one trial (Gerli 2007) (see Table 1), only half of the participants declared that they wanted to become pregnant before the study began; we have therefore included this trial, but have not used the data in the meta-analysis (see Characteristics of included studies).

Duration of treatment ranged from 10 to 12 days (Battaglia 2002) to 12 months (Nasr 2010). Nine trials (Eryilmaz 2011; Ghomian 2019; Hefny 2018; Ismail 2014; Maged 2015; Mostajeran 2018; Rizk 2005; Salehpour 2012; Sen Sharma 2017) gave treatment for four to five days during the menstrual cycle and the treatment was repeated per unsuccessful cycle.

One trial (Bentov 2014) was terminated before the end due to the publication of a paper (Levin 2012) describing the negative effects of polar body biopsy, an adjunctive treatment in this trial, on the development of the embryo. The trial began in 2010 and ran until 2012, enrolling 39 women. This study was included in the meta-analysis but was rated at high risk of bias in two domains; 'incomplete outcome reporting' and in 'other bias'.

Participants

The trials randomly assigned 7760 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 45 years; at the upper age range Battaglia 1999 enrolled women who were between 37 and 44 years, and Fernando 2018 enrolled women as young as 18 years old.

Twenty-seven trials (Behrouzi 2017; Cheraghi 2016; Choi 2012; Daneshbodi 2013; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Ghomian 2019; Hefny 2018; Heidar 2019; Ismail 2014; Jamilian 2018; Keikha 2010; Maged 2015; Mohammadbeigi 2012; Mokhtari 2016; Nasr 2010; Mostajeran 2018; Panti Abubakar 2015; Rasekhjahromi 2018; Razavi 2015; Rizk 2005; Salehpour 2012; Schachter 2007; Sen Sharma 2017; Siavashani 2018; Zadeh Modarres 2018) included women with PCOS. Other participants in the trials were enrolled for endometriosis, ovulation failure, tubal blockages, recurrent implantation failure, poor ovarian reserve and unexplained subfertility. One trial included women aged 35 to 42 years with poor oocyte quality and poor response (Rizzo 2010). Schillaci 2012 looked at the use of myo-inositol for two different groups of women: those with PCOS and those with poor response. Only those women with poor ovarian response are included in this review, and the group of women with PCOS will be included in the update of Showell 2018 (*Inositol for subfertile women with polycystic ovary syndrome*). Nine trials (Agrawal 2012; Al-Alousi 2018; Batioglu 2012; Battaglia 1999; Fernando 2018; Griesinger 2002; Taylor 2018; Tunon 2017; Westphal 2006) included women with more than one fertility problem: these reasons included a percentage of male-partner subfertility, unexplained subfertility, ovulatory problems, poor responders, PCOS, tubal blockages and endometriosis. One

trial included a small percentage of women whose subfertility was caused by the male partner (Griesinger 2002).

One trial enrolled only women who were aged over 40 (Valeri 2015), and Taylor 2018 enrolled women of advanced maternal age (36 to 42 years). 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".

Thirty-three studies included women undergoing IVF/ICSI (Al-Alousi 2018; Batioglu 2012; Battaglia 1999; Battaglia 2002; Bentov 2014; Caballero 2016; Carlomagno 2012; Cheraghi 2016; Choi 2012; Eryilmaz 2011; Espino 2019; Fernando 2018; Griesinger 2002; Heidar 2019; Jahromi 2017; Jamilian 2018; Kim 2006; Kim 2010; Lisi 2012; Lu 2018; Mokhtari 2016; Ozkaya 2011; Polak de Fried 2013; Rizzo 2010; Salehpour 2009; Schillaci 2012; Siavashani 2018; Taylor 2018; Tunon 2017; Valeri 2015; Xu 2018; Youssef 2015; Zadeh Modarres 2018). Twenty studies included women undergoing natural intercourse or ovulation induction with timed intercourse or IUI (Agrawal 2012; Badawy 2006; Behrouzi 2017; Cicek 2012; Deeba 2015; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Ghomian 2019; Hefny 2018; Ismail 2014; Maged 2015; Mohammadbeigi 2012; Mokhtari 2019; Mostajeran 2018; Panti Abubakar 2015; Rasekhjahromi 2018; Rizk 2005; Salehpour 2012; Sen Sharma 2017). The remaining 10 studies enrolled women who were either having, no adjunctive treatment, or each trial included a number of differing treatments, i.e. some women having IVF while others were having IUI, and only one trial enrolled women undergoing laparoscopic ovarian drilling (Nasr 2010).

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

Interventions

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

Comparison of antioxidants versus placebo, no treatment and standard treatment included the following: combinations of antioxidants; L-arginine, vitamin E, myo-inositol, *D*-chiro-inositol, carnitine, selenium, vitamin B complex, vitamin C, vitamin D+calcium, CoQ10, melatonin, folic acid and omega-3 polyunsaturated fatty acids. Combined antioxidants were labelled as Octatron® (Youssef 2015), multiple micronutrients (Agrawal 2012; Deeba 2015; Ozkaya 2011; Panti Abubakar 2015), Fertility Blend (Westphal 2006) and Seidivid (Tunon 2017). The time that women received treatment or control in these trials ranged from 2½ menstrual cycles to six months. Four of these trials (Agrawal 2012; Deeba 2015; Panti Abubakar 2015; Westphal 2006) enrolled women undergoing ovulation induction with timed intercourse, and three (Ozkaya 2011; Tunon 2017; Youssef 2015) included women undergoing IVF/ICSI. More details of these combination antioxidants are given in the Characteristics of included studies. The remaining 56 trials gave single antioxidants. The duration of treatment in these trials ranged from 10 to 12 days to one year with a one-year follow-up.

The comparison 'antioxidants versus antioxidants' included only four trials (El Sharkwy 2019a; Espino 2019; Fernando 2018; Keikha 2010). El Sharkwy 2019a studied the effects of *N*-acetylcysteine (NAC) versus L-carnitine, while Espino 2019 and Fernando 2018 looked at different doses of melatonin and were also included in the placebo comparison. Keikha 2010 looked at NAC versus vitamin C. Only El Sharkwy 2019a, Espino 2019 and Fernando 2018 were used in the meta-analysis, as Keikha 2010 did not report on live birth, clinical pregnancy or adverse events. The head-to-head comparisons were included in an attempt to assess whether one antioxidant was more effective than another.

In summary:

- 33 included trials compared antioxidants versus placebo: Al-Alousi 2018; Badawy 2006; Battaglia 2002; Bentov 2014; Cheraghi 2016; Choi 2012; Daneshbodi 2013; El Sharkwy 2019b; Fernando 2018; Griesinger 2002; Hashemi 2017; Hefny 2018; Heidar 2019; Ismail 2014; Jahromi 2017; Jamilian 2018; Kim 2006; Mier-Cabrera 2008; Mohammadbeigi 2012; Mokhtari 2016; Mokhtari 2019; Mostajeran 2018; Nasr 2010; Ozkaya 2011; Panti Abubakar 2015; Polak de Fried 2013; Rizk 2005; Salehpour 2009; Salehpour 2012; Siavashani 2018; Taylor 2018; Westphal 2006; Zadeh Modarres 2018;
- 26 trials compared antioxidants with 'no treatment' or standard treatment: Agrawal 2012; Batioglu 2012; Battaglia 1999; Behrouzi 2017; Caballero 2016; Carlomagno 2012; Cicek 2012; Deeba 2015; El Refaeey 2014; Eryilmaz 2011; Espino 2019; Gerli 2007; Ghomian 2019; Lisi 2012; Lu 2018; Maged 2015; Rasekhjahromi 2018; Rashidi 2009; Razavi 2015; Rizzo 2010; Schachter 2007; Schillaci 2012; Sen Sharma 2017; Valeri 2015; Xu 2018; Youssef 2015;
- four trials compared one antioxidant with another antioxidant (head-to-head comparisons): El Sharkwy 2019a; Espino 2019; Fernando 2018; Keikha 2010;
- 18 trials compared antioxidants plus a co-intervention with a placebo or no treatment plus a co-intervention at the same dosage: Badawy 2006; Behrouzi 2017; Cheraghi 2016; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Ghomian 2019; Hefny 2018; Maged 2015; Mostajeran 2018; Rasekhjahromi 2018; Rashidi 2009; Razavi 2015; Rizk 2005; Rizzo 2010; Salehpour 2012; Schachter 2007; Sen Sharma 2017. The co-interventions used were clomiphene citrate, letrozole and metformin;
- in two trials (Kim 2010;Tunon 2017), the control was unspecified, and we tried unsuccessfully to contact these authors by email and by post.

Seven trials (Cheraghi 2016; Espino 2019; Fernando 2018; Griesinger 2002; Maged 2015; Rashidi 2009; Schachter 2007) were multi-arm and fitted into more than one of the above categories. In one trial (Cheraghi 2016) all women were prescribed the oral contraceptive pill as a pretreatment to ICSI.

Outcomes

Live birth

The primary outcome for this review was live birth. Thirteen studies reported on live birth: Agrawal 2012; Battaglia 2002; Bentov 2014; Cicek 2012; Espino 2019; Fernando 2018; Jahromi 2017; Nasr 2010; Panti Abubakar 2015; Polak de Fried 2013; Schachter 2007; Tunon 2017; Xu 2018. We sent emails and letters to authors of all other included trials to ask whether they had any data on live birth. We received live birth data from Battaglia 2002, Panti Abubakar 2015, and Polak de Fried 2013 by email. Agrawal 2012, Cicek 2012 and

Schachter 2007 reported on ongoing pregnancy, which we used as a surrogate for live birth. Caballero 2016 reports on live birth but numbers per treatment and control groups are not available, despite our attempts to contact these authors.

Clinical pregnancy

Forty-two trials reported on clinical pregnancy rates in the text of the trial reports or through direct communication with the authors: Agrawal 2012; Badawy 2006; Batioglu 2012; Battaglia 1999; Battaglia 2002; Behrouzi 2017; Bentov 2014; Caballero 2016; Carlomagno 2012; Cheraghi 2016; Choi 2012; Cicek 2012; Deeba 2015; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Eryilmaz 2011; Espino 2019; Fernando 2018; Gerli 2007; Griesinger 2002; Ismail 2014; Jahromi 2017; Kim 2010; Lisi 2012; Lu 2018; Maged 2015; Mokhtari 2019; Mostajeran 2018; Nasr 2010; Panti Abubakar 2015; Polak de Fried 2013; Rashidi 2009; Rizk 2005; Rizzo 2010; Salehpour 2012; Schachter 2007; Sen Sharma 2017; Tunon 2017; Westphal 2006; Xu 2018 Youssef 2015. Two trials reported only biochemical pregnancy or conception (Al-Alousi 2018; Ghomian 2019) and another six trials reported only 'pregnancy rates' (Heidar 2019; Mier-Cabrera 2008; Mohammadbeigi 2012; Razavi 2015; Schillaci 2012; Siavashani 2018) (see data in Table 2). Rasekhjahromi 2018 provides pregnancy data, but we were unable to use it in the meta-analysis, as the conference abstract only provided an overall pregnancy rate, with no definition of pregnancy, and with no breakdown into the different groups. Hefny 2018 reports on pregnancy but provides no data. Eleven trials did not report any pregnancy outcomes (Daneshbodi 2013; Hashemi 2017; Jamilian 2018; Keikha 2010; Kim 2006; Mokhtari 2016; Ozkaya 2011; Salehpour 2009; Taylor 2018; Valeri 2015; Zadeh Modarres 2018). We tried to contact authors of all the trials that did not report clinical pregnancy rates.

Adverse events

Twenty eight trials, in both the antioxidant versus placebo/no treatment and the head-to-head comparisons reported on adverse events.

The following adverse events were reported:

- Miscarriage: 27 trials either reported on miscarriage, or we calculated the numbers from the differences between live birth and clinical pregnancy rates (Agrawal 2012; Badawy 2006; Battaglia 1999; Battaglia 2002; Behrouzi 2017; Bentov 2014; Choi 2012; Cicek 2012; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Eryilmaz 2011; Espino 2019; Fernando 2018; Ismail 2014; Jahromi 2017; Nasr 2010; Panti Abubakar 2015; Polak de Fried 2013; Rizzo 2010; Rizk 2005; Schachter 2007; Sen Sharma 2017; Tunon 2017; Westphal 2006; Xu 2018; Youssef 2015). We did not include the data from Rizk 2005 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. Choi 2012 stated that miscarriage rates were similar for each group but there were no data reported in the abstract. There were six early miscarriages reported by Fernando 2018 that occurred in the biochemical to the clinical pregnancy stage, four from 120 women in the combined treatment arms and two of 40 women in the placebo group, with no miscarriages from the clinical pregnancy stage to live birth. Nasr 2010 also stated that all miscarriages occurred in the biochemical stage.
- Multiple pregnancy: Nine trials reported on multiple pregnancy (Badawy 2006; Behrouzi 2017; El Refaeey 2014; Ismail 2014; Nasr 2010; Polak de Fried 2013; Rizk 2005; Salehpour 2012; Youssef 2015). We did not include Rizk 2005 in the meta-analysis for multiple pregnancy, as no pregnancies occurred in the control group, and adding these data would have skewed the analysis.
- Gastrointestinal disturbances: Three trials reported on nausea (Cicek 2012; Maged 2015; Westphal 2006). No cases of gastrointestinal disturbances were reported in treatment or control groups in Cicek 2012;
- Ectopic pregnancy: Four trials reported ectopic pregnancies (Agrawal 2012; Behrouzi 2017; Fernando 2018; Jahromi 2017);
- Ovarian hyperstimulation syndrome (OHSS): two trials reported on OHSS (Kim 2006; Rizk 2005).There were no cases of OHSS in treatment or control groups in Rizk 2005, and Kim 2006 did not provide data for OHSS;
- Preterm birth: two trials (Fernando 2018; Nasr 2010) reported on preterm birth. The births reported by Fernando 2018 were between 34 and 37 weeks, and Nasr 2010 did not define the gestation of the preterm births.

Fernando 2018 also reported on headache, congenital abnormality (a missing kidney), low birth weight, placenta previa, pre-eclampsia and fatigue.

We tried to contact authors of all the trials that did not report adverse events. We could not assume that there were no adverse events in trials where these were not reported.

Design

All 63 included trials were of parallel-group design. Three trials (Fernando 2018; Griesinger 2002; Schachter 2007) were four-armed, which used different dosages of melatonin, vitamin C versus placebo and doses of vitamin B complex versus no treatment respectively, and four trials were three-armed (Cheraghi 2016; Espino 2019; Maged 2015; Rashidi 2009).

The sample size of the included trials ranged from 12 participants (Schillaci 2012) to 804 participants (Badawy 2006). The 12 participants from the Schillaci 2012 trial are a subgroup of poor responders using inositol, with the other population being women with PCOS (n = 17) who will be included in Showell 2018. Taylor 2018 is the second smallest trial with 21 participants. Nineteen trials included in the meta-analysis (Agrawal 2012; Battaglia 2002; Behrouzi 2017; Bentov 2014; Cicek 2012; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Eryilmaz 2011; Fernando 2018; Ismail 2014; Jahromi 2017; Lisi 2012; Lu 2018; Mokhtari 2019; Mostajeran 2018; Nasr 2010; Salehpour 2012; Xu 2018) reported carrying out a power calculation.

Funding

Funding sources were reported by only 27 of the 63 included trials. Three studies (Bentov 2014; Espino 2019; Taylor 2018) reported the support of Ferring Pharmaceuticals. Bentov 2014 also reported that one of the authors had a consultancy agreement with Fertility Neutraceuticals, responsible for manufacturing and distribution of the CoQ10 product, and is also on the Science Advisory Board for Ferring. Taylor 2018 was also supported by Theralogix Science, a manufacturer of vitamins and supplements. Espino 2019 was supported by FundeSalud, jointly financed by Ferring and the Government. Valeri 2015 reported funding by

a pharmaceutical company, and Carlomagno 2012 included an author who was an employee of a pharmaceutical company. Schachter 2007 and Tunon 2017 were supported by the companies that were producing the supplements that were used in the trials. One trial reports self-funding (Agrawal 2012), and 17 reported gaining funding from their institutions (Behrouzi 2017; Carlomagno 2012; Cheraghi 2016; Fernando 2018; Ghomian 2019; Hashemi 2017; Heidar 2019; Jahromi 2017; Jamilian 2018; Lu 2018; Mier-Cabrera 2008; Razavi 2015; Salehpour 2009; Siavashani 2018; Westphal 2006; Xu 2018; Zadeh Modarres 2018) Two trials (Mokhtari 2019; Mostajeran 2018) reported that they had no financial support. See details in Characteristics of included studies.

Excluded studies

We retrieved the full text of trials that we identified as potentially eligible for inclusion (see Figure 1). We excluded 58 trials; 34 of these were because the population did not meet criteria for inclusion in this review: Aflatoonian 2014; Ardabili 2012; Baillargeon 2004; Benelli 2016; Bonakdaran 2012; Cheang 2008; Ciotta 2012; Costantino 2009; Dastorani 2018; Elgindy 2010; Fatemi 2017; Firouzabadi 2012; Genazzani 2008; Hebisha 2016; Hernández-Yero 2012; Iuorno 2002; Jamilian 2016a; Jamilian 2016b; Kamencic 2008; Kilicdag 2005; Le Donne 2012; Li 2013; Mokhtari 2016a; Moosavifar 2010; Nestler 1999; Nestler 2001; Nordio 2012; Oner 2011; Pasha 2011; Pizzo 2014; Santanam 2003; Taheri 2015; Vargas 2011; Yoon 2010. 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 quasi-controlled trials and therefore were not randomised: Aksoy 2010; Al-Omari 2003; Crha 2003; Henmi 2003; Nazzaro 2011; Papaleo 2007; Tamura 2008. Ten had inappropriate treatment or control for inclusion: Asadi 2014; Elnashar 2007; Farzadi 2006; Hashim 2010; Immediata 2014; Kermack 2017; Papaleo 2008; Raffone 2010; Salem 2012; Twigt 2011. Four trials (Alborzi 2007; Aleyasin 2009; Balasch 1997; Creus 2008) were excluded as they were using pentoxifylline, a treatment that would have been included in the review prior to this update. Two trials (Elnashar 2005 and Siavashani 2016) were conference abstracts of other excluded trials (Elnashar 2007 and Jamilian 2016a respectively). Two were secondary analyses (Pal 2016; Ruder 2014). One was a duplicate study (Ghotbi 2007) of the excluded study Alborzi 2007, and we excluded Nichols 2010 after the lead investigator confirmed that this trial had been abandoned before recruitment because of lack of funding. One trial (Rezk 2004), previously excluded, was now added as a sub-study of the included study Rizk 2005.

Ongoing trials

In the 2017 update four ongoing trials became included trials (Agrawal 2012; Bentov 2014; Mohammadbeigi 2012; Youssef 2015); two became excluded trials (Ardabili 2012 (formerly known as Pourghassem 2010), and Pasha 2011). One (Unfer 2011) became an included trial in the review Showell 2018, so that five of the original 12 trials remained ongoing (NCT01019785; IRCT201112148408N1; CTRI/2012/08/002943; NCT01782911; NCT01267604). Three further ongoing trials (Fernando 2014; NCT03023514; NCT02058212) were added in the 2017 update (Fernando 2014 became the included trial Fernando 2018 in the latest update of this review).

We include 33 ongoing trials in this review update. In addition to the seven ongoing trials from previous versions of this review, we identified a further 26 ongoing trials: ChiCTR1800019772; ChiCTR-IPR-15006369; EUCTR2015-004233-27-IT; IRCT201009131760N9; IRCT201207156420N11; IRCT2012120311430N2; IRCT201306115942N2; IRCT20150831023831N2; IRCT201510266917N3; IRCT2016022821653N5; IRCT20160410027311N6; ISRCTN23488518; JPRN-UMIN000016992; NCT01659788; NCT01665547; NCT01896492; NCT02239107; NCT02993588; NCT03085030; NCT03117725; NCT03306745; NCT03396380; NCT03476564; NCT04019899; PACTR201902584533870; TCTR20171109001.

Risk of bias in included studies

See Figure 2 for a summary of risks 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.

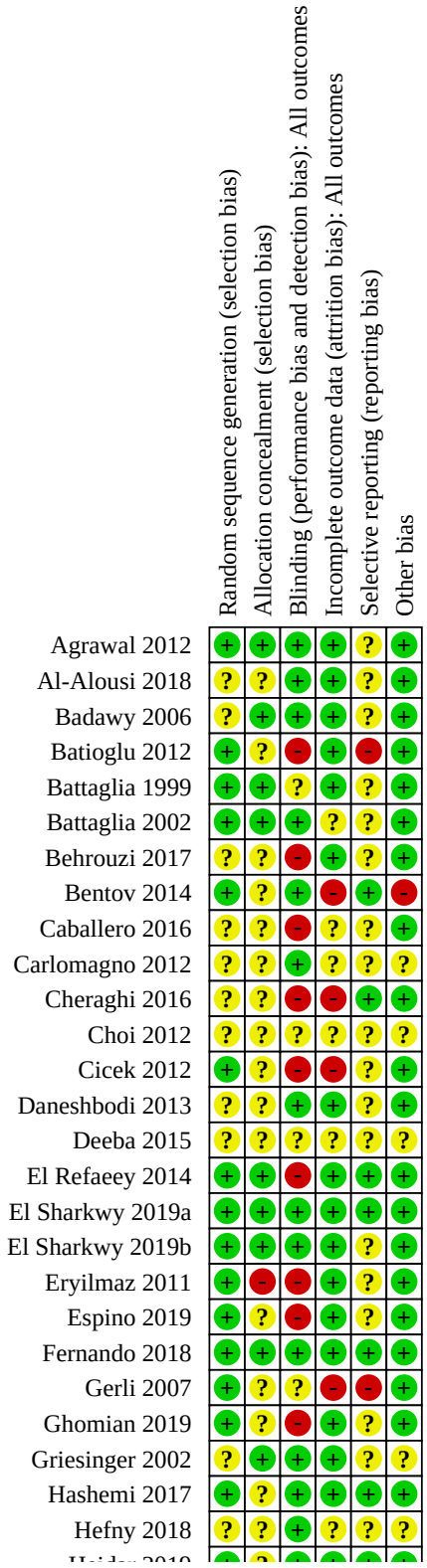


Figure 2. (Continued)

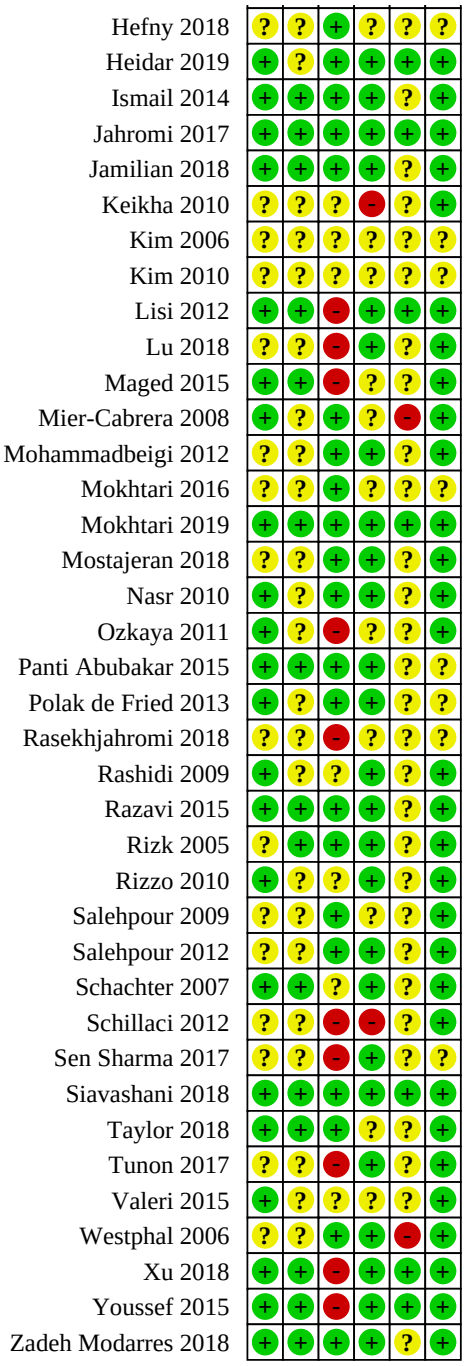
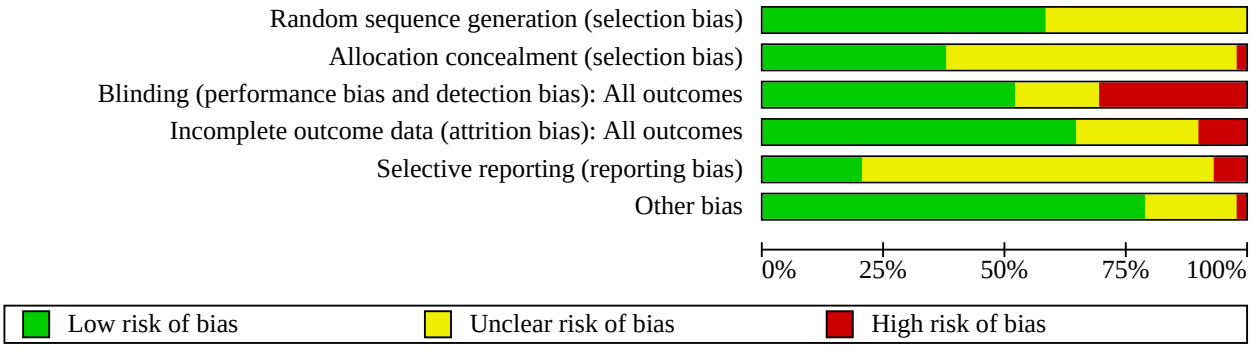


Figure 3. Methodological risk of bias graph: review authors' judgements about each methodological bias item presented as percentages across all included trials.



Allocation

Sequence Generation

All of the 63 included trials were randomised with a parallel design. Thirty-seven trials described their methods of sequence generation, which typically were computer-generated or used a random-number table: Agrawal 2012; Batioglu 2012; Battaglia 2002; Battaglia 1999; Bentov 2014; Cicek 2012; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Eryilmaz 2011; Espino 2019; Fernando 2018; Gerli 2007; Ghomian 2019; Hashemi 2017;Heidar 2019; Ismail 2014; Jahromi 2017; Jamilian 2018; Lisi 2012; Maged 2015; Mokhtari 2019; Mier-Cabrera 2008; Mohammadbeigi 2012; Nasr 2010; Ozkaya 2011; Polak de Fried 2013; Rashidi 2009; Razavi 2015; Rizzo 2010; Schachter 2007; Siavashani 2018; Taylor 2018; Valeri 2015; Xu 2018; Youssef 2015; Zadeh Modarres 2018. One trial (Panti Abubakar 2015) used a coin toss. Twenty-six trials simply reported the trial as randomised with no description of method, and were judged to be at unclear risk of bias for sequence generation: Al-Alousi 2018; Badawy 2006; Behrouzi 2017; Caballero 2016; Carlomagno 2012; Cheraghi 2016; Choi 2012; Daneshbodi 2013; Deeba 2015; Griesinger 2002; Hefny 2018; Keikha 2010; Kim 2006; Kim 2010; Lu 2018; Mier-Cabrera 2008; Mokhtari 2016; Mostajeran 2018; Rasekhjahromi 2018; Rizk 2005; Salehpour 2009; Salehpour 2012; Schillaci 2012; Sen Sharma 2017; Tunon 2017; Westphal 2006. There were no trials that we judged as high risk for this domain. We conducted a sensitivity analysis on the exclusion of trials that we considered to be at high risk in any of the 'Risk of bias' domains.

Allocation concealment

We judged 24 trials to be at low risk for allocation concealment: Agrawal 2012; Badawy 2006; Battaglia 1999; Battaglia 2002; Bentov 2014; El Sharkwy 2019a; El Sharkwy 2019b; El Refaeey 2014; Fernando 2018; Griesinger 2002; Ismail 2014; Jahromi 2017; Jamilian 2018; Lisi 2012; Maged 2015; Mokhtari 2019; Razavi 2015; Rizk 2005; Schachter 2007; Siavashani 2018; Taylor 2018; Xu 2018; Youssef 2015; Zadeh Modarres 2018. One trial (Eryilmaz 2011) replied through email correspondence that no allocation concealment was used and so was deemed to be at high risk. The remainder either did not describe any methods of allocation concealment or the description was not clear. We tried unsuccessfully to contact these authors about allocation concealment techniques.

Blinding

We considered that the blinding status of participants could influence findings for the outcomes of live birth, pregnancy and adverse effects, as antioxidants are easily available and it would be possible for participants to self-medicate. If the participants were not blinded or the trial was not placebo-controlled, or both, we therefore considered the trial to be at high risk. Forty-one of the 63 included trials described some form of blinding of participants or investigators, or both.

One trial (Taylor 2018) was quadruple-blinded. Six were triple-blinded, with participants, clinicians/investigators and outcome assessors blinded: Agrawal 2012; Badawy 2006; Battaglia 2002; El Sharkwy 2019b; Fernando 2018; Mier-Cabrera 2008. Ten were double-blinded with blinding of participants and clinicians: Al-Alousi 2018; Bentov 2014; El Sharkwy 2019a; Griesinger 2002; Hashemi 2017; Jamilian 2018; Razavi 2015; Rizk 2005; Salehpour 2009; Westphal 2006. Eighteen stated that they were double-blinded but did not declare who was blinded: Cheraghi 2016; Carlomagno 2012; Daneshbodi 2013; Gerli 2007; Ghomian 2019; Hefny 2018; Heidar 2019; Ismail 2014; Jahromi 2017; Keikha 2010; Mokhtari 2016; Mokhtari 2019; Mostajeran 2018; Polak de Fried 2013; Siavashani 2018; Tunon 2017; Valeri 2015; Zadeh Modarres 2018. Tunon 2017 states that the trial is double-blinded but there is no description of what type of control is used in the study, so we considered it to be at high risk for this domain, as it might be a 'no-treatment trial'. Ghomian 2019 and Valeri 2015 were also no-treatment trials but reported being double-blinded.

Six trials were single-blinded: the participants were blinded in Panti Abubakar 2015 and Salehpour 2012; the embryologists were blinded in Espino 2019; and the outcome assessors were blinded in Lisi 2012, El Refaeey 2014 and Mohammadbeigi 2012.

The remaining 22 trials did not report any blinding; however, 13 of these used 'no treatment' as the control, making blinding for these trials problematic. We therefore considered these trials to be at high risk for this domain: Battaglia 1999; Batioglu 2012; Behrouzi 2017; Caballero 2016; Carlomagno 2012; Cicek 2012; Eryilmaz 2011; Lu 2018; Maged 2015; Rasekhjahromi 2018; Sen Sharma 2017; Xu 2018; Youssef 2015. Only Xu 2018 stated that it was an open study. Nine trials did not report on blinding: Choi 2012; Deeba 2015; Kim 2006; Kim 2010; Ozkaya 2011; Rashidi 2009; Rizzo 2010; Schachter 2007; Schillaci 2012.

We rated Espino 2019 at high risk of bias for the blinding domain. In the treatment-versus-control arm of the trial, the control is 'no treatment' so blinding was not possible, although the paper states that; "Embryo quality was graded by blinded embryologists" (page 2/11). However, we consider it to be at low risk in the head-to-head comparison; "Melatonin treatments comprised immediate-release melatonin formula (Guinama, Valencia, Spain) that was encapsulated in identical two-piece gelatine capsules (containing 3 mg or 6 mg melatonin) and dispensed in identical 50-capsule containers". We were unable to use two different judgements in the 'Risk of bias' table, so we used the 'high risk' judgement in the 'Risk of bias' table and covered the 'low risk' judgement for the head-to-head comparison in the text here, in the Effects of interventions section and in the footnotes of the appropriate forest plot, in order to ensure that the study was removed in the sensitivity analysis.

Incomplete outcome data

Fourteen trials included in the meta-analysis had no losses to follow-up: Badawy 2006; Batioglu 2012; Battaglia 1999; Espino 2019; Lisi 2012; Maged 2015; Nasr 2010; Polak de Fried 2013; Rashidi 2009; Rizk 2005; Rizzo 2010; Schachter 2007; Sen Sharma 2017; Westphal 2006. Four trials reported losses but used intention-to-treat (ITT) analysis: Agrawal 2012; Fernando 2018; Ismail 2014; Youssef 2015. Fourteen trials had losses and described from which groups they were lost, but did not use ITT in the reporting of trials; however, we used ITT for them in the meta-analysis: Battaglia 2002; Behrouzi 2017; El Refaeey 2014; El Sharkwy 2019a; El Sharkwy 2019b; Jahromi 2017; Lu 2018; Mier-Cabrera 2008; Mokhtari 2019; Mostajeran 2018; Panti Abubakar 2015; Salehpour 2012; Tunon 2017; Xu 2018.

Bentov 2014 had explained loss to follow-up but reported data as percentages, so it is unclear if ITT was used. This trial was also terminated before finishing enrolment, and we therefore rated it at high risk for this domain. Cheraghi 2016 explained the losses but was considered at high risk for attrition, as the losses were over 25% of the randomised women.

Three trials (Cicek 2012, Eryilmaz 2011; Griesinger 2002;) had losses to follow-up with no explanation of which groups were affected, but we took data from these trials as totals were given after dropouts, and we assumed that the groups were equal on allocation.

The data from the following 26/63 included trials could not be added to the meta-analysis. Ten of these trials had different reported outcomes from those of the review, Jamilian 2018 and Zadeh Modarres 2018 had no attrition, and two trials (Ghomian 2019; Siavashani 2018) both used intention-to-treat. Four trials (Al-Alousi 2018; Hashemi 2017; Heidar 2019; Salehpour 2009) explained their losses to follow-up. We judged Schillaci 2012 to be at high risk for the attrition domain as the paper provided preliminary results only, the numbers given in the text are different from numbers in the baseline characteristics table and there appear to be two dropouts from the intervention group which go unexplained. Mokhtari 2016 was judged as unclear as no mention of attrition was given.

Gerli 2007 had more than 30% dropouts from the treatment group, and data were unavailable for the 15 other trials: Caballero 2016; Carlomagno 2012; Choi 2012; Daneshbodi 2013; Deeba 2015; Hefny 2018; Keikha 2010; Kim 2006; Kim 2010; Mohammadbeigi 2012; Ozkaya 2011; Rasekhjahromi 2018; Razavi 2015; Taylor 2018; Valeri 2015. We tried to contact authors when the data were unavailable.

Selective reporting

We considered a trial to be at low risk for selective reporting if a trial registration number or protocol was provided and the clinical outcomes of live birth or clinical pregnancy or both were reported. Thirteen trials (Bentov 2014; Cheraghi 2016; El Refaeey 2014; El Sharkwy 2019a; Fernando 2018; Hashemi 2017; Heidar 2019; Jahromi 2017; Lisi 2012; Mokhtari 2019; Siavashani 2018; Xu 2018; Youssef 2015) were classified as low risk.

Four trials were considered to be at high risk of bias for various reasons. These include higher clinical pregnancy numbers reported than biochemical pregnancy numbers (Batioglu 2012); in Gerli 2007 only half the population declared wanting to become pregnant, with miscarriages reported but with no information on which groups they occurred in. Mier-Cabrera 2008 stated that they would collect live births but these was not reported and there was no trial registration number. Westphal 2006 combined the miscarriage and side-effect data from their trial with an extra three months of data from a non-randomised source.

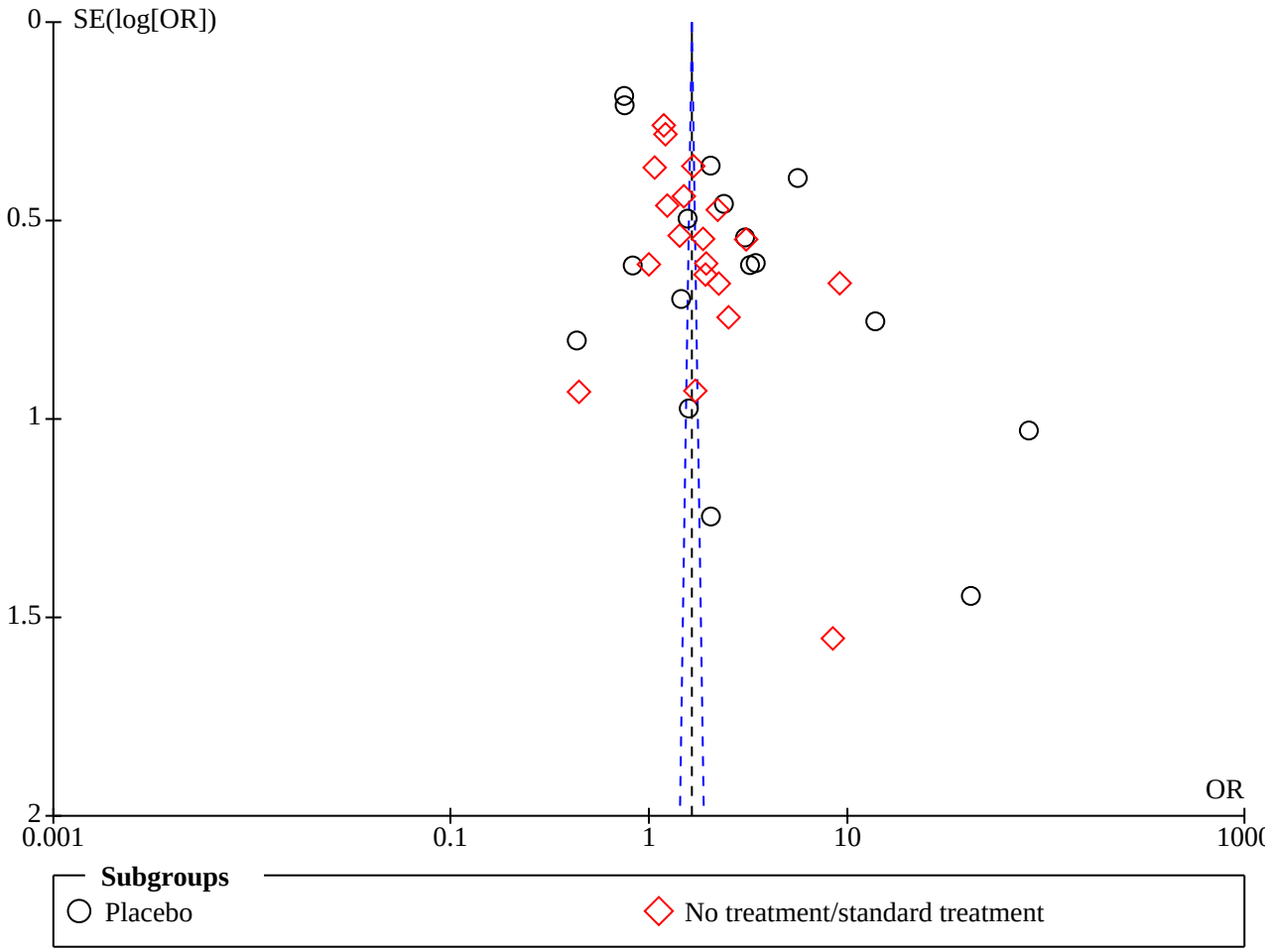
We assigned unclear risks of bias to the remaining 46 trials (see Characteristics of included studies). The trials were classified as 'unclear' firstly if they had a trial registration number but no report of clinical outcomes in a trial where you would expect these to be reported, and secondly if no trial registration number was provided but clinical outcomes such as live birth or clinical pregnancy were reported.

Failure to report live birth in subfertility trials is common, and is a major source of bias (Clarke 2010); it should be the default primary outcome in fertility trials. Only 13 trials reported live birth: Agrawal 2012; Battaglia 2002; Bentov 2014; Caballero 2016; Cicek 2012; Caballero 2016; Fernando 2018; Jahromi 2017; Nasr 2010; Panti Abubakar 2015; Polak de Fried 2013; Tunon 2017; Xu 2018; this represents an increase of only six trials from the 2017 version of this review (three of the original trials (Aleyasin 2009a; Ciotta 2011; Unfer 2011) were removed as they were now included in Showell 2018).

Two trials (Agrawal 2012; Schachter 2007) reported ongoing pregnancy and Espino 2019 reported full-term pregnancies, which we took to be live birth in the analysis. Mier-Cabrera 2008 stated that they would report live birth, but reported only pregnancy. Caballero 2016 was not included in the meta-analysis as the numbers per group were not available. Tunon 2017 did not provide clarification of the control used, so for the purposes of this meta-analysis we consider the trial to be a no-treatment control. Adverse events were not well reported in most studies. We attempted to contact all authors about live birth and adverse outcomes.

A funnel plot for clinical pregnancy (Figure 4) was symmetrical, except for an absence of studies in the lower left of the pyramid. This suggests a small-study effect, indicating the potential for publication bias whereby small unpublished studies with negative results were not represented. Estimates of the intervention effect tend to be more beneficial in smaller studies and thus introduce the potential for selective reporting and publication bias.

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

We rated Bentov 2014 at high risk in this domain, for women receiving varying adjunctive treatments and early termination of the study, respectively. See details in Characteristics of included studies.

Reasons for studies with data 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. Ninety-two women were randomly assigned, 45 to the treatment group and 47 to the control group. Twenty-three from the treatment group and 19 from the control group wished to conceive; four from the treatment group and one from the control group became pregnant. This trial also had more than 30% dropouts from the treatment group.

Effects of interventions

See: **Summary of findings 1** Antioxidant(s) compared to placebo or no treatment/standard treatment for female subfertility; **Summary of findings 2** Head-to-head antioxidants for female subfertility

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

Primary outcome: Live birth

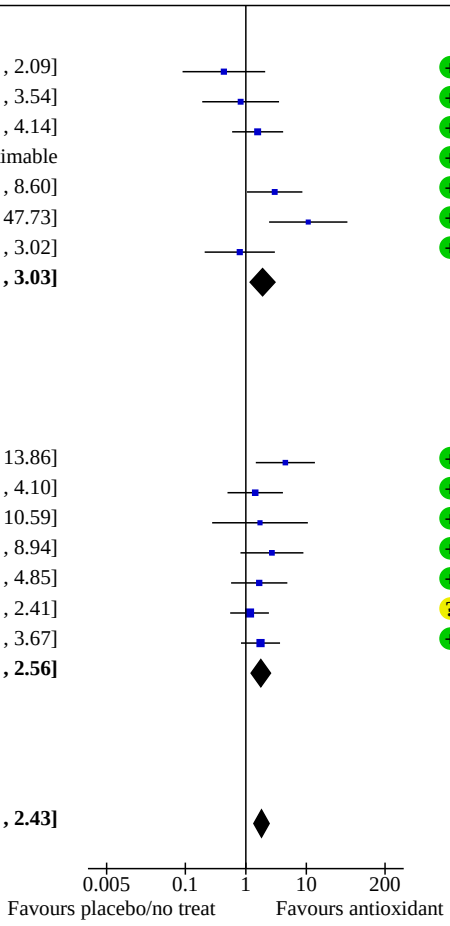
1.1 Live birth; antioxidants versus placebo or no treatment/standard treatment

See Analysis 1.1.

Due to the very low-quality evidence we are uncertain whether antioxidants improve live birth rate compared with placebo or no treatment/standard treatment (odds ratio (OR) 1.81, 95% confidence interval (CI) 1.36 to 2.43; P < 0.001, I^2 = 29%; 13 RCTs, 1227 women; very low-quality evidence; Figure 5). This suggests that among subfertile women with an expected live birth rate of 19%, the rate among women using antioxidants would be between 24% and 36% (Summary of findings 1).

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).

Study or Subgroup	Antioxidant Events	Antioxidant Total	Placebo/No treatment Events	Placebo/No treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.1.1 Placebo							
Battaglia 2002 (1)	3	18	6	19	7.0%	0.43 [0.09 , 2.09]	+ + + ? ? +
Bentov 2014 (2)	4	17	6	22	5.8%	0.82 [0.19 , 3.54]	+ ? + - + -
Fernando 2018 (3)	26	120	6	40	10.2%	1.57 [0.59 , 4.14]	+ + + + + +
Jahromi 2017	0	40	0	40		Not estimable	+ + + + + +
Nasr 2010 (4)	20	30	12	30	5.8%	3.00 [1.05 , 8.60]	+ ? + + ? +
Panti Abubakar 2015	18	100	2	100	2.4%	10.76 [2.42 , 47.73]	+ + + + ? ?
Polak de Fried 2013	5	26	6	26	7.0%	0.79 [0.21 , 3.02]	+ ? + + ? ?
Subtotal (95% CI)		**351**		**277**	**38.1%**	**1.89 [1.18 , 3.03]**	
Total events:	76		38				
Heterogeneity: Chi² = 12.36, df = 5 (P = 0.03); I² = 60%							
Test for overall effect: Z = 2.65 (P = 0.008)							
1.1.2 No treatment							
Agrawal 2012 (5)	18	30	7	28	4.2%	4.50 [1.46 , 13.86]	+ + + + ? +
Cicek 2012 (6)	10	53	7	50	8.4%	1.43 [0.50 , 4.10]	+ ? - - ? +
Espino 2019 (7)	6	20	2	10	2.7%	1.71 [0.28 , 10.59]	+ ? - + ? +
Schachter 2007 (8)	13	24	7	23	4.7%	2.70 [0.82 , 8.94]	+ + ? + ? +
Schachter 2007 (9)	14	27	11	28	7.5%	1.66 [0.57 , 4.85]	+ + ? + ? +
Tunon 2017 (10)	24	60	22	60	19.0%	1.15 [0.55 , 2.41]	? ? - + ? +
Xu 2018	22	93	14	93	15.4%	1.75 [0.83 , 3.67]	+ + - + + +
Subtotal (95% CI)		**307**		**292**	**61.9%**	**1.77 [1.22 , 2.56]**	
Total events:	107		70				
Heterogeneity: Chi² = 4.60, df = 6 (P = 0.60); I² = 0%							
Test for overall effect: Z = 3.03 (P = 0.002)							
Total (95% CI)		**658**		**569**	**100.0%**	**1.81 [1.36 , 2.43]**	
Total events:	183		108				
Heterogeneity: Chi² = 16.86, df = 12 (P = 0.15); I² = 29%							
Test for overall effect: Z = 4.03 (P < 0.0001)							
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%							



Footnotes

(1) Women are also undergoing IVF/ICSI
(2) Study terminated due to embryo safety reasons before reaching target number of enrolled women
(3) 3 active arms; the numbers for the active groups have been combined
(4) Women are also undergoing laparoscopic ovarian drilling
(5) Ongoing pregnancy rate
(6) Ongoing pregnancy rate. Women undergoing IUI
(7) Considered high risk as no blinding (low risk for the head-to-head comparison where there is blinding). 3-armed trial; treatment groups were combined
(8) Ongoing pregnancy rate. 84 of these women underwent IVF/ICSI and 18 ovulation induction.
(9) Ongoing pregnancy rate. 82 of these women underwent IVF/ICSI and 18 ovulation induction
(10) Combined antioxidants

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

In the 13 trials that reported live birth (Agrawal 2012; Battaglia 2002; Bentov 2014; Cicek 2012; Espino 2019; Fernando 2018; Jahromi 2017; Nasr 2010; Panti Abubakar 2015; Polak de Fried 2013; Schachter 2007; Tunon 2017; Xu 2018), the OR for live birth was 1.81 and for clinical pregnancy was 1.80. When we pooled all 35 studies that reported clinical pregnancy, the OR for clinical pregnancy was lower, at 1.65. This suggests that the clinical pregnancy rate in the 13 trials that reported live birth may have been a small overestimation of the effect of the antioxidants, and hence that the live birth rate in these trials may also be a small overestimate (Summary of findings 1).

The test for subgroup differences showed no evidence of a difference between the placebo and no-treatment subgroups (Chi^2 = 0.05, df = 1, P = 0.83, I^2 = 0%).

1.2 Live birth; type of antioxidant

See Analysis 1.2.

We considered each type of antioxidant separately. Only four comparisons contained more than one trial, including Schachter 2007, a four arm trial.

1.2.1 Nasr 2010; compared *N*-acetylcysteine with placebo (OR 3.00, 95% CI 1.05 to 8.60; P = 0.04, 60 women).

1.2.2 Battaglia 2002; compared L-arginine with placebo (OR 0.43, 95% CI 0.09 to 2.09; P = 0.30, 37 women).

1.2.3 Bentov 2014; compared CoQ10 with placebo and Xu 2018 compared CoQ10 with no treatment (OR 1.50, 95% CI 0.78 to 2.88; P= 0.23, I^2 = 0%; 2 RCTs, 225 women). Antioxidants were not associated with an increased live birth rate compared with placebo or with no treatment in women taking CoQ10.

1.2.4 Polak de Fried 2013; compared Vitamin D with placebo (OR 0.79, 95% CI 0.21 to 3.02; P = 0.73; 52 women).

1.2.5 Schachter 2007, a four-armed trial with two arms comparing a Vitamin B complex with no treatment and Vitamin B complex plus metformin versus metformin (also considered to be 'no treatment'), showing no association with increased live birth rate compared to no treatment (OR 2.07, 95% CI 0.93 to 4.57; P = 0.07, I^2 = 0%; 102 women).

1.2.6 Agrawal 2012 and Tunon 2017 compared combined antioxidants with no treatment, and Panti Abubakar 2015 compared combined antioxidants with placebo. Combined antioxidants were associated with an increased live birth rate compared with placebo or no treatment (OR 2.59, 95% CI 1.52 to 4.40; P < 0.001, I^2 = 78%; 3 RCTs, 378 women).

1.2.7 Cicek 2012 compared Vitamin E to no treatment (OR 1.43, 95% CI 0.50 to 4.10; P = 0.51; 103 women).

1.2.8 Fernando 2018 and Jahromi 2017 compared melatonin with placebo and Espino 2019 compared it with no treatment (OR 1.60, 95% CI 0.68 to 3.76; P = 0.28, I^2 = 0%; 3 RCTs, 270 women). Antioxidants were not associated with an increased live birth rate compared with placebo or no treatment in women taking melatonin.

The test for subgroup differences showed no evidence of a difference between the subgroups of antioxidant type (Chi^2 = 7.96, df = 7, P = 0.34, I^2 = 12%).

1.3 Live birth rate; indications for subfertility

See Analysis 1.3.

1.3.1 Polycystic ovary syndrome

Three trials reported on women with PCOS: Panti Abubakar 2015; Nasr 2010; and Schachter 2007 (a four-armed trial, which contributed to two comparisons in this analysis). Antioxidants were associated with an increased live birth rate compared with placebo or no treatment in women with PCOS (OR 3.34, 95% CI 1.90 to 5.86; P < 0.001, I^2 = 28%; 3 RCTs, 362 women). Each trial included different antioxidants: N-acetylcysteine, combined antioxidants and Vitamin B complex.

1.3.2 Tubal subfertility

One trial (Battaglia 2002) enrolled women with tubal subfertility undergoing IVF (OR 0.43, 95% CI 0.09 to 2.09; P = 0.30; 37 women).

1.3.3 Varying indications

Three trials (Agrawal 2012; Fernando 2018; Tunon 2017) enrolled women with various causes of subfertility (OR 1.70, 95% CI 1.02 to 2.83; P = 0.04, I^2 = 50%; 3 RCTs, 338 women). Antioxidants were associated with an increased live birth rate compared with placebo or no treatment in women with varying indications for subfertility.

1.3.4 Unexplained subfertility

Two trials (Cicek 2012; Espino 2019) enrolled women with unexplained subfertility (OR 1.50, 95% CI 0.60 to 3.72: P = 0.38, I^2 = 0%: 2 RCTs, 133 women).

1.3.5 Poor ovarian reserve

Two trials (Jahromi 2017; Xu 2018) enrolled women with poor ovarian reserve, but Jahromi 2017 reported no live births in either the treatment or control groups (OR 1.75, 95% CI 0.83 to 3.67; P = 0.14; 2 RCTs, 266 women).

1.4 Live birth; IVF/ICSI

See Analysis 1.4.

Nine trials (Battaglia 2002; Bentov 2014; Espino 2019; Fernando 2018; Jahromi 2017; Polak de Fried 2013; Schachter 2007; Tunon 2017; Xu 2018) compared antioxidants with placebo or no treatment in women having IVF/ICSI treatment and reporting live birth. Antioxidants were not associated with an increased live birth rate compared with placebo or no treatment in women undergoing IVF/ICSI (OR 1.36, 95% CI 0.96 to 1.93; P = 0.08, I^2 = 0%; 9 RCTs, 806 women). Jahromi 2017 reported no live births in either the treatment or control groups.

Secondary outcome: Clinical pregnancy

Only 35 of the 63 included trials presented or provided data that could be used in this meta-analysis. We could not use the data for the remaining 28 trials in the meta-analysis, as they provided either only 'pregnancy' or biochemical pregnancy data (see Table

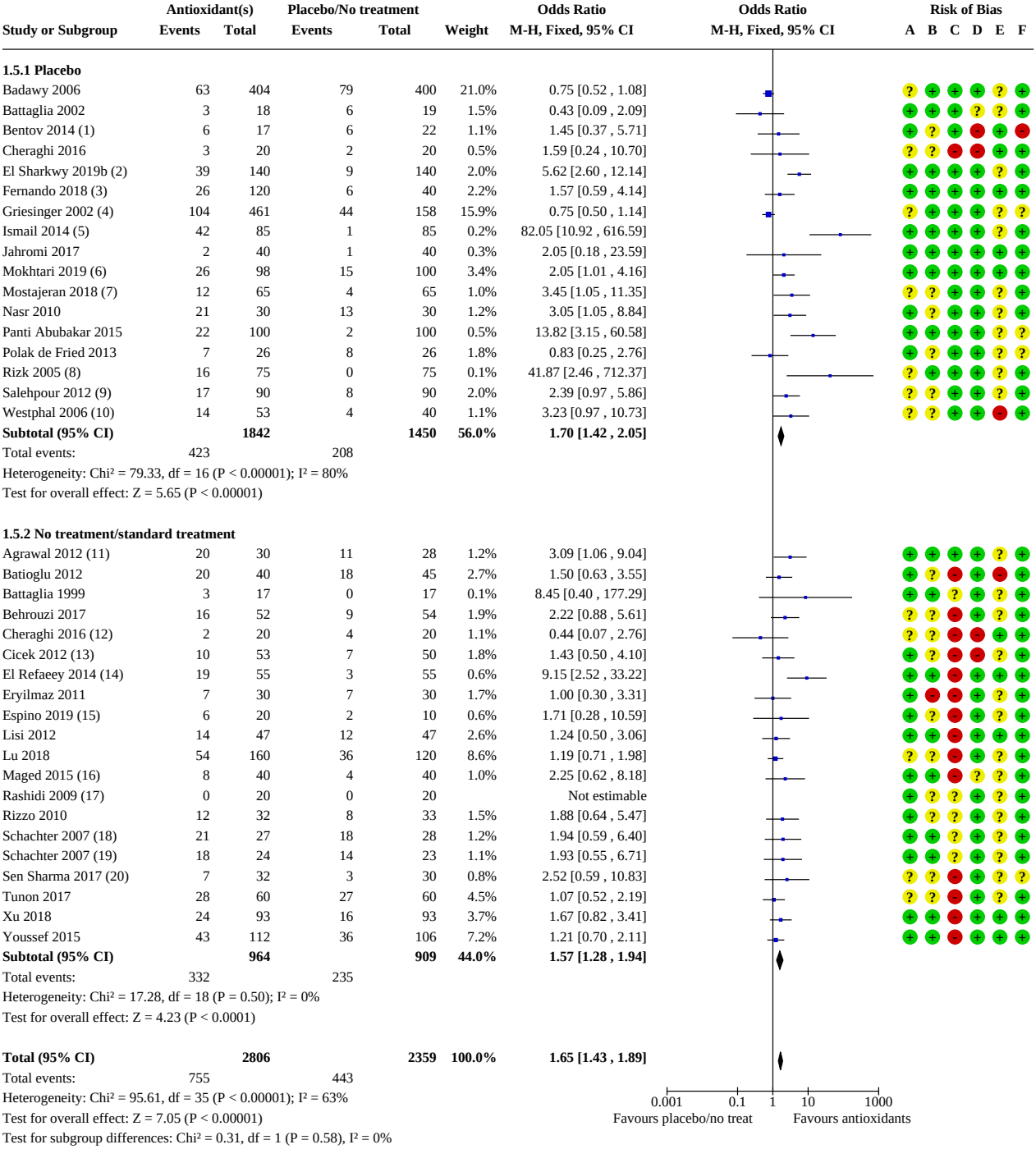
2), only bio-markers or embryo/oocyte numbers, or insufficient information in the reports, which were mainly conference abstracts. We tried to contact these authors to obtain the clinical pregnancy data; some responded saying that they did not have the data, while others did not respond at all.

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

See Analysis 1.5.

Antioxidants may improve the clinical pregnancy rate compared with placebo or no treatment (OR 1.65, 95% CI 1.43 to 1.89; P < 0.001, I^2 = 63%; 35 RCTs, 5165 women; low-quality evidence; Figure 6). This suggests that among subfertile women with an expected clinical pregnancy rate of about 19%, the rate among women using antioxidants would be between 25% and 30% (Summary of findings 1). Heterogeneity was moderately 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).



Footnotes

(1) Study terminated due to embryo safety reasons
(2) CC plus metformin and L-carnitine versus CC plus metformin and placebo
(3) 3 active arms; the numbers for the active groups have been combined
(4) The 3 active arms versus placebo of this trial have been combined
(5) timed intercourse PCOS clomiphene + carnitine vs clomiphene + placebo
(6) Women with PCOS undergoing IUI
(7) Timed intercourse with ovulation induction. Letrozole + NAC vs letrozole + placebo
(8) N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate

Figure 6. (Continued)

(7) Timed intercourse with ovulation induction. Letrozole + NAC vs letrozole + placebo
(8) N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate
(9) NAC + clomiphene vs placebo + clomiphene
(10) Women are conceiving naturally. Only first 3 months data used
(11) Agrawal 2012 and Lisi 2012 use folic acid 400 mcg (standard care) as control
(12) 4-armed trial; NAC plus metformin versus metformin
(13) Women undergoing IUI
(14) Data per woman over 2 cycles of timed intercourse. CoQ10 + clomiphene versus clomiphene
(15) 3-armed trial; treatment groups were combined
(16) N-acetylcysteine plus clomiphene citrate versus no treatment + clomiphene citrate
(17) Natural conception
(18) Vitamin B complex plus metformin vs metformin alone. Cumulative pregnancy rate over 3 months
(19) Cumulative pregnancy rate over 3 cycles
(20) Co-enzyme Q10 + clomiphene citrate versus clomiphene citrate. Timed intercourse

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

The test for subgroup differences showed no evidence of a difference between the placebo and no-treatment subgroups (Chi^2 = 0.31, df = 1, P = 0.58, I^2 = 0%).

Sensitivity analyses

Using a random-effects model did not change the direction of the results, and the I^2 remained at 63%.

1. We conducted a sensitivity analysis, excluding trials with a high risk of bias in any domain.

Sixteen trials (Batioglu 2012; Behrouzi 2017; Bentov 2014; Cheraghi 2016; Cicek 2012; El Refaeey 2014; Eryilmaz 2011; Espino 2019; Lisi 2012; Lu 2018; Maged 2015; Sen Sharma 2017; Tunon 2017; Xu 2018; Youssef 2015; Westphal 2006) had a rating of high risk in any one or more of the 'Risk of bias' domains (mostly in the domain of blinding in the no-treatment trials) (see Characteristics of included studies). When these trials were removed in a sensitivity analysis, there remained an association between antioxidants and an increased clinical pregnancy rate when compared to placebo (OR 1.74, 95% CI 1.45 to 2.08; P < 0.001, I^2 = 78%; 19 RCTs, 3449 women). Heterogeneity was high.

2. We conducted a sensitivity analysis, excluding studies that used a fertility drug (metformin, clomiphene or letrozole) as a control plus a placebo or no treatment (these agents were in both the intervention and control arms, with an antioxidant in addition in the intervention arm). When these 13 trials were removed from the analysis (Badawy 2006; Behrouzi 2017; Cheraghi 2016; El Refaeey 2014; El Sharkwy 2019b; Espino 2019; Ismail 2014; Maged 2015; Mostajeran 2018; Rizk 2005; Salehpour 2012; Schachter 2007; Sen Sharma 2017) there remained an association between antioxidants and an increased clinical pregnancy rate compared no treatment (OR 1.40, 95% CI 1.17 to 1.67; P < 0.001, I^2 = 31%; 24 RCTs, 2968 women). Two trials (Cheraghi 2016; Schachter 2007) were multi-armed, but only those arms with a fertility drug plus placebo/no treatment were removed in this analysis.

1.6 Clinical pregnancy; type of antioxidant

See Analysis 1.6.

We considered each type of antioxidant separately.

1.6.1 N-acetylcysteine was associated with an increased clinical pregnancy rate when compared with placebo, no treatment or standard treatment (OR 1.36, 95% CI 1.05 to 1.77; P = 0.02, , I^2 = 71%; 8 RCTs, 1590 women). Heterogeneity was very high, perhaps as a result of the high risk of bias for blinding in Behrouzi 2017; Cheraghi 2016; Maged 2015, and the unclear risk of bias for sequence generation in Badawy 2006; Behrouzi 2017; Cheraghi 2016 Mostajeran 2018; Rizk 2005; Salehpour 2012, or the additional treatment of laparoscopic drilling that women received in Nasr 2010.

1.6.2 Combined antioxidants (similar antioxidants were combined in each trial) were associated with an increased clinical pregnancy rate when compared to placebo or no treatment (OR 1.90, 95% CI 1.33 to 2.70; P < 0.001, I^2 = 70%; 5 RCTs, 689 women). Heterogeneity was high, with two of the trials enrolling small numbers of women.

1.6.3 Melatonin was associated with an increased clinical pregnancy rate when compared with placebo, no treatment or standard treatment (OR 1.66, 95% CI 1.12 to 2.47; P = 0.01, I^2 = 0%; 7 RCTs, 678 women).

1.6.4 There was no clear evidence of a difference in clinical pregnancy rates between Vitamin E and no treatment (OR 1.43, 95% CI 0.50 to 4.10; P = 0.51; 103 women).

1.6.5 There was no clear evidence of a difference in clinical pregnancy rates between ascorbic acid and placebo (OR 0.91, 95% CI 0.66 to 1.25; P = 0.55, I^2 = 46%; 2 RCTs, 899 women).

1.6.6 There was no clear evidence of a difference in clinical pregnancy rates between L-arginine and placebo or no treatment (OR 1.05, 95% CI 0.32 to 3.46; P = 0.94, I^2 = 67%; 2 RCTs, 71 women).

1.6.7 There was no clear evidence of a difference in clinical pregnancy rates between myo-inositol plus folic acid and placebo or no treatment (OR 1.24, 95% CI 0.50 to 3.06: P = 0.64; 94 women).

1.6.8 CoQ10 was associated with an increased clinical pregnancy rate when compared to placebo or no treatment (OR 2.49, 95% CI 1.50 to 4.13; P < 0.001, I^2 = 47%; 4 RCTs, 397 women).

1.6.9 L-carnitine was associated with an increased clinical pregnancy rate when compared to placebo (OR 11.14, 95% CI 5.70 to 21.81; P < 0.001, I^2 = 85%; 2 RCTs, 450 women). The high heterogeneity may be due to the very high numbers of clinical pregnancy in the treatment group (42/85) when compared to the low numbers in the control group (1/85) in Ismail 2014.

1.6.10 There was no clear evidence of a difference in clinical pregnancy rates between vitamin D and placebo (OR 0.83, 95% CI 0.25 to 2.76; P = 0.76; 2 RCTs, 92 women). Rashidi 2009 reported no clinical pregnancies in either treatment or control group.

1.6.11 There was no clear evidence of a difference in clinical pregnancy rates between vitamin B complex in the two arms of Schachter 2007 and placebo or no treatment (OR 1.94, 95% CI 0.82 to 4.58; P = 0.13, I^2 = 0%; 1 RCT, 102 women).

The test for subgroup differences showed that there were differences between the type of antioxidant subgroups (Chi^2 = 51.55, df = 10, P < 0.001, I^2 = 80.6%).

1.7 Clinical pregnancy rate; indications for subfertility

See Analysis 1.7.

1.7.1 Polycystic ovary syndrome

Antioxidants were associated with an increased clinical pregnancy rate when compared with placebo, no treatment or standard treatment in women with PCOS (OR 4.24, 95% CI 3.23 to 5.56; P < 0.001, I^2 = 51%; 15 RCTs, 1908 women).

1.7.2 Unexplained subfertility

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women with unexplained subfertility (OR 0.84, 95% CI 0.61 to 1.16; P = 0.29, I^2 = 0%; 4 RCTs, 997 women).

1.7.3 Tubal subfertility

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women with tubal subfertility (OR 1.05, 95% CI 0.32 to 3.46; P = 0.94, I^2 = 67%; 2 RCTs, 71 women).

1.7.4 Varying indications

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women with varying indications (OR 1.14, 95% CI 0.85 to 1.52; P = 0.38, I^2 = 54%; 6 RCTs, 1135 women).

1.7.5 Poor responders

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women who were poor responders (OR 1.88, 95% CI 0.64 to 5.47; P = 0.25; 1 RCT, 65 women).

1.7.6 Poor ovarian reserve

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women with poor ovarian reserve (OR 1.70, 95% CI 0.86 to 3.37; P = 0.13, I^2 = 0%; 2 RCTs, 266 women).

1.7.7 Endometriosis

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women with endometriosis (OR 1.19, 95% CI 0.71 to 1.98; P = 0.51; 1 RCT, 280 women).

1.8 Clinical pregnancy rate; IVF/ICSI

See Analysis 1.8.

There was no clear evidence of a difference in clinical pregnancy rates when antioxidants were compared with placebo, no treatment or standard treatment in women undergoing IVF/ICSI (OR 1.15, 95% CI 0.95 to 1.40; P = 0.15, I^2 = 0%; 18 RCTs, 2341 women).

Secondary outcome: Adverse events

1.9 Adverse events

See Analysis 1.9; Figure 7

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

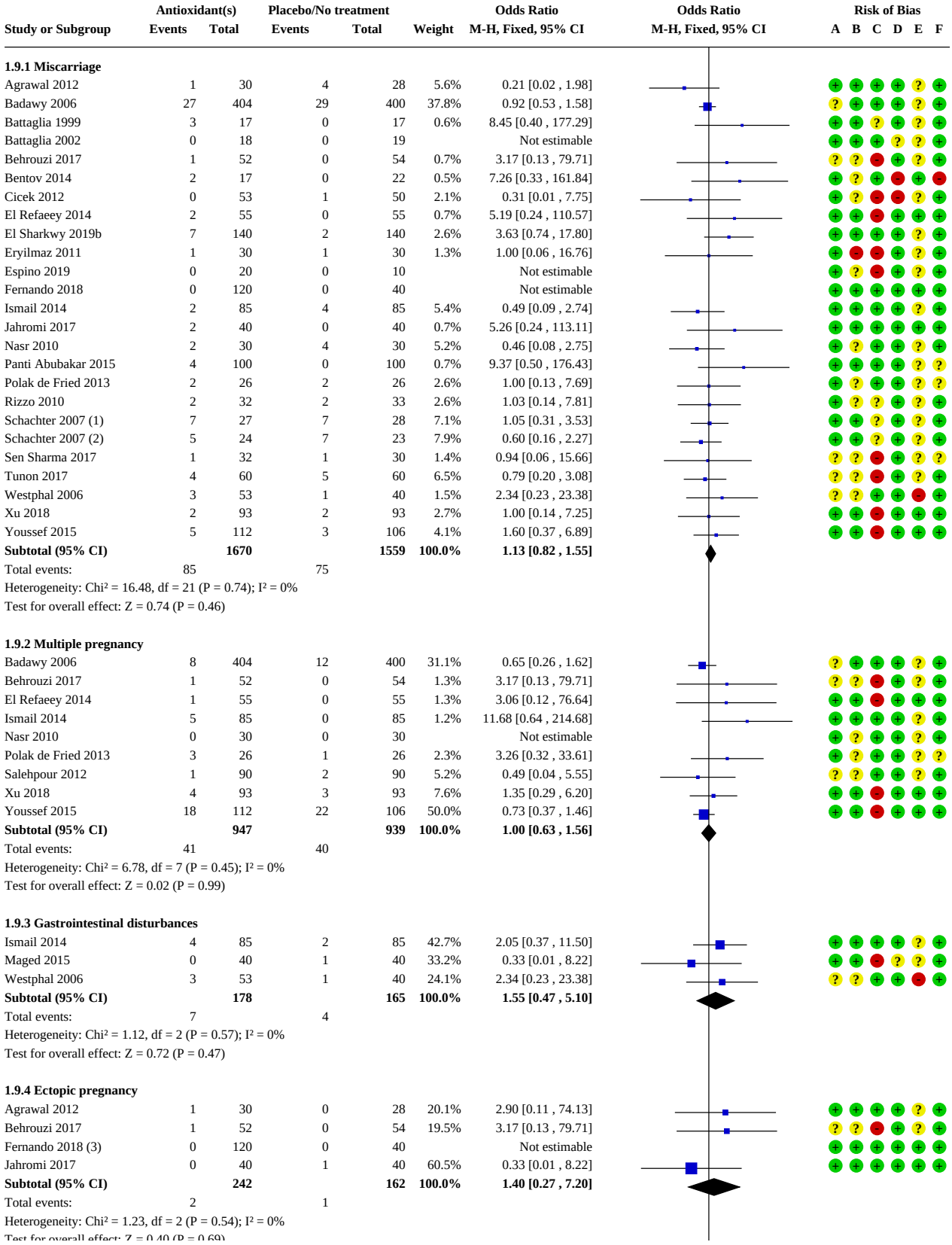
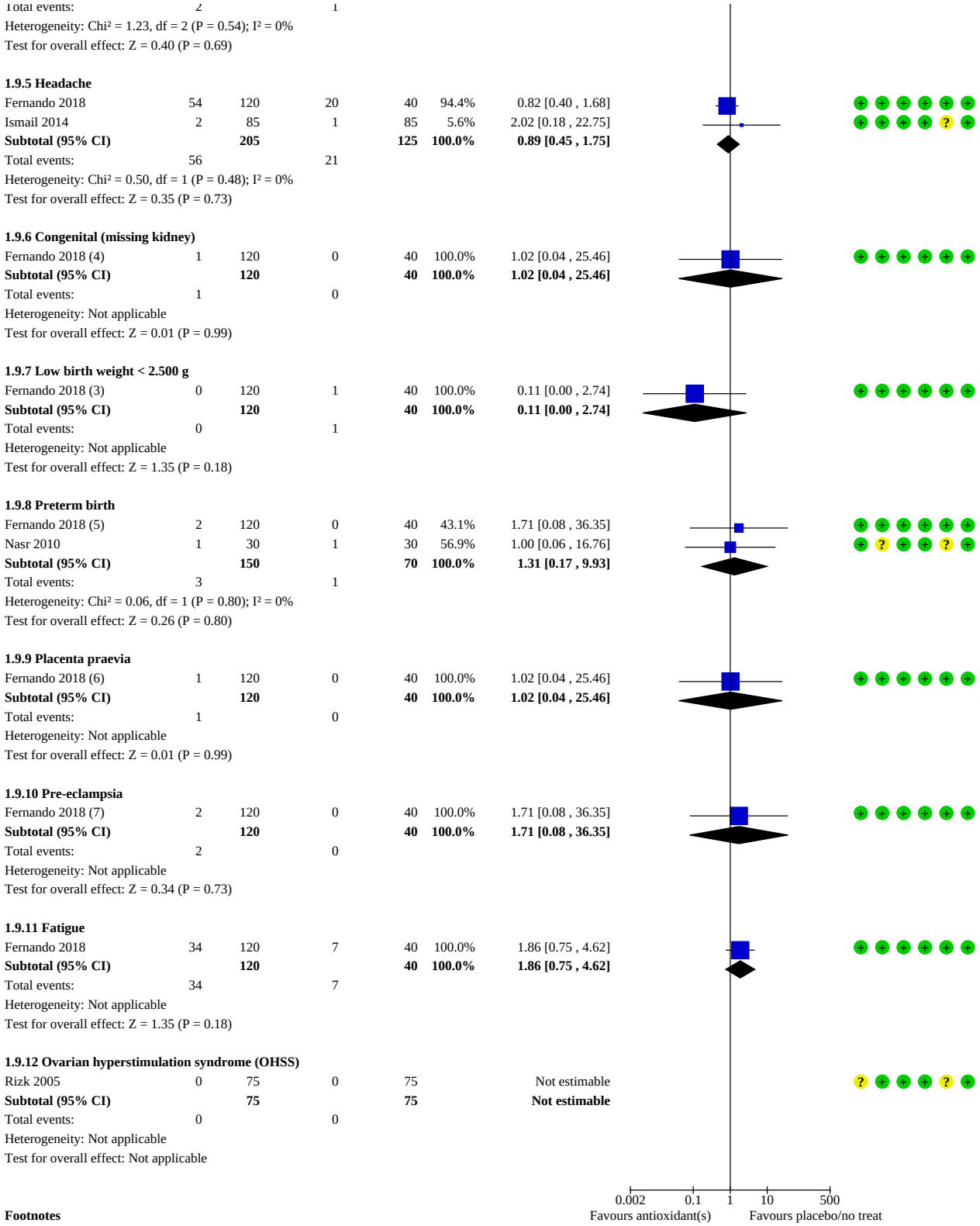


Figure 7. (Continued)



Footnotes

(1) Vitamin B complex plus metformin versus metformin (no treatment)

(2) Vitamin B complex versus no treatment

(3) 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups and the placebo have been combined

Figure 7. (Continued)

(2) Vitamin B complex versus no treatment
(3) 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups and the placebo have been combined
(4) The missing kidney was in the 2 mg melatonin group. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups and the pl
(5) Births between 34 and 37 weeks were in the 2 mg and 8 mg melatonin group. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the
(6) Placenta praevia was in the 2 mg melatonin group. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups and the place
(7) Pre-eclampsia was in the 4 mg and 8 mg melatonin arms. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups and th

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

We subgrouped adverse event data according to the types of events that occurred, as reported by the trials. These included miscarriage, multiple pregnancy, gastrointestinal disturbances, ectopic pregnancy and headache, congenital (missing kidney), low birth weight, preterm birth, placenta previa, pre-eclampsia, fatigue and OHSS. There was no evidence to suggest an association between antioxidants and adverse events, but data were limited, with 24 trials reporting on miscarriage, nine trials reporting on multiple pregnancy, three reporting on gastrointestinal upsets, four reporting ectopic pregnancy, two reporting headache and preterm birth, and one reporting on congenital abnormality (missing kidney), low birth weight, placenta previa, pre-eclampsia, fatigue and OHSS.

1.9.1 Miscarriage

There was no difference in miscarriage rates when antioxidants were compared with placebo or no treatment (OR 1.13, 95% CI 0.82 to 1.55; P = 0.46, I^2 = 0%; 24 RCTs, 3229 women; low-quality evidence). 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 7% (Summary of findings 1). Most of the trials in this analysis were small, although one trial (Badawy 2006) enrolled 804 women. There were no events in three of the studies (Battaglia 2002; Espino 2019; Fernando 2018).

1.9.2 Multiple pregnancy

There was no difference in multiple pregnancy rates when antioxidants were compared with placebo or no treatment (OR 1.00, 95% CI 0.63 to 1.56; P = 0.99, I^2 = 0%; 9 RCTs, 1886 women; low-quality evidence; Figure 7). This means that if the multiple pregnancy rate in the control population is 4%, use of antioxidants instead would be expected to result in a multiple pregnancy rate between 3% and 7% (Summary of findings 1). There were no events reported in one of the studies (Nasr 2010).

1.9.3 Gastrointestinal disturbances

Three trials reported on gastrointestinal disturbances (Cicek 2012; Maged 2015; Westphal 2006). There was no difference in gastrointestinal disturbances when antioxidants were compared with placebo or no treatment (OR 1.55, 95% CI 0.47 to 5.10; P = 0.47, I^2 = 0%; 3 RCTs, 343 women; low-quality evidence; Figure 7). This means that with a rate of 2% gastrointestinal disturbances in the control population, use of antioxidants would be expected to result in a rate of between 1% and 11% (Summary of findings 1).

1.9.4 Ectopic pregnancy

Four trials (Agrawal 2012; Behrouzi 2017; Fernando 2018; Jahromi 2017) reported on ectopic pregnancy. There was no difference between the groups (OR 1.40, 95% CI 0.27 to 7.20; P = 0.69, I^2 = 0%; 4 RCTs, 404 women, low-quality evidence). This means that with a rate of 0.6% ectopic pregnancy in the control population, use of antioxidants would be expected to result in an ectopic pregnancy rate between 0.2% and 4% (Summary of findings 1).

1.9.5 Headache

Two trials (Fernando 2018; Ismail 2014) reported on headache. There was no difference between the groups (OR 0.89, 95% CI 0.45 to 1.75; P = 0.73, I^2 = 0%; 2 RCTs, 330 women; moderate-quality evidence).This means that with a rate of 17% headache in the control population, use of antioxidants would be expected to result in a headache rate between 8% and 26%.

1.9.6 Congenital abnormality (missing kidney)

Fernando 2018 reported on a congenital abnormality. There was no clear evidence of a difference between the groups (OR 1.02, 95% CI 0.04 to 25.46; P = 0.99; 160 women; very low-quality evidence).

1.9.7 Low birth weight < 2.500 g

Fernando 2018 reported on a low birth weight. There was no clear evidence of a difference between the groups (OR 0.11, 95% CI 0.00 to 2.74; P = 0.18; 160 women; very low-quality evidence).

1.9.8 Preterm birth

Two trials (Fernando 2018; Nasr 2010) reported on a preterm birth. There was no clear evidence of a difference between the groups (OR 1.31, 95% CI 0.17 to 9.93; P = 0.80, I^2 = 0%; 2 RCTs, 220 women; moderate-quality evidence).This means that with a rate of 1% preterm birth in the control population, use of antioxidants would be expected to result in a preterm birth rate between 0.2% and 13%.

1.9.9 Placenta previa

Fernando 2018 reported on placenta previa. There was no clear evidence of a difference between the groups (OR 1.02, 95% CI 0.04 to 25.46; P = 0.99; 160 women; very low-quality evidence).

1.9.10 Pre-eclampsia

Fernando 2018 reported on pre-eclampsia. There was no clear evidence of a difference between the groups (OR 1.71, 95% CI 0.08 to 36.35; P = 0.73; 160 women; very low-quality evidence).

1.9.11 Fatigue

Fernando 2018 reported on fatigue. There was no clear evidence of a difference between the groups (OR 1.86, 95% CI 0.75 to 4.62; P = 0.18; 160 women; very low-quality evidence).

1.9.12 Ovarian hyperstimulation syndrome

Rizk 2005 reported on OHSS but there were no events in either the antioxidant or placebo group.

2. Head-to-head antioxidants

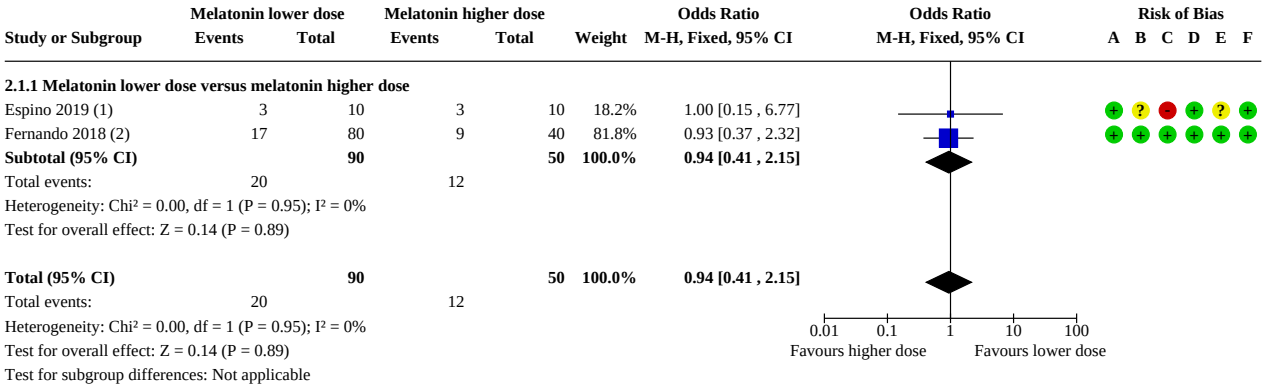
Three trials (El Sharkwy 2019a; Espino 2019; Fernando 2018) were included in the head-to-head comparison. El Sharkwy 2019a enrolled women with PCOS undergoing ovulation induction, Espino 2019 included women with unexplained subfertility undergoing IVF, and Fernando 2018 enrolled women with varying indications who were also undergoing IVF.

Primary outcome: Live birth

2.1 Live birth; type of antioxidant

See Analysis 2.1; Figure 8

Figure 8. Forest plot of comparison: 2 Head-to-head antioxidants, outcome: 2.1 Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments).



Footnotes
(1) 3mg melatonin vs 6mg. Low risk for blinding here but high risk for the melatonin vs no treatment comparison
(2) Numbers in the melatonin arms 2mg and 4mg were combined versus 8mg

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

We considered each type of antioxidant separately.

2.1.1 Two trials (Espino 2019; Fernando 2018) reported on live birth. There was no difference between the lower and higher dose of melatonin (OR 0.94, 95% CI 0.41 to 2.15; P = 0.89, I^2 = 0%; 2 RCTs, 140 women; low-quality evidence). This suggests that among subfertile women with an expected live birth rate of 24%, the rate among women using a lower dose of melatonin compared to a higher dose would be between 12% and 40% (Summary of findings 2).

Sensitivity analysis

We were unable to perform a sensitivity analysis in any of the head-to-head analyses as there were no trials with a high risk of bias in any domain. Espino 2019 appears to have a high risk of bias for blinding in the 'Risk of bias' table (see Characteristics of included studies), but this is only the case for the antioxidant versus placebo/no treatment comparison. In the head-to-head comparison Espino 2019 explains the blinding clearly."Melatonin treatments comprised immediate-release melatonin formula (Guinama, Valencia, Spain) that was encapsulated in identical two-piece gelatine capsules (containing 3 mg or 6 mg melatonin) and dispensed in identical 50-capsule containers". However in the treatment versus control comparison, the control is 'no treatment', so blinding not possible, although; "Embryo quality was graded by blinded embryologists"

2.2 Live birth; indications for subfertility

See Analysis 2.2

2.2.1 Unexplained subfertility

Espino 2019 enrolled women with unexplained subfertility. There was no clear evidence of a difference between the groups (OR 1.00, 95% CI 0.15 to 6.77; P = 1.00; 20 women).

2.2.2 Varying indications

Fernando 2018 enrolled women with varying indications. There was no clear evidence of a difference between the groups (OR 0.93, 95% CI 0.37 to 2.32; P = 0.88; 120 women).

2.3 Live Birth; IVF/ICSI

See Analysis 2.3

Two trials (Espino 2019; Fernando 2018) enrolled women who were undergoing IVF.There was no clear evidence of a difference in live birth rates in women undergoing IVF when lower versus higher doses of melatonin were used (OR 0.94, 95% CI 0.41 to 2.15; P = 0.89, I^2 = 0%; 2 RCTs, 140 women).

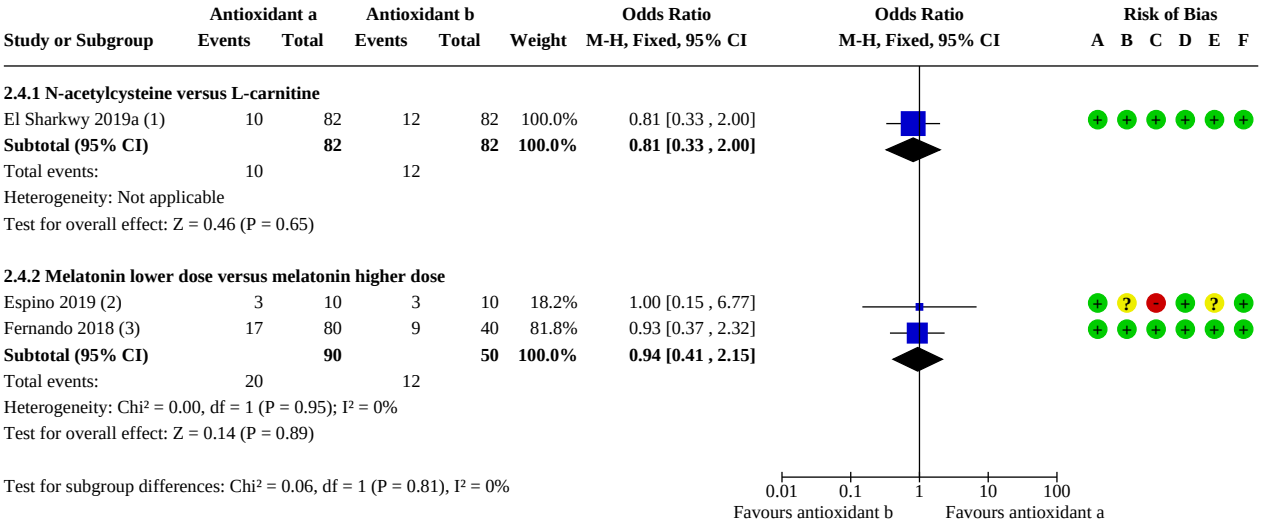
Secondary outcome: Clinical pregnancy

Three trials (El Sharkwy 2019a; Espino 2019; Fernando 2018) reported on clinical pregnancy.

2.4 Clinical pregnancy; type of antioxidant

See Analysis 2.4; Figure 9.

Figure 9. Forest plot of comparison: 2 Head-to-head antioxidants, outcome: 2.4 Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments).



Footnotes

(1) CC plus 600 mg N-acetylcysteine + placebo versus CC plus 3 g of oral l-carnitine + placebo (OI)
(2) Melatonin 3 mg versus 6 mg
(3) Numbers in the melatonin arms 2 mg and 4 mg were combined versus 8 mg

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

2.4.1 El Sharkwy 2019a reported on *N*-acetylcysteine versus L-carnitine. There was no clear evidence of a difference between these two antioxidants (OR 0.81, 95% CI 0.33 to 2.00; P = 0.65; 164 women).

2.4.2 Espino 2019 and Fernando 2018 reported on different doses of melatonin. There was no difference in rates of clinical pregnancy between a lower and higher dose of melatonin (OR 0.94, 95% CI 0.41 to 2.15; P = 0.89, I^2 = 0%; 140 women; low-quality evidence). This suggests that among subfertile women with an expected clinical pregnancy rate of 24%, the rate among women using a lower dose of melatonin compared to a higher dose would be between 12% and 40% (Summary of findings 2).

2.5 Clinical pregnancy; indications for subfertility

See Analysis 2.5

2.5.1 Polycystic ovary syndrome

El Sharkwy 2019a enrolled women with PCOS. There was no clear evidence of a difference between the groups (OR 0.81, 95% CI 0.33 to 2.00; P = 0.65; 164 women).

2.5.2 Unexplained subfertility

Espino 2019 enrolled women with unexplained subfertility. There was no clear evidence of a difference between the groups (OR 1.00, 95% CI 0.15 to 6.77; P = 1.00; 20 women).

2.5.3 Varying indications

Fernando 2018 enrolled women with various reasons for their subfertility. There was no clear evidence of a difference between the groups (OR 0.93, 95% CI 0.37 to 2.32; P = 0.88; 120 women).

2.6 Clinical pregnancy; IVF/ICSI

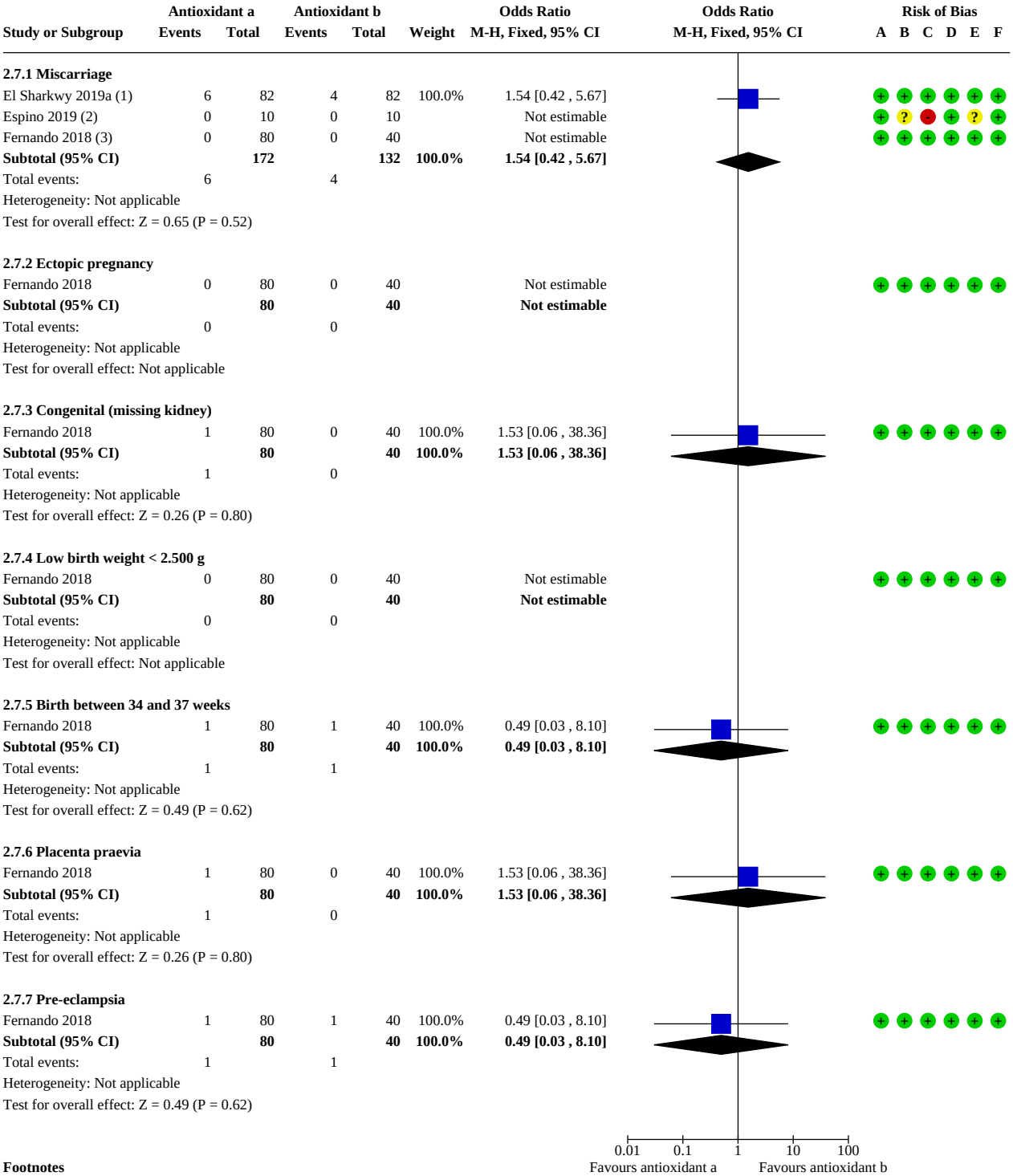
Two trials(Espino 2019; Fernando 2018) reported on women who were undergoing IVF/ICSI. There was no clear evidence of a difference between the groups (OR 0.94, 95% CI 0.41 to 2.15; P = 0.89, I^2 = 0%; 140 women).

Secondary outcome: Adverse events

2.7 Adverse events

See Analysis 2.7; Figure 10

Figure 10. Forest plot of comparison: 2 Head-to-head antioxidants, outcome: 2.7 Adverse events.



Footnotes

(1) Antioxidant 'a' is NAC versus Antioxidant 'b' L-carnitine

(2) Melatonin 3 mg versus 6 mg

(3) Numbers in the melatonin arms 2mg and 4mg combined versus melatonin 8mg

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

Figure 10. (Continued)

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

We subgrouped adverse event data according to the type of events that occurred, as reported by the trials. These included miscarriage, ectopic pregnancy and headache, congenital (missing kidney), low birth weight, birth between 34 and 37 weeks placenta previa and pre-eclampsia. There was no evidence to suggest an association between antioxidants and adverse events, but data were very limited, with only three trials reporting on miscarriage, and only one trial reporting on the remaining adverse events.

2.7.1 Miscarriage

Three trials (El Sharkwy 2019a; Espino 2019; Fernando 2018) report on miscarriage, but there were no events in Espino 2019 or Fernando 2018. There was no clear evidence of a difference between NAC and L-carnitine in El Sharkwy 2019a (OR 1.54, 95% CI 0.42 to 5.67; P = 0.52; 3 RCTs, 304 women; low-quality evidence). This suggests that among subfertile women with an expected miscarriage rate of 3.0%, the rate among women using a NAC versus L-carnitine would be between 1.3% and 15% (Summary of findings 2).

Fernando 2018 reported on ectopic pregnancy and headache, congenital (missing kidney), low birth weight, birth between 34 and 37 weeks, placenta previa and pre-eclampsia.

2.7.2 Ectopic pregnancy

There were no ectopic pregnancies in either the lower- or higher-dose melatonin.

.2.7.3 Congenital (missing kidney)

There was no clear evidence of a difference between the lower- or higher-dose melatonin (OR 1.53, 95% CI 0.06 to 38.36; P = 0.80; 120 women).

2.7.4 Low birth weight < 2.500 g

There were no babies born with low birth weight in either the lower- or higher-dose melatonin groups.

2.7.5 Birth between 34 and 37 weeks

There was no clear evidence of a difference between the lower- or higher-dose melatonin (OR 0.49, 95% CI 0.03 to 8.10; P = 0.62; 120 women).

2.7.6 Placenta previa

There was no clear evidence of a difference between the lower- or higher-dose melatonin (OR 1.53, 95% CI 0.06 to 38.36; P = 0.80; 120 women).

2.7.7 Pre-eclampsia

There was no clear evidence of a difference between the lower- or higher-dose melatonin (OR 0.49, 95% CI 0.03 to 8.10; P = 0.62; 120 women).

DISCUSSION

Summary of main results

Effectiveness of antioxidants versus placebo or no treatment

Very low-quality evidence means that we are uncertain whether antioxidants improve the live birth rate compared with placebo or no treatment/standard treatment. Thirteen trials with a total of 1227 women reported on live birth (Summary of findings 1). The differences between the trials (heterogeneity) were low (I^2 = 29% with a fixed-effect model).

We conducted subgroup analyses, in accordance with our protocol, by type of comparison and type of antioxidant. The association between antioxidants and an increased live birth rate persisted. There was an association between the use of combination antioxidants and increased live birth, but heterogeneity was high. When we considered specific indications for subfertility, there was an association between the use of antioxidants and increased live birth among women with polycystic ovary syndrome (PCOS) and those trials that enrolled women with varying indications for subfertility.

We found no difference between antioxidants and an increased live birth rate among women undergoing IVF or ICSI.

We performed a sensitivity analysis excluding trials at high risk of bias in any domain, and those that used folic acid or a fertility drug as a control (these were in both the intervention and control arms with an antioxidant in addition in the intervention, and classified as no treatment). When these trials were removed from the analysis there remained an association between antioxidants and an increased live birth rate, with heterogeneity moderately low.

Antioxidants may improve clinical pregnancy rate when compared with either placebo or no treatment, although the quality of this evidence was assessed as low (Summary of findings 1). Heterogeneity was moderate, but there was no evidence that the effects differed by type of control (placebo or no treatment). We conducted sensitivity analyses excluding trials at high risk of bias and those using a standard or co-intervention agent as their control. There remained an association between increased clinical pregnancy rates and antioxidants in the analysis when these trials were removed.

When we considered individual antioxidant interventions separately, *N*-acetylcysteine, 'combined antioxidants', melatonin, CoQ10 and L-carnitine showed an association between antioxidant and an increased clinical pregnancy rate, although heterogeneity in the *N*-acetylcysteine, 'combined antioxidants and L-carnitine

groups was high. We found no difference between ascorbic acid, L-arginine, vitamin D or vitamin B complex and clinical pregnancy rate, although these subgroups contained only three or fewer trials.

When we considered specific 'indications for subfertility', we found an association between antioxidants and increased clinical pregnancy in women with PCOS. Heterogeneity here was moderate, which is probably due to the varying antioxidants, as shown by a significant result in the test for subgroup differences. We found no difference between antioxidants and clinical pregnancy rates in women with unexplained subfertility, with tubal subfertility, with varying indications, or in trials that enrolled women with poor ovarian reserve.

There was no association between antioxidants and clinical pregnancy rates in women undergoing IVF or ICSI.

There was insufficient evidence to draw any conclusions about adverse events such as miscarriage, multiple pregnancy, gastrointestinal disturbances, ectopic pregnancy, headache or preterm birth when comparing antioxidants with placebo or no treatment/standard treatment. We rated the quality of evidence for miscarriage, multiple pregnancy and gastrointestinal disturbances as moderate to very low (Summary of findings 1). The outcomes of congenital abnormality, low birth weight, placenta previa, pre-eclampsia, fatigue and ovarian hyperstimulation syndrome were reported by only one trial.

Effectiveness of antioxidants versus antioxidants—head-to-head

Low-quality evidence indicates that there was no difference between lower- and higher-dose melatonin in live birth rates. Two trials with a total of 140 women reported on live birth (Summary of findings 2). The differences between the trials (heterogeneity) were low (I^2 = 0% with a fixed-effect model).

One trial enrolled women with unexplained subfertility and the other enrolled women with varying indications for subfertility, so we were unable to make any assumptions about the use of different doses of melatonin for different indications of subfertility. We were also unable to perform a sensitivity analysis, as neither trial was rated at high risk of bias in any domain.

We found no clear difference between different doses of melatonin and an increased live birth rate among women undergoing IVF or ICSI.

Three trials with a total of 304 women reported on clinical pregnancy. There was no clear evidence of a difference between lower and higher doses of melatonin for increased clinical pregnancy rates, with the quality of this evidence assessed as low (Summary of findings 2). Heterogeneity was low. A single trial studied the effect of *N*-acetylcysteine versus L-carnitine on clinical pregnancy.

The three trials in this analysis all enrolled women with differing indications for subfertility.

There was no difference with lower or higher doses of melatonin and clinical pregnancy in women undergoing IVF or ICSI. We were also unable to perform a sensitivity analysis as neither trial was considered to be at low or unclear risk of bias in any domain.

There was insufficient evidence to draw any conclusions about adverse events such as miscarriage, multiple pregnancy, gastrointestinal disturbances, ectopic pregnancy, headache or preterm birth when comparing different antioxidants.

Overall completeness and applicability of evidence

Of the 63 trials included in this review, 42 reported on clinical pregnancy but only 13 trials reported on live birth. Miscarriage, harmful events and costs of the included trials generally were not well reported. Twenty-five trials reported on miscarriage, nine reported on multiple pregnancy, three trials discussed gastrointestinal disturbances, four ectopic pregnancy, two ovarian hyperstimulation syndrome, two preterm birth, and one for headache, congenital abnormality (a missing kidney), low birth weight, placenta previa, pre-eclampsia and fatigue. The trials were generally quite small, and heterogeneity between them was considered low overall, with the exception of the clinical pregnancy analysis.

The antioxidants melatonin and CoQ10 may have had beneficial effects on the outcomes of this review, and although this was also the case for combination antioxidants and *N*-acetylcysteine, these analyses showed large differences between the trials so we could not be sure about this result. Similarly, the indications for subfertility within the trials were representative of the general subfertile population, but apart from trials on PCOS (with 16 trials across all comparisons), there were very few trials specific to one indication for subfertility (six for varying indications, four for unexplained subfertility, two for tubal subfertility, two for poor ovarian reserve, one for endometriosis, and one for poor responders), 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 adjunctive interventions such as laparoscopic ovarian drilling, timed intercourse or IVF/ICSI. Apart from PCOS, it was therefore difficult to show any benefit or harm from antioxidants for a particular indication of subfertility.

Only three trials were included in the head-to-head analysis, and only two of them used the same antioxidants, which we grouped as lower and higher doses of melatonin; we found no differences in live birth, clinical pregnancy or adverse events between the different dosages.

Quality of the evidence

The quality of the evidence according to the 'Summary of findings' tables (Summary of findings 1; Summary of findings 2) was considered to be low to very low for all outcomes in the antioxidant versus placebo/no treatment and in the head-to-head comparisons. Heterogeneity for the live birth outcome in the antioxidant versus placebo/no treatment comparison was 29%, and 63% for clinical pregnancy.

The overall quality of evidence was limited by serious risks of bias associated with poor reporting of methods, imprecision and inconsistency, leading to a downgrading of the evidence. 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 their 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 not symmetrical, which suggests that the high number of small studies may have had an excessively positive effect on the overall results. This high risk of bias in the included trials is also described in other antioxidant reviews (Lu 2012; Showell 2011) 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 (see Differences between protocol and review). None of these changes were made as a result of the findings of included studies, but rather to improve the structure of the review.

Agreements and disagreements with other studies or reviews

The results of our review are in agreement with those of other published reviews. Sekhon 2010 and Grajecki 2012 concluded that, despite numerous advances made in this area and possible positive effects of antioxidants, there is a need for further investigation using better-quality randomised controlled trials within a larger population to determine the efficacy and safety of these supplements. A Cochrane Review, *Antioxidants for male subfertility* (Smits 2019), found a small significant effect in favour of antioxidants for pregnancy and live birth and no apparent association with any reported adverse events, but there were too few similar trials to provide conclusive evidence. Another Cochrane Review (Showell 2018) showed uncertainty in the use of myo-inositol for women with PCOS.

Similar to the results of our review, Arhin 2017 states that "within the limits of this review micronutrients appear to positively influence the outcomes of pregnancy rate and live birth in couples undergoing IVF and calls for larger clinical trials to strengthen the evidence". However this review includes both women and men and also includes non-random studies.

Zhang 2020, looks at the use of CoQ10 for poor responders and discusses one of our included studies (Xu 2018), it concludes that CoQ10 has good prospects for women who were poor responders but results need to be confirmed with further studies. This is in line with the conclusions of CoQ10 in our review. Also in agreement with our review, the Pundir 2019 overview says there is low- or very low-quality evidence to suggest that supplementation with NAC can improve ovulation and pregnancy rates in women with PCOS, but these need to be further evaluated by adequately-powered and well-conducted randomised controlled trials. Thakker 2015 also says, albeit with more positivity, that "NAC showed significant improvement in pregnancy and ovulation rate as compared to placebo. The findings need further confirmation in well-designed randomised controlled trials to examine clinical outcomes such as live birth rate in longer follow-up periods".

Similarly to the conclusions of our review, Lagana 2018 found that the use of myo-inositol in women without PCOS made little difference to any other outcomes except for the reduction in the amount of gonadotropins used in IVF. A systematic review by Pacis 2015 did not find any evidence to support the use of vitamin D in women undergoing ART. Another three systematic reviews (Fang 2017; Irani 2014; Thomson 2012) looked at vitamin D for subfertile women with PCOS. They reported that there is some evidence for the beneficial effects of vitamin D supplementation on menstrual dysfunction, but the current evidence is limited and additional randomised controlled trials are required.

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, but not with vitamin C or selenium. The review included healthy participants and participants with various stable diseases. 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 participants taking these antioxidants. The review authors found that selenium may have preventative effects on gastrointestinal cancers. Neither review supports the use of antioxidants as a preventative measure, and they call for tighter regulations. Bjelakovic 2008 suggests that antioxidants should be regulated as drugs.

A review of systematic reviews, Elnashar 2019 agreed with our review, in that they found an association with antioxidants and an increase in clinical pregnancy rates, which was also the case for women with PCOS. However, unlike our review there was no association found with live birth and the use of antioxidants. The overview summarises that there is a need for further randomised trials within larger populations to determine efficacy and safety.

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

Further appropriately-powered and well-designed randomised placebo-controlled trials are needed to assess any evidence for benefits or harms or both 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 pregnancy and adverse events. More high-quality head-to-head trials are also needed in order to assess which antioxidants provide benefits or harms when compared to other antioxidants for subfertile women.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agrawal 2012

Study characteristics	
Methods	Prospective randomised trial
Participants	Women attending a teaching hospital fertility clinic undergoing ovulation induction for timed intercourse (N = 58). Mean 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	1. Multiple micronutrients (MMN): (n = 30) 1 tablet a day until completion of study (3 treatment cycles). Women who became pregnant could continue if they wished. 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 Mean age = 32.2 ± 0.65 2. Folic acid (n = 28): 1 tablet a day. Mean age = 32.5 ± 0.83

Agrawal 2012 *(Continued)*

	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 3 cycles even if pregnancy was attained.
Outcomes	Clinical pregnancy Ongoing pregnancy Miscarriage Ectopic pregnancy
Notes	2 women did not complete the study—1 from each group. Reasons given: 1 woman in the control group stopped because she wanted to take the micronutrients, and 1 in the treatment group stopped because of nausea Trial is self-funded. Author stated in an email received 13th February that the trial was not funded. Recruited between Febuary and August 2009 Trial registration number: Unknown Location: London UK Informed consent Ethical approval Sample size power calculation performed ITT performed Emailed author 12th January 2012 about whether the women had IUI or timed intercourse. Author replied on 7th February 2012 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 9th August 2012 asking about any live birth data. Author replied saying that live birth data were unavailable.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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". Comment: Email sent 12th January 2012 asking for methods of randomisation. Author replied 13th February 2012 saying, "the subjects were randomised into 2 groups through computer randomisation".
Allocation concealment (selection bias)	Low risk	Quote: "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	Quote: "Women, caregivers and investigators were blinded to the treatment allocation".
Incomplete outcome data (attrition bias)	Low risk	ITT was performed and explanations given for the 2 dropouts (1 from each group)

Agrawal 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Trial registration number unknown. Outcomes, including clinical pregnancy and live birth were stated in the text, are reported.
Other bias	Low risk	No other bias found

Al-Alousi 2018

Study characteristics	
Methods	Randomised controlled trial
Participants	Women attending a fertility clinic, undergoing ICSI (N = 118 randomised) Inclusion criteria: Women aged between 20 and 40 years, mean age for all participants 29.37 years. BMI between 18 and 34.99 kg/m^2, 1st or 2nd cycle of ICSI, and fresh sperm sample (not aspirated) Exclusion criteria: Women who have medical disorders e.g. diabetes mellitus, hypertension or thyroid diseases, sperm collection from epididymal aspiration, PESA and TESE, frozen sperm, consumption of any medications in the last 12 weeks that may influence hormonal assay, history of any diet in the previous 3 months, tobacco and alcohol consumption, and supplementation of n-3 PUFAs in the past 3 months
Interventions	1. The women of group A were given omega-3 for 8 weeks, before starting the ICSI protocol (N = 60). 1000 mg x 1 capsule every day composed of 180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA). Mean age = 29.22 ± 5.74 2. Placebo for 8 weeks, before starting the ICSI protocol (N = 58). Capsule contains 500 mg paraffin manufactured by Alzahravi Pharmacology Company. Mean age = 29.60 ± 5.34
Outcomes	Embryo quality Number of follicles Number of oocytes Fertilisation rates Ratio of follicle/retrieved oocytes Number of metaphase II oocytes Number of grade I embryos Pregnancy
Notes	3 women did not complete the study — 1 from the intervention and 2 from the control, reasons not given Location: Al-Sadr Teaching Hospital/ Fertility Center/ IVF Department in Najaf Al-Ashraf City, Iraq Timeframe: from January 2017 to February 2018 Trial registration number: unknown Informed consent: unknown Ethical approval: unknown Sample size power calculation performed Funding: Unknown

Al-Alousi 2018 *(Continued)*

	Conflict of interests: unknown ITT not performed The outcome pregnancy is possibly biochemical; there is no definition but mention "pregnancy test", positive or negative Author emailed 14 January 2020 with questions on pregnancy definition, other clinical outcomes, trial registration number and RoB details Author email: tk_says@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown methods of randomisation
Allocation concealment (selection bias)	Unclear risk	Unknown methods of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome group: Double-blind Quote: " Neither the researcher nor women knew which group takes then-3 or placebo till the end of the research. All The placebo and omega-3 capsules look similar and cannot be distinguished from each other (same form of package, same shape, same size and colour)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women dropped out after randomisation – groups explained but reasons not given
Selective reporting (reporting bias)	Unclear risk	Trial registration unavailable
Other bias	Low risk	No other bias found

Badawy 2006

Study characteristics

Methods	Prospective randomised double-blind controlled trial
Participants	Women attending a fertility outpatient clinic for management of unexplained fertility problems (n = 804) Mean age: Treatment group: 27.9 years; Control group 28.1 years Inclusion criteria: All women had at least 1 year of marriage without conception, unexplained subfertility and normal ovulating cycles; tubes were patent Exclusion criteria: any known reason for subfertility Timed intercourse
Interventions	1. *N*-acetyl-cysteine 1200 mg: 1 tablet a day plus clomiphene citrate 50 mg: 1 tablet twice a day for 5 days, starting on day 2 of the cycle (n = 404)

Badawy 2006 *(Continued)*

	2. Placebo plus clomiphene citrate: 50 mg 1 tablet twice a day (n = 400) Duration of treatment: 1 cycle Timed intercourse
Outcomes	Number and size of follicles Hormonal profiles Endometrial thickness Clinical Pregnancy Miscarriage Multiple pregnancy No loss to follow-up
Notes	Conducted in 1 centre in Mansoura, Egypt. Ethical approval and informed consents obtained Trial ran from October 2003 to April 2005 Funding source not reported Contacted author 13th February 2013 regarding methods of randomisation. Author replied 11 February 2013 giving data for multiple pregnancy and miscarriage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of sequence generation apart from: Quote: "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	Participants, investigators, outcome assessor and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Outcomes stated in the text—multiple pregnancy and miscarriage—reported on, although not initially stated as outcomes of interest
Other bias	Low risk	No other bias found

Batioglu 2012

Study characteristics

Methods	Randomised controlled trial

Batioglu 2012 *(Continued)*

Participants	Women with primary infertility between 20 and 40 years undergoing IVF (N = 85) Inclusion criteria: regular menstruation, no hormonal or non-hormonal drug therapy for less than 3 months and no systemic illness Exclusion criteria: serious endometriosis, serious male factor (azoospermia) hypogonadism with an FSH level < 13. Also participants with cycles cancelled were excluded
Interventions	1. Melatonin 3 mg: 1 tablet a day (n = 40) 2. No treatment (N = 45)
Outcomes	Primary outcome: number of morphologically-mature oocytes retrieved (MII 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, study dates not reported

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	ITT used. No dropouts were reported
Selective reporting (reporting bias)	High risk	Trial registration number not available. Unclear why chemical pregnancy numbers are lower than clinical pregnancy numbers
Other bias	Low risk	No other bias found

Battaglia 1999

Study characteristics

Methods	Randomised controlled trial
Participants	Women attending fertility clinic having failed an IVF cycle (poor responders) (N = 34). Mean age: 40 ± 2.1 years, range 37 - 44 years. Undergoing IVF Inclusion: Infertile women with tubal infertility who had not taken hormonal treatments 4 months prior to 1st IVF treatment

Battaglia 1999 *(Continued)*

	Exclusion: Intercurrent illness, BMI > 30, endometriosis, ovarian functional cyst or ovariectomy, regular exercise, heavy smokers (> 10 a day), diastolic blood pressure > 90 mmHg
Interventions	1. Oral L arginine 16 g: 1 tablet a day (N = 17) 2. No treatment (N = 17) Duration: from day 1 of the menstrual cycle to end of the IVF cycle
Outcomes	Hormonal and biochemical evaluation IVF cancellation rates Oocyte and embryo number Clinical pregnancy rates
Notes	Conducted in Italy, study dates not reported Funding source not reported

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
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Outcomes reported including clinical pregnancy
Other bias	Low risk	No other bias found

Battaglia 2002

Study characteristics

Methods	Randomised controlled trial
Participants	Women attending Modena University Infertility Clinic (N = 37) Mean age (mean ± SD): 33.8 ± 3.1 years (range 28 - 37 years), mean duration of infertility 6.8 ± 3.8 (range 4 - 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

Battaglia 2002 *(Continued)*

	Exclusion criteria: participants with intercurrent illness, BMI ≥ 30, endometriosis, ovarian functional cyst, PCOS, unilateral ovarian resection or ovariectomy, participants who took regular exercise, heavy smokers (> 10 cigarettes a day), 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
Interventions	1. L-arginine 4 grams: 4 times a day (N = 18) 2. 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, study dates not reported 32 participants completed the trial, with 5 dropouts due to poor response. Funding source not reported Author was emailed 16th August 2012 and 12th Febrary 2013 with request for the number of live births for each group. Author replied on 14th Febrary 2013, providing data for live birth and miscarriage

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random number table".
Allocation concealment (selection bias)	Low risk	Quote: "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, and investigators stated Quote: "All 34 patients completed the trial". Comment: Numbers given for dropouts from each group. We contacted the authors regarding this ITT not used. Five were said to be cancelled because of "poor response".
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available but key outcomes reported, including live birth
Other bias	Low risk	No other bias found

Behrouzi 2017

Study characteristics	
Methods	Randomised controlled trial
Participants	PCOS women candidates for IUI (N = 100) Inclusion criteria: age 18 - 38 years, having 2 of 3 criteria of chronic oligo-or anovulation, clinical or laboratory signs of hyperandrogenism, PCOS sonographic findings (based on the Rotterdam criteria). Also the presence of normal laboratory tests of thyroid, prolactin, and normal hysterosalpingography and a normal transvaginal ultrasound Exclusion criteria: the presence of an ovarian cyst, FSH > 10 IU/L, and women with OHSS, and male infertility
Interventions	1. 100 mg CC (Clomid©, Hoechest Marion Russel, Cairo, Egypt) and 5 mg letrozole (Novartis Pharma Services, Basel, Switzerland) + 1.2 gr NAC (Sedico, Cairo, ARE) daily, from day 3 to 7 of the menstrual cycle for 1 cycle. NAC was given to the participants in the form of powder inserted in small pockets to be diluted into 1 standard glass of water and taken orally in 2 daily divided doses. Mean age (years) 27.53 ± 4.16 (N = 49) 2. The control group had the same drug regimen without NAC. Mean age (years) 27.14 ± 4.49 0.64 (N = 48) Duration of treatment: 1 cycle
Outcomes	Number of mature follicles Number of GONAL-F injections Endometrial thickness (mm) Days of HCG administration Days of IUI performing Pregnancy rate; clinical pregnancy is defined in the text (page 204) Miscarriage rate Ectopic pregnancy rate Twin pregnancy
Notes	100 women were mentioned in the text as randomised (page 204) but 106 women in the flow diagram, the reasons and numbers for dropouts match the flow diagram information Location: Kosar Department of Obstetrics and Gynecology, Shahid Motahhari Hospital, Urmia University of Medical Sciences, Iran Timeframe: Unknown Trial registration number: IRCT2016030826962NI Informed consent: "Subjects were informed that their participation was voluntary and written consent was obtained from all participants". Ethical approval: "This study was approved by the ethics committee of Urmia University of Medical Sciences (Ir.UMSU.rec.1393.179)" Sample size power calculation: performed Funding: The work is granted by the Research Deputy of Urmia University Conflict of interests: Authors report no conflicts of interest ITT: Not performed Author email: ta.behroozi@gmail.com

Behrouzi 2017 *(Continued)*

Author phone number: (+98) 4432225777

Author emailed on the 15 January 2020 and asked to confirm methods of randomisation, allocation concealment and whether they have any live birth data. Email undeliverable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “the participants were randomized using closed envelopes (A and B) in two groups:” “simple random method”
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	Control is 'no treatment'; no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers were accounted for but no reasons given
Selective reporting (reporting bias)	Unclear risk	Trial registration number given but we were unable to find details on WHO Portal or clinicaltrials.gov. Clinical pregnancy and miscarriage rate reported
Other bias	Low risk	No other bias found

Bentov 2014

Study characteristics

Methods	Double-blind placebo-controlled randomised trial
Participants	IVF/ICSI patients (N = 39) Inclusion criteria: infertility requiring IVF–ICSI and age 35 – 43, mean age; CoQ10 39.0 ± 0.79 and placebo 39.1 ± 0.52 Exclusion criteria: body mass index (BMI) >38 kg/m2; early follicular phase (day 2 – 4) serum FSH level >20 mIU/mL; abnormal uterine cavity as evidenced by sonohysterogram or hysterosalpingography; any current use of 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 for the use of CoQ10, superfact, menopur, hCG, estrase, and progesterone suppositories; any ovarian or abdominal abnormality that may interfere with adequate TVS evaluation; absence of 1 or both ovaries; clinically relevant systemic disease (e.g. insulin-dependent diabetes, adrenal dysfunction, organic intracranial lesion, PCOS, hyperprolactinemia, or hypothalamic tumor) 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 the study enrolment; any medical condition that may interfere with the absorption, distribution, metabolism, or excretion of the study drugs; gastrointestinal diseases; malabsorption syndromes; and liver dysfunction; unexplained gynaecological bleeding; ejaculated sperm not sufficient for ICSI; abnormal controlled ovarian hyperstimulation (COH) screening 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 the study; the 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,

Bentov 2014 *(Continued)*

	nortriptyline, protriptyline, and trimipramine), multivitamins, or any vitamin supplementation except folic acid
Interventions	1. CoQ10 600 mg: 1 tablet a day with breakfast (N = 17) 2. Placebo - identical capsules containing rice oil and starch (N = 22) Duration of treatment up to 3 cycles if pregnancy did not occur. All participants took either CoQ10 or placebo for 2 months. On day 3 of the following cycle, they started ovarian stimulation for IVF while continuing the consumption of the supplements.
Outcomes	Primary outcome: number of euploid eggs per retrieval Secondary outcome: cumulative pregnancy rate per retrieval and cumulative livebirth rate per retrieval
Notes	12 (5 dropouts) CoQ10 group and 15 (7 dropouts) in the placebo completed the study and 10 in the CoQ10 and 14 of the placebo group completed an IVF/ICSI cycle. Overall there were 15 dropouts from recruitment until the end of the study; 6 women withdrew from the study for personal reasons, 3 for conceiving spontaneously, 2 for poor compliance, 1 for failing to achieve the target BMI, and 3 because of poor ovarian response Participant enrolment to the study began in 2010 and was terminated in June 2012 before sample size reached, due to a paper published in May 2012 by Levin et al describing the negative effects of polar body biopsy on embryogenesis. In the CoQ10 group, 30.8% of the women were treated with the long luteal GnRH agonist protocol, compared with 7.7% in the placebo group. The rest of the participants in both groups were treated with the short microdose flare protocol 2 centres Toronto, Canada Trial registration no: NCT01048385 Informed consent: yes Ethics approval: yes Funding; Ferring Pharmaceuticals provided Menopur Conflict of interests; one of the authors has a consultancy role with Fertility Neutraceuticals involved in the manufacturing and distribution of CoQ10 Email sent to author regarding live birth, clinical pregnancy, dropouts and allocation concealment on 24th November 2015 'bentov@lunenfeld.ca', no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned in chronological order according to the day of study enrolment to a computer-generated randomization"
Allocation concealment (selection bias)	Unclear risk	Quote: "Each enrolled participant received a pre-assigned package containing either placebo or CoQ10 for the duration of the study".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The study was a double blind, placebo-controlled, randomized trial". "Both the physician and the patient were blinded regarding assignment of the patients".

Bentov 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At the point the study was terminated (June 2012), we had recruited a total of 39 patients who were evaluated and randomized (17 to the CoQ10 group and 22 to the placebo group). Only 27 had started the treatment with the supplements (12 of the CoQ10 group and 15 of the placebo group). In all, 24 patients completed the treatment cycle and had a polar body biopsy (PB-BX) and embryo transfer done (10 of the CoQ10 group and 14 of the placebo group). Six patients withdrew from the study for personal reasons, three for conceiving spontaneously, two for poor compliance, one for failing to achieve the target BMI, and three because of poor ovarian response."
Selective reporting (reporting bias)	Low risk	Both primary and secondary outcomes, including live birth, were reported in the Methods were reported in the Results. Protocol available.
Other bias	High risk	Quote: "However, because of the premature termination of the study, the CoQ10 group had only one-third and the control group half of the target number". Comment: Early termination of trial for embryo safety reasons may cause an overestimation of the effect of the intervention

Caballero 2016

Study characteristics	
Methods	Randomised controlled trial
Participants	Women attending an IVF clinic (N = 78) Inclusion criteria: poor responders 36 - 40 years in a previous IVF cycle according to Bologna criteria (N = 78) Exclusion criteria: Unknown
Interventions	1. Coenzyme Q10 600 mg 2x/day for 12 weeks. Mean age 37.8 (N = Unknown) 2. No treatment for 12 weeks. Mean age 37.2 (N = Unknown) Treatment over 12 weeks
Outcomes	Number of oocytes retrieved Number of good-quality embryos Implantation rate Clinical pregnancy rate (fetal heartbeat at 7 weeks) Live birth
Notes	Location: IFER Instituto de Ginecologia v Fertilidad, Buenos aires, Argentina Timeframe: Unknown Trial registration number: Unknown Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: Unknown Conflict of interests: Unknown ITT: Unknown Author email: consultas@ifer.com.ar (institution email)

Caballero 2016 *(Continued)*

	Author phone number:
	Conference abstract
	Author emailed via institutional email 15.01.20.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	Control is 'no treatment' but it unclear whether the assessors were blinded or not
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Live birth mentioned in the Methods but not reported, although this is a conference abstract so may not have the data yet. Trial registration number unavailable
Other bias	Low risk	No other bias found

Carlomagno 2012

Study characteristics

Methods	Double-blind RCT
Participants	Women undergoing ICSI (N not stated)
Interventions	1. Myo-inostol 4 g and folic acid 400 µg: 1 tablet of each a day (n not stated) 2. Folic acid 400 µg: 1 tablet a day (n not stated) Taken for 3 months before ICSI and throughout pregnancy
Outcomes	Total rFSH units Number of stimulation days Fertilisation and cleavage rate Embryo quality Biochemical pregnancy rate Clinical pregnancy rate
Notes	Conducted in Italy, study dates not reported Conference abstract; percentages given but no total participant numbers available

Carlomagno 2012 *(Continued)*

	Funding by an institutional grant. An author was an employee of a pharmaceutical company
	Email sent to author 24th November 2015 Gianfranco.carlomagno@gmail.com; no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to two groups; MI treated or placebo"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Unclear risk	Conference abstract - baseline numbers unclear

Cheraghi 2016

Study characteristics

Methods	Prospective randomised placebo-controlled pilot trial
Participants	Infertile Iranian women with PCOS, aged from 25 - 35 years, undergoing ICSI treatment (N = 80) Inclusion criteria: Women who met the Rotterdam criteria for PCOS Exclusion criteria: Hypersensitivity to either MET (metformin) or NAC, infertility factors other than anovulation, male infertility, pelvic organic pathologies, congenital adrenal hyperplasia, thyroid dysfunction, Cushing's syndrome, hyperprolactinaemia, androgen-secreting neoplasia, diabetes mellitus, consumption of medications affecting carbohydrate metabolism and hormonal analogues other than progesterone 2 months prior to enrolment in the study and severe hepatic or kidney disease
Interventions	4 groups (N = 20 in each, 5 dropouts from each) 1. Placebo oral rehydration salts; 3 times a day 2. Metformin 500 mg: 1 tablet 3 times a day 3. NAC 600 mg: 1 tablet 3 times a day 4. Metformin 500 mg: 1 tablet 3 times a day + NAC 600 mg: 1 tablet 3 times a day All treatments were administered for 6 weeks
Outcomes	Oocyte and embryo quality Endocrine parameters

Cheraghi 2016 *(Continued)*

	Clinical pregnancy Side effects
Notes	Location: Iran Timeframe: study ran from July 2012 to February 2013 Trial registration number: IRCT201204159476N1 Informed consent: yes Ethical approval: yes Sample size power calculation: unknown Funding: Arak University Conflict of interests: authors declare no conflicts of interest ITT: No, 15 women per group were analysed Author email: M-soleimani@araku.ac.ir Author emailed regarding RoB, live birth and miscarriage information; no reply. Author emailed again 15.01.20.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	State "random" but method not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blinded placebo-controlled, but the placebo group received oral rehydration salts, which are usually in solution, while the treatments were tablets
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts accounted for, but > 25% dropout
Selective reporting (reporting bias)	Low risk	Trial registration number available. Clinical pregnancy reported
Other bias	Low risk	No other bias found

Choi 2012

Study characteristics

Methods	Prospective, randomised controlled trial
Participants	Infertile women with PCOS (N = 100) undergoing IVF/ICSI
Interventions	1. Calcium 400 mg + vitamin D 1000 IU: 1 of each tablet a day (N = 50) 2. Placebo (N = 50) Given on the starting day of OC pretreatment, followed by controlled ovarian stimulation (COS) using GnRH antagonist for IVF/ICSI. Calcium 400 mg/day with vitamin D 1000 IU/d or placebo was administered once daily from the starting day of OC to the day of human chorionic gonadotropin (hCG) injection

Choi 2012 *(Continued)*

Outcomes	Total dose and days of rhFSH administered Numbers of retrieved, mature and fertilised oocytes, and grade 1 or 2 embryos FF TNF-a and IL-6 concentrations at oocyte retrieval Embryo implantation rate Clinical pregnancy rate Miscarriage rate
Notes	Korea, study dates not reported Conference abstract Funding source not reported No data for clinical pregnancy or live birth stated in the conference abstract; emailed co-author CH Kim; chnkim@amc.seoul.kr, asking about risk of bias, any full publication of the trial and whether they had any clinical pregnancy and miscarriage data. No reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "infertile patients with PCOS were randomized"
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available, clinical pregnancy and miscarriage rate reported
Other bias	Unclear risk	Conference abstract - unclear baseline characteristics

Cicek 2012

Study characteristics

Methods	Randomised controlled trial
Participants	Women with a diagnosis of unexplained infertility undergoing ovulation induction and IUI (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	1. Vitamin E: 400 IU: one tablet per day from 3rd to 5th day of the menstrual cycle until the hCG injection. (N = 53)

Cicek 2012 *(Continued)*

	2. No treatment (N = 50) 4 women were lost to follow-up as a result of incorrect dose consumption (N = 3) and cycle cancellation (N = 1). ITT 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 9th August 2012 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 ITT. No reply

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. ITT not used
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available, clinical pregnancy reported
Other bias	Low risk	No other bias found

Daneshbodi 2013

Study characteristics

Methods	Randomised double-blind placebo-controlled clinical trial
Participants	Overweight and obese women with PCOS, (N = 84) Inclusion criteria: PCOS diagnostic criteria based on the Rotterdam Criteria, age between 20 and 40 years, and BMI of 25 - 40 Exclusion criteria: Metabolic disease, thyroid disease, hyperprolactinaemia, hypercortisolaemia, congenital adrenal hyperplasia, Cushing's syndrome, pituitary disorder, neoplasm, renal and liver dis-

Daneshbodi 2013 *(Continued)*

	eases, history of intake of any drug during the last 3 months that may affect the insulin sensitivity or hormonal profile such as: oral contraceptives, glucocorticoids, ovulation induction agents, antidiabetic and anti-obesity drugs, oestrogenic, antiandrogenic or anti-hypertensive medication, being on any diet in the last 6 months, any addiction to tobacco and alcohol, taking omega-3 supplement in the last 3 months, menopause, allergy to sea foods, and the use of anti-coagulant medicine. Women were excluded if they needed OCP for treatment, were not willing to be in the study, did not obey the protocols of the study, or could not digest more than 20% of supplements
Interventions	1. Oral omega 3; 3 capsules of omega-3 every day for 8 weeks. Each capsule of omega-3 contained 180 mg EPA and 120 mg DHA. Mean age was 26.9 ± 5.9 years 2. Placebo; included 1 g paraffin (Zahravi, Iran), Mean age was 26.9 ± 5.0 years Duration of treatment; 8 weeks
Outcomes	Biochemical markers (FSH, LH, prolactin)
Notes	17 October 2012 we added the full-text Nadjarzadeh 2015, becoming the primary reference. The original report for this study was a conference abstract, Daneshbodi 2013. We were able to additional data to the table of characteristics and risk of bias, but we retained the original name of the study as Daneshbodi 2013 Conducted in Iran, study dates not reported Iranian Registry of Clinical Trial (Registry no IRCT2012071410281N1 and IRCT201112318564N1) Funding source not reported, authors state no conflict of interests Author emailed for RoB and pregnancy data. No reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Methods unknown Quote: “Subjects were randomly divided in to two groups of A and B to reduce the bias.”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded (placebo control)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In this study, one of the participants became pregnant and left the study. 5 participants dropped out because of taking less than 20% of our capsules. The remaining 78 participants completed the study. Finally, 78 people (92.8%) among the patients, 39 patients in the group receiving omega-3 and 39 patients in the group receiving placebo, finished the eight week trial."
Selective reporting (reporting bias)	Unclear risk	Trial registration number is available, but no pregnancy outcomes reported
Other bias	Low risk	No other bias found

Deeba 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Infertile women at Bangladesh fertility unit (N = 156) undergoing ovulation induction with clomiphene citrate
Interventions	1. Multinutrient supplementation; unknown included antioxidants and dosage 2. Folic acid; unknown dosage
Outcomes	Chemical pregnancy Clinical pregnancy Ovulation rate
Notes	Conference abstract only, limited details Set in Bangladesh, study dates not reported Funding source not reported Author emailed for RoB information and data. No reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
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	Trial registration number not available. Clinical pregnancy reported in Methods but not in the Results; this is a conference abstract, so they may not have the data yet
Other bias	Unclear risk	Conference abstract - unclear baseline characteristics

El Refaeey 2014

Study characteristics	
Methods	Prospective randomised controlled trial
Participants	Women with clomiphene-citrate-resistant PCOS attending a fertility outpatient clinic Timed intercourse (N = 110)

El Refaeey 2014 *(Continued)*

	Inclusion criteria: diagnosis of PCOS. All women were previously treated with 150 mg clomiphene citrate daily for 5 days per cycle, for 2 or 3 cycles with persistent anovulation or ovulate with very thin endometrium (< 5 mm). All women had patent fallopian tubes Exclusion criteria: women with hyperprolactinaemia, hypercorticism and thyroid dysfunction and women receiving medications such as cholesterol-lowering drugs, beta-blockers and tricyclic antidepressants
Interventions	1. CoQ10 60 mg: 3 capsules a day + clomiphene citrate 150 mg: 1 tablet a day, from cycle days 2 – 6 starting on cycle day 2 and until the day of hCG administration (N = 55) 2. Clomiphene citrate 150 mg: 1 tablet a day from cycle day 2 for 5 days (N = 55) The mean duration of CoQ10 treatment in the 1st cycle was 16.2 ± 2.1 days and in the 2nd cycle 17.1 ± 2.9 days
Outcomes	Primary outcomes: number of growing and mature follicles, serum oestradiol, serum progesterone, ovulation rate, endometrial thickness Secondary outcomes: clinical pregnancy (ultrasound visualisation of gestational sac with pulsating fetal pole) and miscarriage (spontaneous termination of a clinical pregnancy before 20 weeks of gestation)
Notes	Sample size calculation done 4 dropouts from the intervention and 5 from the control group Egypt Trial duration January 2010 to January 2013 The study was approved by the departmental ethical committee and all participants gave informed consent before inclusion in the trial (committee reference no. 231, approved December, 12 2009) This trial is registered at ClinicalTrials.gov (ID NCT01910766) Email to author regarding live birth data and allocation concealment sent 26th November 2015. No reply. Endometrial thickness; significant difference in favour of the treatment group vs control

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated using a computer generated random table"
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes" "Allocation process was done by a third party (nurse)"
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The physicians monitoring the cycles were blinded to the protocol of each group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts accounted for from each arm
Selective reporting (reporting bias)	Low risk	Trial registration number available. All outcomes were reported as stated in the Methods, including clinical pregnancy and miscarriage

El Refaeey 2014 *(Continued)*

Other bias	Low risk	No other bias found

El Sharkwy 2019a

Study characteristics	
Methods	Parallel double-blind randomised controlled clinical trial
Participants	Women with CC-resistant PCOS attending the infertility clinic Ovulation induction (N = 164) Inclusion criteria: Age 18 – 40 years; infertility for > 1 year; PCOS, defined by the revised Rotterdam 2003 criteria 7 as the presence of 2 of 3 features (oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovary); and CC resistance, defined as failure to achieve adequate follicular maturation after 3 consecutive induction cycles with CC at a dose of 150 mg/day for 5 days. Exclusion criteria: Other causes of infertility (e.g. male or tubal factor), endocrine disorders such as thyroid dysfunction and hyperprolactinaemia, and hormonal treatment or intake of any medications affecting carbohydrate or lipid metabolism in the 3 months before the study
Interventions	1. 150 mg/day of CC from day 3 until day 7 of the menstrual cycle, plus 600 mg of oral *N*-acetylcysteine (a sachet of powder for dilution in water) and a placebo capsule similar to the L-carnitine capsule, 3 times daily. Mean age 26.6 ± 1.5 (N = 82) 2. 150 mg/day of CC from day 3 until day 7 of the menstrual cycle, plus 3 g of oral L-carnitine and placebo sachets containing an oral rehydration solution specifically designed to look similar to those containing *N*-acetylcysteine Mean age 26.2 ± 2.8 (N = 82) Treatment period: 3 months
Outcomes	Clinical pregnancy Ovulation Metabolic profile (insulin resistance markers and lipid profile)
Notes	Location: Department of Obstetrics and Gynecology Faculty of Medicine, Zagazig University Egypt Timeframe: between 01 January 2017 and 31 March 2018 Trial registration number: NCT03164421 Informed consent: yes Ethical approval: from Zagazig University Sample size power calculation: yes Funding: unknown Conflict of interests: no conflicts stated ITT: no Author email: Ibrahimsharkwy@yahoo.com Emailed author 15 January 2020 to ask if they have live birth data or any other adverse event data. No reply as of 26 August 2020.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “Consenting eligible women were randomly allocated to receive either CC plus N-acetylcysteine or CC plus l-carnitine via computer generated randomization tables that guaranteed a 1:1 distribution of women between the two study groups.” (page 61)

El Sharkwy 2019a *(Continued)*

Allocation concealment (selection bias)	Low risk	The allocations were concealed in opaque, sealed, and serially-numbered envelopes. The randomisation code was known only to the pharmacist who dispensed the medications (page 61)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The women and the physicians were blind to the allocation." (page 61)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition accounted for. Quote: "Two women in the l-carnitine group were subsequently lost to follow-up and excluded from the analysis"
Selective reporting (reporting bias)	Low risk	Trial registration number is available, clinical pregnancy reported
Other bias	Low risk	No other bias found

El Sharkwy 2019b

Study characteristics	
Methods	Parallel double-blinded randomised controlled clinical trial
Participants	Women with PCOS and CC resistance who attended the infertility clinic. Ovulation induction (N = 280) Inclusion criteria: Clomiphene citrate-resistant obese women with PCOS diagnosed on the basis of the revised Rotterdam 2003 criteria. The presence of 2 out of 3 criteria (oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovary) was recommended as diagnostic of PCOS. CC resistance was defined as failure to achieve adequate follicular maturation after 3 consecutive induction cycles with CC at 150 mg/d for 5 days Exclusion criteria: Smokers, drug users, those with other causes of infertility such as a male factor or tubal factor, and those with endocrine disorders such as thyroid dysfunction and hyperprolactinaemia
Interventions	1. CC plus metformin and L-carnitine: 150 mg/d CC from day 3 to day 7 of menstrual cycle plus oral L-carnitine (3 g) and metformin 850 mg (1 tablet daily), then the dose was doubled after 1 week to 1700 mg/d (2 tablets daily). Mean age 25.7 years ± 1.7 (N = 140) 2. CC plus metformin and placebo: 150 mg/d CC from day 3 to day 7 of menstrual cycle plus placebo and metformin 850 mg (1 tablet daily), then the dose was doubled after 1 week to 1700 mg/d (2 tablets daily). Mean age 26.1 ± 2.2 (N = 140) Treatment for 3 months
Outcomes	Clinical pregnancy Hormonal level and metabolic profile changes Ovulation First trimester (13 weeks) miscarriage rates
Notes	Location: Department of Obstetrics and Gynecology Faculty of Medicine, Zagazig University, Egypt Timeframe: between January 2017 and March 2018 Trial registration number: not provided Informed consent: yes Ethical approval: yes Sample size power calculation:yes

El Sharkwy 2019b *(Continued)*

	Funding: unknown Conflict of interests: the authors have no conflict of interest to disclose ITT: no Author email: IbrahimSharkwy@yahoo.com The paper states that "This trial has some limitations, the side effects of the medications were not evaluated, we did not include non-PCOS obese women as a control group, and the live birth rate was not considered" (page 704). Miscarriage rates were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was created by the computer" (page 702)
Allocation concealment (selection bias)	Low risk	Quote: "The Allocation was concealed in opaque, sealed, and serially numbered envelopes" (page 702)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All women, treating physicians, and investigators were blinded to treatment allocation" (page 702)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome group: Quote: "The consenting 280 women were randomly allocated to group 1 (N = 140) or group 2 (N = 140). Six women were excluded from analysis due to loss of follow up: two women in group 1 and four women in group 2" (page 702) All dropout numbers explained and accounted for. ITT not used
Selective reporting (reporting bias)	Unclear risk	Clinical pregnancy and miscarriage are reported. Live birth and side effects of medication are not reported. Trial registration number is not available
Other bias	Low risk	No other bias found

Eryilmaz 2011

Study characteristics

Methods	Randomised single-centre controlled clinical trial
Participants	Women undergoing IVF with sleep disturbances (N = 63) from 24 - 38 years Inclusion criteria: unexplained infertility, no ovulatory problems, normal hysterosalpingogram or laparoscopy and normal semen sample Exclusion criteria: chronic drug usage, history of > 1 fertilisation failure, hypertension, diabetes, uterine myoma, ovarian cyst and smoking
Interventions	1. Melatonin 3 mg; 1 tablet a day, taken at 22:00 to 23:00 from 3rd to 5th day of the menstrual cycle until the hCG injection (N = 30) 2. No treatment (N = 30)
Outcomes	Primary outcome: oocyte quality

Eryilmaz 2011 *(Continued)*

	Secondary outcomes: fertilisation failure rate, number of follicles, number of oocytes retrieved, number of MII 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 9th August 2012 regarding which group or groups lost the 3 women. Data added. Tried to contact the author again regarding live birth data 5th February 2013. Author replied on 7th February 2013, 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
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	Trial registration number not available. Clinical pregnancy reported
Other bias	Low risk	No other bias found

Espino 2019

Study characteristics

Methods	Randomised controlled trial
Participants	Infertility clinic, IVF (N = 30) Inclusion criteria: Unexplained infertility (UI) were women subjected to a second IVF cycle who presented normal ovulation and any tubal pathology as ascertained by menstrual history and hysterosalpingogram and their spouses were normospermic according to WHO criteria Exclusion criteria: < 18 years, active smokers, or were concurrently using other adjuvant therapies (e.g. Chinese herbs) (to avoid confounding factors since such herbs may contain high melatonin concentrations). Women were also excluded if they had a history of autoimmune disorders/hypersensitivity to melatonin or its metabolites (to avoid potential side-effects) or were unable/unwilling to comply with the study procedures. Patients and healthy volunteers were excluded if they had misused alcohol in the preceding 3 months

Espino 2019 *(Continued)*

Interventions	1. Group 3: women who took a daily dose of 3 mg of melatonin; melatonin was taken 1 hour before going to sleep for a period spanning from the first appointment to control ovarian stimulation until the day of follicular puncture, i.e. for 40 days. Mean age; 34.73 ± 3.03 (N = 10) 2. Group 2: UI women who did not take melatonin. Mean age; 35.93 ± 3.20 (N = 10) 3. Group 4: UI women who took a daily dose of 6 mg of melatonin; melatonin was taken 1 hour before going to sleep for a period spanning from the first appointment to control ovarian stimulation until the day of follicular puncture, i.e. for 40 days. Mean age; 36.22 ± 2.71 (N = 10) NB Group 1 is a group of 10 normal fertile women but these were not randomised
Outcomes	Biomarkers of oxidative balance Number and quality of oocytes Percentage of fertilised oocytes Number of transferable embryos Percentage of clinical pregnancies/cycle Miscarriage Number of full-term pregnancies
Notes	Location: Centre for Assisted Human Reproduction (CERHA, Badajoz, Spain) Timeframe: unknown Trial registration number: unknown Informed consent: yes Ethical approval: yes Sample size power calculation: unknown Funding: This study was supported by FundeSalud (CO-14-87 and UEx 063/15; jointly financed by Ferring, MSD, and EMB) and Junta de Extremadura (GR18040). J. Espino holds a fellowship financed by Ministerio de Ciencia, Innovación y Universidades (IJCI-2016-28030). Conflict of interests: The authors declare that they do not have any conflict of interest ITT: yes Author email: jespino@unex.es Author phone/fax number: +34-924-289-388 NB the data for CP and LB has been entered as per woman, on the assumption that there was only one cycle and that there were no multiple pregnancies. I have emailed the author (16 January 2020) for clarification, with no reply as at 25 August 2020.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Such patients were divided randomly into three groups of 10 women by using a computer-generated random number list" (page 2/11)
Allocation concealment (selection bias)	Unclear risk	Unknown allocation concealment methods
Blinding (performance bias and detection bias) All outcomes	High risk	The RoB domain for blinding is high risk in the melatonin versus no-treatment comparison and low risk only for the head-to-head treatments; Quote: "Melatonin treatments comprised immediate-release melatonin formula (Guinama, Valencia, Spain) that was encapsulated in identical two-piece gelatine capsules (containing 3 mg or 6 mg melatonin) and dispensed in identical 50-capsule containers". However in the treatment versus control, the

Espino 2019 *(Continued)*

		control is 'no treatment' so blinding not possible, although; "Embryo quality was graded by blinded embryologists" (page 2/11).
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Clinical pregnancy reported. No trial registration number available
Other bias	Low risk	No other bias found

Fernando 2018

Study characteristics	
Methods	Randomised controlled trial
Participants	Inclusion criteria: Women were eligible if they (i) were undergoing their first cycle of IVF/ICSI, (ii) were undergoing an antagonist cycle, (iii) were aged between 18 and 45, and (iv) had a BMI between 18 and 35 (Mean age 35.4 ± 4.2) (N = 160) Exclusion criteria: Untreated endometriosis, uterine malformations, large distorting fibroids or endometrial polyps, autoimmune disease, concurrent use of other adjuvant therapies, malignancy, preimplantation genetic screening, known sensitivity to melatonin, or if concurrently taking medications known to interact with melatonin (antidepressants, antiepileptics, or hypnotics)
Interventions	1. Melatonin 2 mg 2/day (Mean age 35.0 ± 4.1) (N = 41) 2. Melatonin 4 mg 2/day (Mean age 36.0 ± 4.2) (N = 39) 3. Melatonin 8 mg 2/day (Mean age 35.4 ± 4.4) (N = 40) 4. Placebo (Mean age 35.2 ± 4.2) (N = 40) Quote: "one capsule twice per day (once between 08:00 and 10:00 and once between 20:00 and 22:00) from day 2 of their cycle until the night before oocyte retrieval"
Outcomes	Clinical pregnancy rate (presence of a live intrauterine pregnancy detected on transvaginal ultrasound scan at 6 – 8 weeks' gestation) Live birth rate Oocyte and embryo number and quality Number of oocytes fertilised Number of embryos used Rates of miscarriage Pregnancy complications Adverse events including cycle cancellations ("Each participant also kept a diary documenting compliance and adverse events")
Notes	Location: Monash IVF: Australia Timeframe: between September 2014 and September 2016 Trial registration number: ACTRN12613001317785 Informed consent: yes

Fernando 2018 *(Continued)*

Ethical approval: yes
Sample size power calculation: paper states "There were no previously well-designed randomised placebo controlled studies on which to base a power calculation for clinical pregnancy or live birth rate. Therefore, this was designed as a pilot study with a sample size of convenience"
Funding: SF is supported by a NHMRC Clinical Postgraduate Research Scholarship (APP1074342). Study funding was provided by the Ella Macknight Memorial Scholarship (RANZCOG) and the Monash IVF Research and Education Foundation (PY12_15). EW is supported by an NHMRC Program Grant (APP1113902).
Conflict of interests: "LR is a Minority shareholder in Monash IVF Group, has unrestricted grants from MSD® , Merck-Serono® , and Ferring® and receives consulting fees from Ferring®"
ITT: yes
Author email: shavi.fernando@hudson.org.au

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each dose of trial medication was randomly allocated a letter designation (“A” to “D”) using a random number generator by the trial’s independent Data Safety and Monitoring Board (DSMB). To prevent selection bias, randomization was performed using the minimization method, accounting for factors known to affect the outcome used in small trials (20). Weighted minimization was performed using age (weighting of 20), parity (weighting of 10), BMI (weighting of 5), and smoking status (weighting of 1) in real-time at enrolment using minimization software (MUI Online Minimization R, powered by Qminim R)"
Allocation concealment (selection bias)	Low risk	Quote: "This allocation was only known to the DSMB and the hospital pharmacy responsible for labelling and dispensing the medication until after completion of the trial"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All trial investigators, clinicians, and participants remained blinded throughout the trial. All medication bottles and capsules were of identical appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout numbers from each group provided along with reasons and used ITT
Selective reporting (reporting bias)	Low risk	Trial registration number available. All outcomes reported in Methods are in the Results. Live birth and clinical pregnancy data provided
Other bias	Low risk	No other bias found

Gerli 2007

Study characteristics

Methods	Double-blind randomised trial
Participants	Women with oligomenorrhoea or amenorrhoea and PCOS were recruited from gynaecology, endocrine and fertility clinics. Women were < 35 years of age, mean age 29.7 (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".

Gerli 2007 *(Continued)*

	Exclsion criteria: hyperprolactinaemia, hormone treatment, abnormal thyroid function, congenital adrenal hyperplasia
Interventions	1. Infolic®, a combination of myo-inositol 2g plus folic acid 400 µg: 1 tablet twice a day (N = 45). Mean age 29.0 2. Folic acid 400 µg: 1 tablet twice a day (N = 47). Mean age 29.7 Duration: 16 weeks
Outcomes	Ovulation frequency Hormonal levels Pregnancy
Notes	"Ethical committee approval was obtained before the study, and written informed consent was given by each patient". Trial carried out in Italy, study dates not reported Power calculation carried out High dropouts, > 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 Funding source not reported 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 12th June 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was effected in a double blind fashion; patients received either MYO combined with folic acid (Inofolic®) or only folic acid as placebo, according to the code provided by computer-generated randomization."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind fashion" ("placebo control" however control is folic acid so considered to be no treatment)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "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 ITT for the pregnancy outcome. 1 miscarriage was reported but no details of whether this occurred in the treatment or the control group. Miscarriage not prespecified as an outcome of interest. Trial registration number not available
Other bias	Low risk	No other bias found

Ghomian 2019

Study characteristics	
Methods	Parallel blinded randomised controlled clinical trial
Participants	Women attending an infertility clinic for timed intercourse. The participants were required to have scheduled coitus 24 to 36 hours after the hCG injection. (Mean age 28.6 ± 6.5) (N = 66) Inclusion criteria: (1) age of > 18 years, (2) openness of at least 1 of the uterine tubes based on hysterosalpingogram imaging, (3) lack of endocrine diseases (e.g. hyperprolactinaemia, hypothyroidism, and Cushing's syndrome), (4) normal semen analysis (spermogram) of the partner, and (5) confirmation of infertility due to PCOS based on the Rotterdam criteria by having at least 2 of 3 criteria, including oligomenorrhea or amenorrhea, clinical or laboratory hyperandrogenism, and detection of polycystic ovary in ultrasound Exclusion criteria: a change in the diagnosis of the disease during the research period and participants' unwillingness to co-operate with us in conducting the study
Interventions	1.100 mg of clomiphene (i.e. 2 x 50 mg pills) along with 1200 mg of NAC (i.e. 2 x 600 mg pills, made by Fluid UI MUCIL Co., Iran) (Mean age 28.7 ± 6.9) (N = 33) 2.100 mg of clomiphene (i.e. 2 x 50 mg pills, made by Iran Hormone Co., Iran) (Mean age 28.5 ± 6.2) (N = 33) Taken from the day 3 to day 7 of menstrual cycle
Outcomes	Mean endometrial thickness Mean sizes of the follicles Mean numbers of follicles Positive beta-hCG result
Notes	Location: Milad Infertility Clinic in Mashhad, Iran Timeframe: In 2015 Trial registration number: IRCT2016042727638N1 Informed consent: Yes Ethical approval: Yes Sample size power calculation: Unknown Funding: Department of Research at Mashhad University of Medical Sciences supported the study Conflict of interests: Authors declare that they have no conflict of interests ITT: Yes Author email: ghomiann@mums.ac.ir Email sent to the author 22 January 2020 concerning; the time period of the trial, clinical data, allocation concealment, blinding, and any dropouts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple random sampling technique" "using a random number table, the patients were divided into two groups of control and intervention" (page186)
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias)	High risk	Quote: "This blinded randomized controlled clinical trial" Unknown who was blinded (page 186). The control is no treatment

Ghomian 2019 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of dropouts. ITT used
Selective reporting (reporting bias)	Unclear risk	Trial registration number available but only biochemical pregnancy reported
Other bias	Low risk	No other bias found

Griesinger 2002

Study characteristics	
Methods	Prospective, randomised, placebo-controlled, group comparative, double-blind study
Participants	Subfertile women having 1st IVF cycle aged < 40 years with mean age of 31.73 ± 4.4 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: women with repeated IVF cycles and women with renal or gastrointestinal disease
Interventions	1. Ascorbic acid 1 g: 1 tablet a day (N = 172) 2. Ascorbic acid 5 g: 1 tablet a day (N = 153) 3. Ascorbic acid 10 g: 1 tablet a day (N = 136) 4. Placebo (N = 158) Duration 1 cycle
Outcomes	Clinical pregnancy rate confirmed by fetal heartbeat at 8 weeks Implantation rate per embryo transfer
Notes	1 woman lost to follow-up — no explanation. Tried to contact author. No reply 10% of women had partners with male infertility Trial conducted in 2 clinics in Budapest, Hungary (N = 237) and Vienna, Austria (N = 383) No power calculation performed Pregnancies were confirmed at 8 weeks with no further follow-up; authors contacted regarding this. No reply as of 12th June 2013 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.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Griesinger 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "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	1 set of participant data noted as missing but not explained; authors contacted regarding this
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Clinical outcomes reported
Other bias	Unclear risk	Unequal baseline group numbers

Hashemi 2017

Study characteristics	
Methods	Randomised double-blind placebo-controlled clinical trial, parallel
Participants	Women with repeated implantation failure attending a gynacaeology clinic (no fertility treatment) (N = 40) Inclusion criteria: women with implantation failure; age range of 20 – 35 years old. (says 18 - 37 yrs in the abstract) Exclusion criteria: Having an abnormal uterus and PCOS, glucose intolerance, thyroid disease, having autoimmune diseases or cancer, smoking, and the lack of intention to continue co-operation in the study
Interventions	1. Vitamin E 400-IU (Mean age 32.2 ± 2.3) (N = 20) 2. Placebo (Mean age 31.5 ± 2.3) (N = 20) Treatment is for 12 weeks
Outcomes	Endometrial thickness Metabolic profiles Gene expression related to VEGF Oxidised low-density lipoprotein receptor (LDL) Inflammatory cytokines [IL-1, IL-6, IL-8] Tumour necrosis factor alpha (TNF-a)
Notes	Location: A gynaecology clinic affiliated to Isfahan University of Medical Sciences (IUMS), Isfahan, Iran Timeframe: between June 2016 and September 2016 Trial registration number: IRCT2016050920374N5 Informed consent: yes Ethical approval: yes

Hashemi 2017 *(Continued)*

Sample size power calculation: yes
Funding: The present study was supported by a grant from the Vice-Chancellor for Research, KUMS, and Iran
Conflict of interests: "No potential conflict of interest was reported by the authors"
ITT: yes
Author email: asemi_r@yahoo.com and aghadavod_m@yahoo.com

Author emailed 22 January 2020 asking if any further studies are being done with pregnancy outcomes and allocation concealment. Dr Asemi replied 23 January 2020 saying there were no clinical data and they used "Stratified blocked randomisation" to conceal the allocation. Emailed Dr Asemi 23 January 2020 asking for clarification on allocation concealment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization and allocation into two groups were done using a random number table by a trained staff as blindness" (page 2) Quote: "Stratified blocked randomisation" author reply from email request
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “double-blind placebo-controlled clinical trial” Quote: “Both vitamin E and placebo capsules had similar packaging and patients and researchers were unaware of the content of the package until the end of study”.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants were lost to follow-up, numbers and groups accounted for
Selective reporting (reporting bias)	Low risk	Trial registration available but no clinical outcomes reported
Other bias	Low risk	No other bias found

Hefny 2018

Study characteristics

Methods	Placebo-controlled double-blind randomised clinical trial
Participants	Infertile women attending an Obstetrics and Gynaecology clinic. Women with PCOS undergoing timed intercourse (Mean age = ?) (N = 200) Inclusion criteria: PCOS infertile women Exclusion criteria: Unknown
Interventions	1. Clomiphene citrate 100 mg/day plus NAC 1.2 g/day (N = ?)) 2. Clomiphene citrate 100 mg/day plus placebo (N = ?) Treatment for 5 days starting at day 3 of the cycle
Outcomes	The number of follicles > 18 mm on the day of hCG administration

Hefny 2018 *(Continued)*

	Ovulation rates The mean endometrial thickness Pregnancy No adverse side-effects and no cases of OHSS were observed in the group receiving NAC
Notes	Conference abstract Location: Obstetrics and Gynaecology, El Hussein University Hospital, Cairo, Egypt Timeframe: Unkown Trial registration number: Unkown Informed consent: Unkown Ethical approval: Unkown Sample size power calculation: Unkown Funding: Unkown Conflict of interests:Unkown ITT: Unkown Author email: Unkown and unable to find

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly divided"
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Placebo-controlled double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Heidar 2019

Study characteristics

Methods	Randomised, double-blinded, placebo-controlled trial - parallel
Participants	Women with PCOS attending infertility clinic IVF (N = 40) Inclusion criteria: Women with PCOS, age 18 to 40 years, who were candidate for IVF without prior IVF, were randomly enrolled in this investigation. To confirm PCOS diagnosis, Rotterdam criteria were used Exclusion criteria: Women with metabolic abnormalities such as diabetes, impaired glucose tolerance, and thyroid dysfunction

Heidar 2019 *(Continued)*

Interventions	1. 200 µg/day selenium as selenium yeast (Nature Made, California, USA) (Mean age 32.1 ± 4.7) (N = 20) 2. Placebo (Mean age 32.6 ± 3.5) (N = 20) Treatment for 8 weeks
Outcomes	TNF-α gene expression Gene expression associated with inflammation Endometrial thickness Number of oocytes retrieved Number of fertilised oocytes Fertilisation rate Pregnancy rate Number of embryos
Notes	Location: Mahdieh Hospital, Tehran, Iran Timeframe: between February and August 2018 Trial registration number: IRCT20170513033941N23 Informed consent: yes Ethical approval: yes "Compliance with Ethical Standards" Sample size power calculation: no "Due to a lack of evidence about the appropriate dosage of selenium for infertile patients with PCOS candidate for IVF, we used the above mentioned dose of selenium based on a previous study in patients with PCOS" Funding: This study was supported by a grant from the Vice chancellor for Research, Shahid Beheshti University of Medical Sciences, Tehran, Iran Conflict of interests: "The authors declare that they have no conflict of interest" ITT: no Author email: asemi_r@yahoo.com Emailed author 22 January 2020 asking if women had undergone IVF during the trial, definition of pregnancy data, any live birth data or adverse event data and methods of allocation concealment Dr Asemi replied 23 January 2020 saying yes, women were undergoing IVF at the time of the trial. Emailed Dr Asemi 23 January 2020 asking for clarification on allocation concealment and clinical pregnancy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To randomize enrolled patients, computer-generated random numbers were used"
Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation and randomization were concealed from both the participants and researchers until final analyses completion"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “double-blinded, placebo-controlled trial” Quote: “Placebos and selenium supplements were exactly matched in terms of appearance, smell, shape, and packaging”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts explained Quote: "Two dropouts were reported in each intervention group, due to personal reasons"

Heidar 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial registration number available, clinical outcomes reported only in the Results section
Other bias	Low risk	No other bias found

Ismail 2014

Study characteristics	
Methods	Randomised double-blind, placebo-controlled, parallel-group study
Participants	Infertile women with clomiphene resistant PCOS. Mean age: Treatment group: 24.6 ± 3.2; Control group: 24.8 ± 2.7.Ovulation induction with timed intercourse (N = 170) Inclusion criteria; < 35 years of age, presenting with primary or secondary infertility following regular intercourse for at least 1 year and diagnosed with PCOS with no other abnormalities Exclusion criteria; FSH values ≥ 10IU/ml
Interventions	1. Clomiphene citrate 250 mg: 1 tablet a day from day 3 to day 7 of the cycle plus oral-carnitine 3 g: 1 tablet a day from day 3 until the day of the first positive pregnancy test (N = 85) 2. Clomiphene citrate 250 mg: 1 tablet a day plus placebo (N = 85) All participants received clomiphene citrate from day 3 until day 7 of the cycle.Timed intercourse
Outcomes	Clinical pregnancy rate Miscarriage Multiple pregnancies Ovulation rate Days until hCG injection Endometrial thickness Number of follicles Number of pregnancies Laboratory parameters
Notes	All participants were counselled about their participation in the study. A signed informed consent was obtained. Participants had the right to refuse to participate or to withdraw from the study at any time without being denied their regular full clinical care. Personal information and medical data collected were subject to confidentiality and were not made available to a third party. Women's Health Hospital, Assiut University, Assiut, Egypt The study was conducted between January 2010 and March 2012 Sample size calculation done "The authors have no conflict to disclose" Funding source not reported Email: 'prof.alaaismail@aun.edu.eg' and 'alaaeldeen.mahmoud@med.au.edu.eg'

Ismail 2014 *(Continued)*

	Email sent to author on 26th November 2015 regarding live birth data; author replied on 7th December 2015 saying there are no live birth data 17 October 2019 we added sub-study; Salem 2012, there is some discrepancy between the doses of clomiphene in the two papers - the conference abstract Salem states that group A had 100mg clomiphene while Group b had 150mg and pregnancy data is different but this is probably due to early publication of the conference abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated numbers" Quote: "randomized according to computer-generated randomization tables to ensure an equal number of patients in each arm (1:1 ratio)".
Allocation concealment (selection bias)	Low risk	Quote: "using previously prepared sealed envelopes with computer-generated numbers" Quote: "Throughout the trial, access to the randomization code was available only to the pharmacist who manufactured the placebo and packed the envelopes and was not available to any of the treating physicians or patients". Quote: "The capsules were placed in sacks and then stored in envelopes numbered from 1 to 170. The envelopes were numbered"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind" Quote: "The placebo capsules were specially manufactured to look identical to the L-carnitine capsules".
Incomplete outcome data (attrition bias) All outcomes	Low risk	18/170 dropouts with numbers per group and reasons given
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. All outcomes stated in the Methods were reported
Other bias	Low risk	No other bias found

Jahromi 2017

Study characteristics

Methods	Double-blinded, randomised, clinical trial – parallel
Participants	Infertile women with diminished ovarian reserve who were referred to the infertility center. IVF (N = 80) Inclusion criteria: Poor ovarian reserve ART for the first time, normal male factor, normal uterine cavity, and presence of 2 of the following 3 criteria: 1) summation of bilateral AFC ≤ 6, 2) AMH ≤ 1, and 3) basal FSH on the 3rd day of menstrual cycle ≥ 10. These cases are routinely candidated for egg donation in our centre. Couples who insisted on having the ART by using their own oocytes were enrolled in this project Exclusion criteria: unknown

Jahromi 2017 *(Continued)*

Interventions	1. Melatonin 3 mg 1 capsule every night starting from the 5th day of the menstrual cycle prior to the cycle that was planned for gonadotropin stimulation (Mean age 35 ± 5.1) (N = 40) 2. Placebo (Mean age 35.1 ± 5.1) (N = 40)
Outcomes	Stimulation duration Estradiol on HCG injection Human menopausal gonadotropin dose Oocytes in germinal vesicle stage Oocytes in maturation stage I (MI) Oocytes in maturation stage II (MII No. of embryos transferred Embryos in grade 1 Embryos in grade 2 Embryos in grade 3 Embryos in grade 4 Women who had mature oocytes (MII) Women who had grade-1 embryos Women who had top-quality embryos Women whose embryos were transferred Biochemical pregnancy Clinical pregnancy Miscarriage
Notes	Location: Infertility Center, Mother and Child Hospital, affiliated to Shiraz University of Medical Sciences, Iran Timeframe: between 2014 and 2015. 12-month period cbeginning in June 2014 Trial registration number: IRCT2014041417264N1 Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding: The present article was partly extracted from a thesis written by Sara Sadeghi and was financially supported by Shiraz University of Medical Sciences (grant # 92-5250) Conflict of interests: "none declared" ITT: no Author email: namavarb@sums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization table" (page 74)
Allocation concealment (selection bias)	Low risk	Quote: "the pharmaceutics specified every package that contained the placebo or melatonin with a code number from 101 to 200 based on a randomization table. The prepared packages, each containing 50 capsules, were offered to the participants orderly based on their entrance into the project. Accordingly, the patients or the clinicians did not know that which package contained the placebo or melatonin" (page 74)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Capsules containing 3 mg melatonin (Nature Made Nutritional Products, Mission Hills, USA) and placebos with the same shapes were prepared for the study by the Pharmaceutics Division of Shiraz University of Medical Sciences. To design a double-blinded, simple randomization" (page 74)
Incomplete outcome data (attrition bias)	Low risk	Reasons and numbers from each group given

Jahromi 2017 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Trial registration number and reports clinical pregnancy
Other bias	Low risk	No other bias found

Jamilian 2018

Study characteristics	
Methods	Randomised double-blind, placebo-controlled trial
Participants	Infertile PCOS women candidate for IVF (but not going through IVF at the time of this trial) without previous IVF, aged 18 – 40 years who were referred to the Research and Clinical Center for Infertility and Kosar Clinic, Arak, Iran (N = 40) Inclusion criteria: Diagnosis of PCOS was done according to the Rotterdam criteria Exclusion criteria: metabolic disorders, including androgen-secreting tumours, thyroid dysfunction, diabetes, or impaired glucose tolerance at enrolment
Interventions	1. 200 µg/day of chromium as chromium picolinate (Nature Made, California, USA). Mean age (years) 32.3 ± 3.0 (N = 20) 2. Placebo (Barij Essence, Kashan, Iran). Mean age (years) 30.3 ± 4.6 0 (N = 20) treatment for 8 weeks
Outcomes	Glycaemic status Insulin resistance (HOMA-IR)
Notes	Location: Endocrinology and Metabolism Research Center, Department of Gynecology and Obstetrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran Timeframe: between May 2017 and August 2017 Trial registration number: IRCT201706075623N120 Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding: This study was supported by a grant from the Vice-chancellor for Research, Arak University of Medical Sciences, Arak, Iran Conflict of interests: "The authors declare that they have no conflict of interest" ITT: yes Author email: Zatollah Asemi (last author) asemi_r@yahoo.com Author emailed 22 January 2020 about clinical outcomes and whether the women went through IVF Author replied 23 January 2020 saying women were not going through IVF at the time of the trial, and there were no clinical outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “Randomization assignment was conducted using computer generated Random numbers.”
Allocation concealment (selection bias)	Low risk	Quote: “Chromium supplements and placebos were in the same form of package. Randomization and allocation were concealed from the researchers and participants until the final analyses were completed. Another person, who was

Jamilian 2018 *(Continued)*

		not involved in the trial and not aware of random sequences, assigned the subjects to the numbered bottles of tablets."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial" Quote: "allocation were concealed from the researchers and participants until the final analyses were completed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Trial registration number provided but no clinical outcomes reported, the title says candidate for IVF would expect that pregnancy outcomes would be provided
Other bias	Low risk	No other bias found

Keikha 2010

Study characteristics	
Methods	Double-blinded randomised control trial
Participants	Women aged 18 - 41 with PCOS which was clomiphene-resistant who attended fertility clinic in Iran (N = 93)
Interventions	1. Oral NAC 1.2 g: 1 tablet a day (N = 53) 2. Vitamin C (?dose) (N = 40)
Outcomes	Oestradiol levels Number of follicles > 18 mm Endometrial thickness
Notes	Conducted in Iran, study began in 2010 (end unknown) Unknown trial duration Funding source not reported Tried to contact author regarding pregnancy data, uneven number in each group. No reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blinded (another antioxidant, not placebo)

Keikha 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Uneven number in each group
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Low risk	No other bias found

Kim 2006

Study characteristics	
Methods	Randomised controlled trial
Participants	Infertile women aged 25 - 39 years with PCOS undergoing IVF (N = 58)
Interventions	1. NAC 400 mg: 1 tablet twice a day (N = unknown) 2. Placebo (N = unknown) Duration 13 - 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 Ovarian hyperstimulation syndrome rates
Notes	Conference abstract only Trial held in Korea, study dates not reported Funding source not reported The authors contacted to request pregnancy outcome data and study protocol to appraise risk of bias elements. No reply as of 14th September 2011

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients randomly assigned..." No description of method of sequence generation

Kim 2006 *(Continued)*

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	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Kim 2010

Study characteristics	
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	1. Omega-3-polyunsaturated fatty acids (o-3 PUFAs) 1000 mg: 1 tablet a day (N = unknown) 2. 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, study dates not reported Funding source not reported Authors emailed 22nd November 2011regarding risk of bias, pregnancy data per woman, numbers in intervention and control groups and inclusion/exclusion criteria. No reply

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Kim 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Prospective randomised controlled study" — no explanation given.
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unknownn.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Clinical pregnancy reported in methods
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Lisi 2012

Study characteristics	
Methods	Randomised open-label, multicentre pilot study
Participants	Infertile women undergoing IVF/ICSI, mean age 34.4 ± 3.4 (N = 100) Exclusion criteria: women with PCOS, with any endocrine or metabolic disease, taking any hormonal treatment, with BMI > 30 kg/m^2
Interventions	1. Myo-inositiol 4000 mg: "into two administrations per day" + folic acid 400 µg: 1 tablet a day (N = 50) 2. Folic acid 400 µg: 1 tablet a day (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, study held from January 2011 to January 2012 Funding source not reported Registration number NCT01338844 Emailed author 13th February 2013 about randomisation, allocation concealment and live birth data. Professor Lisi replied, clarifying these questions
Risk of bias	

Lisi 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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. We sought further information 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 participants were not
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Trial registration number provided. Clinical pregnancy reported
Other bias	Low risk	No other bias found

Lu 2018

Study characteristics	
Methods	Randomised controlled trial
Participants	Women with endometrioisis who underwent IVF-ET were recruited from the Department of Reproductive Medicine (N = 280) Inclusion criteria: 2 years of infertility and required infertility treatment by IVFET for the first time, and had a regular menstrual cycle with a FSH level of < 10IU/L on cycle day 2 were included in this study. Women with endometriosis (EMs) that had been diagnosed by conventional laparoscopy or laparotomy and staged according to the revised American Fertility Society classification were included Exclusion criteria: (1) EMs complicated by endocrine diseases such as diabetes mellitus, POCS, hypothalamic pituitary dysfunction, or thyroid dysfunction; (2) a history of autoimmune disease, cardiovascular disease, and liver and kidney dysfunction; (3) administration of an ICSI to the husband because of severe asthenospermia and oligospermia; (4) treatment with oral contraceptives and gonadotropin-releasing hormone agonists within 3 months; and (5) a history of alcohol and drug abuse and long-term administration of vitamins
Interventions	1. 1000 mg/day of oral VitC (Shanghai Sine Pharmaceutical Laboratories Co. Ltd., Shanghai, China). Mean age 31.5 ± 3.5 (N = 160) 2. No treatment. Mean age 31.9 ± 3.0 (N = 120) Treatment period was from 2 months before IVF-ET treatment until 2 weeks after ET (EMs treatment group)

Lu 2018 *(Continued)*

	Eligible participants were randomised in a ratio of 4:3 There is also a non-endometriosis group called 'control group' in the paper (N = 150) who were not randomised, so data not used
Outcomes	Fertilisation rate was calculated as the number of cleavage embryos divided by the number of metaphase II oocytes. Embryo quality was assessed using Veeck's classification, and grade I and II were considered high-quality embryos Clinical pregnancy was defined as identification of a gestational sac in serum human chorionic gonadotropin-positive patients through ultrasonographic examination. The implantation rate was defined as the number of gestational sacs per transferred embryo
Notes	Location: International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiaotong University, China Timeframe: from June 2013 to December 2016 Trial registration number: unable to be found Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding: This study was funded by the Leading Project of Science and Technology Commission of Shanghai Municipality (Grant Number: 134119a8000). Conflict of interests: "The authors declare that there is no conflict of interest" ITT: no Author email: Weiweicheng038@163.com Author emailed 22 January 2020 for; RoB methods, live birth, miscarriage and adverse events data and trial registration number

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This randomized controlled study" (page 4626)
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment in the paper
Blinding (performance bias and detection bias) All outcomes	High risk	No mention of blinding in the paper, and the control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and numbers explained
Selective reporting (reporting bias)	Unclear risk	Trial registration number unable to be found. Clinical pregnancy reported
Other bias	Low risk	No other bias found

Maged 2015

Study characteristics

Maged 2015 *(Continued)*

Methods	Randomised study
Participants	Women with PCOS (based on Rotterdam criteria, ESHRE/ASRM 2004), the diagnosis of PCOS is determined by the presence of 2 of the following conditions: oligo-ovulation or anovulation, hyperandrogenism and polycystic ovaries detected by ultrasonography with the presence of 12 or more follicles measuring 2 – 9mm in diameter, and/or at least 1 enlarged ovary (410 cm). None of the participants had history of clomiphene citrate resistance (N = 120) Timed intercourse Mean age was 26 years for all 3 groups Exclusion criteria: women with endocrinological abnormalities such as thyroid dysfunction or abnormal prolactin levels, those with hypothalamic or pituitary dysfunctions evaluated by low gonadotropin level, other causes of infertility such as tubal factor evaluated by HSG or laparoscopy, abnormal uterine cavity evaluated by sonohystrography or hysteroscopy and male factor, evaluated by semen analysis. Women with ovarian cysts and those with allergy to the study medications were also excluded from the study. Women who had received any hormonal medications (except progesterone for withdrawal bleeding) within the last 3 months before the study were also excluded
Interventions	1. Clomiphene citrate 100 mg orally in 2 divided doses a day. No treatment (N = 40) 2. NAC 1200 mg in 2 divided doses a day (in the form of powder inserted in small pockets to be diluted into a standard glass of water from day 3 until day 7 of the menstrual cycle) (N = 40) 3. Metformin 500 mg: 1 tablet 3 times a day (N = 40) Treatment period; from day 3 to day 7 of the menstrual cycle, treatment was repeated in non-pregnant cases for 3 successive cycles
Outcomes	Clinical pregnancy (defined as the presence of gestational sac containing fetal hearts on ultrasound scan) Occurrence and day of ovulation Endometrial thickness and pattern Number and size of follicles
Notes	Conducted in Egypt Trial period; September 2012 to March 2014. Funding source not reported Ahmed Mohamed Maged, Obstetrics and Gynecology Department, Kasr Aini Hospital Cairo University, 135 King Faisal Street Haram Giza, Cairo, Egypt. Tel: 0105227404. Fax:35873103. E-mail prof.ahmedmaged@gmail.com. Email sent 13th October 2016 regarding live birth and any dropouts. No reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised at the beginning of each cycle by sealed opaque envelopes containing randomly-generated numbers into 3 groups
Allocation concealment (selection bias)	Low risk	Participants were randomised at the beginning of each cycle by sealed opaque envelopes containing randomly-generated numbers into 3 groups
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding

Maged 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers analysed in each group are not given
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Clinical pregnancy reported
Other bias	Low risk	No other bias found

Mier-Cabrera 2008

Study characteristics	
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. Mean age: Treatment group 32.7 ± 2.36; Placebo group 32.7 ± 2.36 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 agree to participate or missed a medical visit
Interventions	1. Vitamins C 343 mg + Vitamin E 84 mg: in a bar form, 1 bar a day (N = 18) 2. Placebo (N = 18) Duration of trial was 6 months Follow-up for up to 9 months after the trial
Outcomes	Live birth (no data available) Pregnancy (no explanation of whether pregnancies were biochemical, clinical or ongoing). "None of the patients became pregnant during the trial. Once the trial ended, patients were followed up for 9 months for a possible pregnancy". The pregnancy rate was 19% (3 of 16) in the supplementation group and 12% (2 of 18) in the placebo MDA, 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, study dates not reported Funding given as a grant from Consejo Nacional de Ciencia Tecnologia Mexico. Power calculation done. Tried to contact author. Contacted author again 12th February 2013 to ask about clinical pregnancy and live birth. No reply
Risk of bias	

Mier-Cabrera 2008 *(Continued)*

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, Quote: "Thirty-six participants were randomly assigned". Comment: Authors contacted regarding this
Allocation concealment (selection bias)	Unclear risk	Not stated in the paper. Authors contacted regarding this. The response was, Quote: "women were randomly allocated depending on the colour of a ball they took out from a container"
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. Quote: "Randomization codes were unlocked at the end of the study".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 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. Trial registration number not available
Other bias	Low risk	No other bias found

Mohammadbeigi 2012

Study characteristics	
Methods	Randomised controlled trial
Participants	Infertile women with PCOS (N = 44). Natural or timed intercourse Mean age: Treatment group: 26.5 yr (20 - 43); Control group: 29 yrs (23 - 26) Inclusion criteria: primary or secondary infertility due to PCOS according to Rotterdam criteria including oligomenorrhoea, amenorrhoea, clinical or laboratory evidence of increase androgen level or polycystic ovaries in sonography Exclusion criteria: any definite gland disorders such as kaohsiung hypothyroid, hypothyroidism, diabetics and increase in blood prolactin levels
Interventions	1. Clomiphene 50 mg: 1 tablet a day + 400 units of Vitamin D + 1000 mg calcium: 1 tablet a day (N = 22) 2. Clomiphene 50 mg + placebo: 1 tablet a day (N = 22) Duration: 3 menstruation cycles (3 months)
Outcomes	Follicle size Pregnancy (unknown whether this is clinical or biochemical - sonography had been done for all participants up to 3 months but this could be to assess follicle size)
Notes	Conducted in Iran

Mohammadbeigi 2012 *(Continued)*

Trial was run between 2010 and 2011.

Funding source not reported

Email was sent to author on the 30th November 2015 regarding data and risk of bias robab20@yahoo.com - no reply. Dr Vahid Seyfoddin helped translate key points from the paper. New email found nezhat79@gmail.com, email sent 27th September 2016 regarding block size, allocation concealment and clinical pregnancy data

Trial registration number: IRCT201105096426N1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were divided into two groups (22 Intervention and 22 controls) using block randomization method". Comment: Unknown process of selection of blocks
Allocation concealment (selection bias)	Unclear risk	Unknown block number
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Specialists did the randomisation only and the residents managed the study, the radiologists was blinded while using the same instrument and only one practitioner" (placebo control)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All participants completed the study"
Selective reporting (reporting bias)	Unclear risk	Unknown whether the reported pregnancies were biochemical or clinical. Protocol available
Other bias	Low risk	No other bias found

Mokhtari 2016

Study characteristics

Methods	Single-centre, double-blinded, placebo-controlled, randomised trial
Participants	Women (age: 22 - 40) with at least 2 repeated implantation failure (RIF) history. IVF (N = 30)
Interventions	1. NAC 1200 mg/day (N = ?) (Mean age = ?) 2. Placebo (N = ?) (Mean age = ?) For at-least 9 weeks before starting ovarian stimulation
Outcomes	Level of HOXA9 gene
Notes	Conference abstract Location: Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran Timeframe: Unknown Trial registration number: Unknown

Mokhtari 2016 *(Continued)*

Informed consent: Unknown
Ethical approval: Unknown
Sample size power calculation: Unknown
Funding: Unknown
Conflict of interests: Unknown
ITT: Unknown
Author email: Unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown methods
Allocation concealment (selection bias)	Unclear risk	Unknown methods
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blinded, placebo controlled"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available and no clinical outcomes
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Mokhtari 2019

Study characteristics

Methods	Double-blinded randomised clinical trial - parallel
Participants	Women with PCOS attending an infertility clinic for IUI (N = 198) Inclusion criteria: Women with PCOS aged between 20 to 40 years, having husbands with normal spermograms, having normal hysterosalpingography, having the Rotterdam diagnostic criteria for PCOS, no underlying endocrine diseases, and using no hormonal drugs within the past 3 months Exclusion criteria: Being deficient in an adequate ovarian response, suffering from ovarian hyperstimulation syndrome, and no history of treatment for infertility
Interventions	1. Melatonin tablet 3 mg (Nature Made, USA) Mean age 28.4 ± 5.5 (N = 98) 2. Placebo (made by Faculty of Pharmacy, Tehran University of Medical Sciences); mean age 29.3 ± 5.6 (N = 100) Treatment from the 3rd day of menstruation until the day of hCG administration
Outcomes	Chemical pregnancies Endometrial thickness (ET) on the day of IUI

Mokhtari 2019 *(Continued)*

	Clinical pregnancy
Notes	Location: P.O.Box: 1598718311, Department of Obstetrics and Gynecology, IVF Unit, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran Timeframe: from March 2017 to September 2017 Trial registration number: IRCT2017021132489N1 Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding:There is no financial support Conflict of interests:There is no conflict of interests ITT: no Author email: azmoudeh@sina.tums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the participants were divided into an intervention group receiving melatonin and a control group receiving placebo using a balanced block randomization technique. Considering blocks of 4 in this study, the Stata software was used to generate random-number sequences from 1 to 6 until the desired sample size was achieved. Since the total number of modes to set two people in the blocks of 4 was 6 modes, if the generated number exceeded 6, the next number was regenerated regardless of the previous number".
Allocation concealment (selection bias)	Low risk	Quote: "Preparing the random allocation sequences of the participants, putting them in sealed airtight envelopes, and numbering them with a five-digit serial number were all performed by a third person who was not involved in the study design. All the envelopes (n=188) having a random 5-digit serial number were opened immediately after the completion of basic information and examination of the participants. Then, the participants were assigned to the intervention or control groups".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blinded randomized" placebo controlled trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and reasons explained
Selective reporting (reporting bias)	Low risk	Trial registration number provided and clinical pregnancy reported
Other bias	Low risk	No other bias found

Mostajeran 2018

Study characteristics

Methods	Placebo-controlled double-blind randomised clinical trial
Participants	Women attending an infertility centre, Timed intercourse with ovulation induction (N = 130) Inclusion criteria: All infertile women who were referred to our centre with PCOS (based on Rotterdam criteria, ESHRE/ASRM 2004), aged 20 – 35 years, BMI < 35 kg/m2, both tubes patent confirmed by hys-

Mostajeran 2018 *(Continued)*

	terosalpingography, and with partner's normal semen analysis results (total volume > 2 mL, concentration > 20 million/mL, total motility > 50%, and normal morphology > 14%) were included in the study. None of the women or their male partners had any sexual dysfunction interfering with successful intercourse. Exclusion criteria: Thyroid dysfunction, hyperprolactinaemia, history of large ovarian cyst formation (> 6 cm), and asthma and/or allergy to medication were excluded from the study. Women who received any hormonal medication (except for progesterone for withdrawal bleeding) and metformin were also excluded from the study
Interventions	1. Letrozole 5 mg plus 1200 mg NAC (produced by OSVE Company). From the 3rd until the 7th day of the menstrual cycle, NAC was given to the participants in the form of powder inserted in small pockets to be diluted into 1 standard glass of water and taken orally in 2 daily divided doses Average age (year) 29.1 ± 3.7 (N = 65) 2. Letrozole 5 mg plus placebo. Average age (year) 30.3 ± 3.9 (N = 65)
Outcomes	Biochemical pregnancy Clinical pregnancy Size of follicle Ovulation
Notes	Location: Isfahan University Infertility Center, Shahid Beheshti Hospital, Iran Timeframe: between 2015 and 2016 Trial registration number: no Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding: Financial support and sponsorship Nil Conflict of interests: There are no conflicts of interest ITT: no Author email: f_mostajeran@med.mui.ac.ir Author emailed 23 January 2020 asking whether the data for pregnancy in Table 2 is biochemical or clinical pregnancy, about a discrepancy in the numbers and percentages given, plus RoB questions. The email to Dr Mostajeran was undeliverable, so I have resent to Dr Ghoreieshi asking if they will pass it on: elham_ghoreishi63@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized clinical trial" Methods not explained
Allocation concealment (selection bias)	Unclear risk	Methods not explained
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "placebo controlled double blind" Quote: "ORS powder was given to the patients in the same pockets as NAC"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and reasons explained
Selective reporting (reporting bias)	Unclear risk	Trial registration number cannot be found

Mostajeran 2018 *(Continued)*

Other bias	Low risk	No other bias found

Nasr 2010

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled pilot study
Participants	Women undergoing unilateral laparoscopic ovarian drilling (LOD) for clomiphene-resistant PCOS (N = 60) Aged 18 - 38 years; mean age: treatment group 28.4 ± 4.2; placebo group 29.2 ± 3.7, with at least 2 years of infertility due to anovulation, patent fallopian tubes, normal semen analysis Exclusion criteria included no hormonal treatment for 3 months before enrolment and any contraindications to anaesthesia or laparoscopy
Interventions	1. NAC 1.2 grams: 1 sachet a day for 5 days, starting at day 3 of the cycle (immediately after LOD) for 12 consecutive cycles (N = 30) 2. 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	Primary outcome: biochemical pregnancy Secondary outcomes: ovulation, number of follicles, endometrial thickness, clinical 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. Endometrial thickness; significant difference in favour of the treatment group Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomised double-blind placebo-controlled pilot study", "computer-generated random numbers".
Allocation concealment (selection bias)	Unclear risk	Quote: "Sealed envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Quote: "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".

Nasr 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. All outcomes reported
Other bias	Low risk	No other bias found

Ozkaya 2011

Study characteristics	
Methods	Randomised trial
Participants	Women undergoing IVF aged 22 - 43 years. Mean age treatment group: 30.7 ± 4.5; placebo group: 28.8 ± 3.2) (N = 56) 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	1. Multi-vitamin/mineral (containing vitamins A, B, C, D, E and H, calcium, folic acid, nicotinic acid, iron, magnesium, phosphor copper, manganese and zinc): 1 tablet a day (N = 26) 2. Placebo (candy) (N = 30). for 45 days
Outcomes	Follicular fluid
Notes	Conducted in Turkey 3 groups were used in the study. The 1st group consisted of age-matched controls, so we did not use these data in this review. The 2nd and 3rd groups were randomly assigned Author emailed on 1st August 2012 to ask for any data on pregnancy, live birth or adverse events. Author replied on 13th August 2012. No outcomes appropriate to this review.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low 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)	Unclear risk	None mentioned

Ozkaya 2011 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Low risk	No other bias found

Panti Abubakar 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Women with PCOS having clomiphene citrate for ovulation induction (timed intercourse) (N = 200)
Interventions	1. Combined antioxidant supplementation; vitacap which contains vitamin A (Palmitate) 5000 iu, vitamin B1 (thiamine mononitrate) 5 mg, vitamin B6 (pyridoxine HCL) 2 mg, vitamin B12 (cyanocobalamin 5 mg, vitamin C 75 mg, vitamin D3 (cholecalciferol) 400 iu, Vitamin E (d-alpha tecopheryl acetate) 15 mg, nicotinamide 45 mg, folic acid 1000 mcg, ferrous fumerate 50 mg, dibasic calcium phosphate 70 mg, copper sulphate 0.1 mg, manganese sulphate 0.01 mg, zinc sulphate 50 mg, potassium iodide 0.025 mg and magnesium oxide 0.5 mg: 1 vitacap a day (N = 100) 2. Placebo; containing folic acid and fersolate. 1 tablet a day (N = 100) Treatment given for 6 months
Outcomes	Live birth Clinical pregnancy Menstrual regularisation
Notes	Conducted in Nigeria, study dates not reported Conference abstract Funding source not reported kapanti2002@yahoo.co.uk, email sent 18th October 2016. Author replied 20th October 2016 with live birth data. Emailed author re allocation concealment of odd and even envelopes 25th January 2017

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The women were randomized into two groups by picking one of the two closed envelops. within the envelop is written odd or even number. The odd number for intervention and even number for control. The selection of odd and even number for intervention and control group was done by toss of coin"
Allocation concealment (selection bias)	Low risk	Quote: "The women were randomized into two groups by picking one of the two closed envelopes, within the envelope is written odd or even number".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The trial was single blinded. The patient did not know" a placebo was used

Panti Abubakar 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts accounted for
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Outcomes live birth and clinical pregnancy reported
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Polak de Fried 2013

Study characteristics	
Methods	Prospective, randomized, double-blind placebo-controlled trial
Participants	Infertile women undergoing IVF/ICSI, 34 women with ICSI cycles and 18 oocyte donation (N = 52)
Interventions	1. Vitamin D 100.000 IU: 1 tablet per month (N = 26) 2. Placebo (N = 26) Trial duration; 5 consecutive months
Outcomes	Endometrial thickness Number of oocytes retrieved Cancellation rate Number of embryos transferred Implantation rate Clinical pregnancy rate Live birth
Notes	Conducted in Argentina,study dates not reported conference abstract Funding source not reported Author email; ester_polak@cermed.com. Author contacted on the 20th November 2015 regarding risk of bias factors and live birth data. Author replied 14th December 2015 regarding dropouts, miscarriage, adverse effects and live birth. Trial not yet published as a full text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Fifty two patients were computer randomized"
Allocation concealment (selection bias)	Unclear risk	Unknown

Polak de Fried 2013 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double blind" (placebo control)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no dropouts" email from author
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. Reports clinical pregnancy and live birth
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Rasekhjahromi 2018

Study characteristics	
Methods	Randomised control trial
Participants	Women with PCOS attending an infertility clinic. Mean age unknown (N = 144) Inclusion criteria: infertile PCOS women Exclusion criteria: Unknown
Interventions	1. Vitamin E + metformin and dydrogesterone (N = 36) 2. Metformin and dydrogesterone (no treatment) (N = 36) Vitamin E-deficient women were in another 2 groups (intervention and no treatment) of 36 women (N = 72), not included in this review due to vitamin deficiency Unknown treatment time
Outcomes	Follicular size Endometrial thickness BMI Pregnancy
Notes	Conference abstract Location: Iran Timeframe: Unknown Trial registration number: Unknown Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: Unknown Conflict of interests: Unknown ITT: Unknown Author email: Unknown Quote: "In this clinical trial, 144 PCOS infertile patients referred to Dr.rasekh clinic, jahrom, Iran that randomly divided in two groups (groups with sufficient and insufficient levels). Each of these two groups was randomly divided into case and control groups (36 participants in each group). Usual drug regimen of PCOS started for all groups (Metformin and dydrogestrone). Case groups received vitamin E supplemention as an add- on their treatment i.e. vit e deficient".

Rasekhjahromi 2018 *(Continued)*

Emailed 23 January 2020 Dr Hosseinpoor (masoomehosseinpoor@yahoo.com) who has co-authored other papers with Dr Rasekhjahromi, asking questions about; RoB, live birth, clinical pregnancy, and adverse event data. Is there a trial registration number and are there separate data for vit E deficient and sufficient women. When was the trial carried out? No reply as yet - 25 August 2020.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “randomly divided into case and control groups”
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	The control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Rashidi 2009

Study characteristics

Methods	Randomised clinical trial
Participants	Infertile women with PCOS (N = 60). Mean age Treatment group: 24.95 ± 3.56, Control groups 25.8 ± 4.61 and 26.9 ± 4.44 respectively 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	1. Calcium 1000 mg + vitamin D 400 IU (N = 20) This arm is not used in the analysis. 2. Calcium 1000 mg + vitamin D 400 IU + metformin 1500 mg: 1 tablet of each a day (N = 20) 3. Metformin 1500 mg: 1 tablet a day (N = 20) Trial lasted 3 months with a 3-month follow-up.
Outcomes	Follicular response Frequency of menstrual cycle Chemical pregnancy Clinical pregnancy

Rashidi 2009 *(Continued)*

	No pregnancy occurred in any of the groups
Notes	Trial held in Iran, study ran from February 2004 (unknown end date) Funding source not reported Tried to contact authors regarding allocation concealment and blinding 13th February 2013. No reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were divided into 3 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. Trial registration number not available
Other bias	Low risk	No other bias found

Razavi 2015

Study characteristics

Methods	Randomised double-blind placebo-controlled trial
Participants	Infertile women with PCOS 18 - 40 years old (N = 64) Mean age: 25.1 ± 4.5 vs 25.4 ± 4.9 years, P = 0.85 Inclusion criteria: age between 18 and 40 years with PCOS according to Rotterdam criteria Exclusion criteria: elevated levels of prolactin, thyroid disorder, or Type 2 diabetes and congenital adrenal hyperplasia. In addition, all PCOS women had normal baseline renal function tests, bilirubin, and aminotransferases
Interventions	1. Selenium 200 ug: 1 tablet a day + metformin 500 mg: which was elevated in a stepwise manner during the first 3 weeks to incorporate the side effects until the participants were taking a total of 1500 mg a day (N = 32) 2. Placebo plus metformin: same dosage as above (N = 32) Treatment was for 8 weeks The trial ran from October 2014 to December 2014
Outcomes	Pregnancy rates (biochemical)

Razavi 2015 *(Continued)*

	Hormone levels
Notes	Conducted in Iran Trial was supported by an institutional grant. Clinical trial number: IRCT201412295623N33 Contact details: Dr Z Asemi; asemi_r@yahoo.com. Email sent 18th October 2016 regarding clinical pregnancy data and block size. No reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients with PCOS were randomly divided into 2 groups" "Patient allocation and block size were obtained using random number tables".
Allocation concealment (selection bias)	Low risk	Quote: "At the time of randomization,sequentially numbered, sealed envelopes were opened. Allocation to study group was concealed until the main analyses were completed".
Blinding (performance bias and detection bias) All outcomes	Low risk	Supplements and placebos were in the same form of package and the participants and researcher were not conscious of the content of the pack until the end of trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons and numbers for dropouts from each group were provided. ITT used in the analysis
Selective reporting (reporting bias)	Unclear risk	Trial registration number available, only biochemical pregnancy rates reported
Other bias	Low risk	No other bias found

Rizk 2005

Study characteristics

Methods	Placebo-controlled, double-blind, randomised trial
Participants	Women diagnosed with clomiphene citrate-resistant PCOS (N = 150) aged 18 - 39 years, undergoing therapy for infertility. Timed intercourse. Mean age Treatment group: 28.9 ± 4.7, Placebo group 28.4 ± 5.7. Inclusion criteria: clomiphene citrate-resistant, at least 1 patent tube, adequate semen analysis according to 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	1. NAC 1.2 g: 1 tablet a day + clomiphene citrate 100 mg: 1 tablet a day for 5 days, starting at day 3 of the cycle for 1 cycle (N = 75) 2. Placebo + clomiphene citrate 100 mg: 1 tablet a day (N = 75)
Outcomes	Ovulation rate

Rizk 2005 *(Continued)*

	Ongoing pregnancy rate, however only pregnancy rate reported 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 as there were no pregnancies or live birth events in the control group, so 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 7th September 2012 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 Endometrial thickness; significant difference in favour of the treatment group vs control; see conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive CC and either NAC or placebo". Method not described
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was done by a third party (nurse)". Quote: "Using sealed envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "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	Trial registration number not available. No known selective reporting
Other bias	Low risk	No other bias found

Rizzo 2010

Study characteristics

Methods	Prospective, randomised clinical trial

Rizzo 2010 *(Continued)*

Participants	Women with low oocyte quality detected in previous IVF cycles (N = 65). Aged 35 - 42 years. Mean age Treatment group 37.81 ± 2.61, Placebo 38.09 ± 1.97 IVF
Interventions	1. Myo-inositol 2 g + folic acid 200 mg + melatonin 3 mg: each tablet twice a day (N = 32) 2. Myo-inositol 2 g + folic acid 200 mg: each tablet twice a 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 Spontaneous abortion defined as a pregnancy loss from 5 - 12 weeks pregnancy
Notes	Setting: Messina, Italy, study dates not reported 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised: Quote: "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	Trial registration number not available. Data given for all outcomes reported in the text
Other bias	Low risk	No other bias found

Salehpour 2009

Study characteristics

Methods	Randomised, controlled, double-blind trial

Salehpour 2009 *(Continued)*

Participants	Women with PCOS attending IVF clinic (N = 46); Mean age Treatment group: 27; Control group 28 Exclusion criteria: infertility factors apart from anovulation, other pathologies, hormone consumption for less than 2 months before enrolment.
Interventions	1. NAC 200 mg: 1 tablet 3 times a day (N = 23) 2. Placebo (N = 23) 7 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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	Quote: "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; 7 from each arm, reasons generally described but not for each woman
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. All outcomes described in the text were reported
Other bias	Low risk	No other bias found

Salehpour 2012

Study characteristics	
Methods	Randomised placebo-controlled double-blind trial
Participants	Infertile women with PCOS undergoing timed intercourse (N = 180) Women were aged 20 – 35 years Inclusion criteria: infertility duration < 10 years, BMI < 35 kg/m^2, both participant tubes confirmed by hysterosalpingography or laparoscopy and with partner's normal semen analysis results (total volume > 2 cc, concentration > 20 million/ml, total motility > 50%, normal morphology > 14%) Exclusion criteria: thyroid dysfunction, hyperprolactinaemia, hypercorticism, history of large ovarian cyst formation (> 6 cm), history of visual disturbance caused by clomiphene citrate and finally history of asthma and or allergy to medications. Women who had received any hormonal medications (except progesterone for withdrawal bleeding) or medications affecting glucose metabolism for at least 3 months before the study were also excluded; also no sexual dysfunction
Interventions	1. NAC 1.2 g: 1 sachet a day (divided into 2 doses per day) + clomiphene citrate 100 mg: 1 tablet a day (N = 90) 2. Placebo + clomiphene citrate 100 mg/day divided and given in 2 doses a day given for 5 days starting at day 3 of the cycle. Timed intercourse occurred after an hCG trigger (N = 90) 8 women in the 1st group and 4 in the 2nd group left the study due to inappropriate drug intake or discontinued cycle; also 1 woman dropped out of the placebo group due to developing an ovarian cyst
Outcomes	Number of follicles > 18 mm Endometrial thickness Ovulation rates Pregnancy rates Adverse effects including multiple pregnancy Ovarian hyperstimulation syndrome
Notes	Trial carried out in the Shahid Beheshti University of Medical Sciences IVF Center, Taleghani Hospital, Iran between January 2008 and December 2009 Informed consent Power calculation Ethics approved Reprint request to: Dr Azadeh Akbari Sene, IVF Center, Infertility and Reproductive Health Research Center, Taleghani Hospital, Velenjak st, Tehran, Iran. Email: doctor_asturias@yahoo.com. RM-P sent an email 12th December 2015. No reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Then patients were randomly divided into two groups".
Allocation concealment (selection bias)	Unclear risk	Unknown

Salehpour 2012 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. In the 2nd group in addition to 100 mg daily CC, participants received a placebo (oral rehydration solution powder) from day 3 until day 7. ORS powder was given to the participants in the same packets as NAC
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were explained
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. All outcomes described in the text were reported
Other bias	Low risk	No other bias found

Schachter 2007

Study characteristics	
Methods	Randomised trial
Participants	Infertile women diagnosed with insulin-resistant PCOS (N = 102) 18 women were scheduled for ovulation induction and 84 for IVF/ICSI Mean age: 28.8 ± 0.4 years
Interventions	1. Folic acid 0.4 mg a day (N = 23) 2. Metformin 1700 mg a day (2 divided doses of 850 mg tablets) + folic acid 0.4 mg: 1 tablet a day (N = 28) 3. Vitamin B complex (50 mg B6, 400 ug folic acid, 500 ug B12, 1 g trimethylglycine and 6 mg pyridoxal-5-phosphate): 1 tablet a day (N = 24) 4. Metformin 1700 mg a day (2 divided doses of 850 mg tablets) + vitamin B complex: 1 tablet a day (N = 27) Women were recruited over 14 months and outcomes were measured over 3 cycles All groups were given folic acid
Outcomes	Homocysteine levels Cumulative clinical pregnancy rate over 3 cycles Ongoing pregnancy rate
Notes	Israel Tel Aviv, study dates not reported Dr Morey Schachter ivfdoc@asaf.health.gov.il. Email sent 8th December 2015, no reply Laboratory costs were partially funded by a company producing vitamins and supplements
Risk of bias	

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

Schachter 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "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"
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes containing computer-generated random assignation numbers"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unknown
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available. No known selective reporting, ongoing pregnancy rate reported
Other bias	Low risk	No other bias found

Schillaci 2012

Study characteristics	
Methods	Random controlled trial
Participants	Poor responder patients were offered ICSI, due to the expected low oocyte retrieval and in the attempt to increase oocyte fertilization rate. Inclusion criteria: “Poor responder” women have been classified on the basis of their anamnestic history of poor response in previous stimulation cycles (< 3 follicles and oestradiol levels < 600 pg/ml at hCG day), age < 40; infertility duration ≥ 2 years; < 3 previous ART attempts with documented poor response; negative screening for recurrent pregnancy loss (chromosome mapping, ANA, ENA, APA, thrombophilic screening); no other sensitising or ovarian-stimulating therapy from at least 3 months (metformin, ovulation inductors). Included participants were examined by a basal US pelvic transvaginal examination at the recruitment day, within day 5 of a spontaneous cycle or a withdrawal bleeding after progestin administration (N = 12) Exclusion criteria: women with contraindications to ovulation inductors, such as ovarian cysts
Interventions	1. 2 g myo-inositol plus 200 µg folic acid twice a day. Mean age 36 ± 4.5 (N = 6) 2. 400 µg folic acid once a day. Mean age 34.2 ± 5.4 (N = 6) Treatment for from at least 1 month before GnRH-a administration
Outcomes	Number of cycles with response rFSH medium dose (IU) Medium duration of stimulation (days) Number of cycles with > 2 follicles > 16 mm hCG day Number of retrieved oocytes at pick-up Number of pregnancies (unknown definition) Number of abortions Number of cancelled cycles (no hCG) for absent response or < 2 follicles
Notes	Location: IVF Unit, Division of Obstetrics and Gynaecology, University of Palermo, Italy Timeframe: From 2010 January to 2010 September

Schillaci 2012 *(Continued)*

Trial registration number: Unknown
Informed consent: Unknown
Ethical approval: Unknown
Sample size power calculation: Unknown
Funding: Unknown
Conflict of interests: Unknown
ITT: No
Author email: D. Mangione, email not provided. I have tried to contact Professor Schillaci through Research Gate - asking if there was a further publication for these preliminary results, no reply as at 25 August 2020

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	Probably not blinded as treatment group is receiving 2 g myo-inositol plus 200 µg folic acid twice a day whereas the control group is receiving 400 µg folic acid once a day
Incomplete outcome data (attrition bias) All outcomes	High risk	Preliminary results only. Numbers given in the text (p 41) are different from numbers in the baseline characteristics table (p 42). There appears to be 2 dropouts from the intervention group, but reasons not provided
Selective reporting (reporting bias)	Unclear risk	Trial registration number not available
Other bias	Low risk	No other bias found

Sen Sharma 2017

Study characteristics

Methods	Random controlled trial
Participants	Women with PCOS attending Infertility clinic. Timed intercourse. Mean age unknown Inclusion criteria: infertile women with PCOS resistant to treatment with 100 mg CC for 5 days per cycle with persistent anovulation (N = 62) Exclusion criteria: Women with hyperprolactinaemia, thyroid dysfunction or abnormal semen parameters
Interventions	1. CoQ10 from day 1 of cycle (60 mg thrice daily) + CC 100 mg from day 2 to day 6 of cycle + FSH 75 IU intramuscularly on days 3, 5, 7 and 9 (N = 32) 2. CC 100 mg from day 2 to day 6 + FSH 75 IU intramuscularly on days 3, 5, 7 and 9 of cycle (no treatment) (N = 30)
Outcomes	Size of matured follicle Endometrial thickness

Sen Sharma 2017 *(Continued)*

	Clinical pregnancy Miscarriage rate
Notes	Conference abstract Location: Divisional Railway Hospital, Alipurduar Junction, West Bengal, India Timeframe: Unknown Trial registration number:Unknown Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: Unknown Conflict of interests: Unknown ITT: Unknown Author email: Unknown. Dr Debjani SenSharma, unable to find contact details after database, Google and facebook search

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unknown. Women with "persistent anovulation were randomized either to..."
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	The control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Trial registration number unavailable. Does report clinical pregnancy but not live birth
Other bias	Unclear risk	Conference abstract - baseline characteristics unclear

Siavashani 2018

Study characteristics

Methods	Randomised double-blinded, placebo-controlled trial
Participants	Infertile women with PCOS, aged 18 – 40 years undergoing IVF (N = 40) Inclusion criteria: Candidate for IVF without previous history of IVF Exclusion criteria: Women with metabolic abnormalities including thyroid dysfunction, diabetes or impaired glucose tolerance were excluded from the study
Interventions	1. 200 µg/day chromium picolinate (Nature Made, California, USA) Mean age 33.8 ± 1.9 (N = 20) 2. Placebo (Barij Essence, Kashan, Iran) Mean age 33.3 ± 2.7 (N = 20)

Siavashani 2018 *(Continued)*

	Treatment for 8 weeks
Outcomes	Serum high sensitivity C-reactive protein (hs-CRP) levels Metabolic profiles The following outcomes were reported in the Results section of the paper but not in Methods... Endometrial thickness Number of oocytes retrieved Number of oocytes fertilised Fertilisation rate Pregnancy rate Number of embryos
Notes	Location: Taleghani Hospital, Tehran, Iran Timeframe: Between February and May 2018 Trial registration number: IRCT20170513033941N Informed consent: Yes Ethical approval: approved by the research ethics committee of Shahid Beheshti Sample size power calculation: yes Funding: This study was supported by a grant from the Vice-chancellor for Research, Shahid Beheshti University of Medical Sciences, and Tehran, Iran Conflict of interests: Unknown ITT: no Author email: Shahrzad Zadeh Modarres email sharzad.modarres@sbmu.ac.ir, Zatollah Asemi email asemi_r@yahoo.com Emailed authors 30 January 2020 asking whether Siavashani 2016 is part of this trial. Author answered saying that these were different trials Siavashani 2016 is excluded due to wrong population i.e. women with PCOS not intending to become pregnant Pregnancy data have been added to Table 2 as unknown whether it is clinical or biochemical

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “This randomized, double-blinded, placebo-controlled trial” Quote: “Randomization was done using computer-generated random numbers.”
Allocation concealment (selection bias)	Low risk	Quote: "Randomization and allocation process were concealed from both the researchers and participants until the completion of final analyses. Another person, not involved in the trial and unaware of random sequences, assigned the subjects to the numbered bottles of tablets".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blinded, placebo-controlled trial” Quote: “Chromium supplements and placebos were matched in terms of shape, appearance, smell and packaging”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three dropouts were reported in each intervention group, due to personal reasons". Comment: So, overall 34 participants [infertile women with PCOS candidate for IVF receiving chromium (N = 17) and placebo (N = 17)] completed the study

Siavashani 2018 *(Continued)*

		(Figure 1). Using ITT approach, all 40 participants (20 in each group) were included in the final data analysis.
Selective reporting (reporting bias)	Low risk	Has a trial registration number and pregnancy is reported, although this is reported in the Results section (not in Methods); also no definitions of pregnancy, so uncertain whether biochemical or clinical
Other bias	Low risk	No other bias found

Taylor 2018

Study characteristics	
Methods	Pilot double-blind randomised controlled parallel trial
Participants	Inclusion criteria: Women of 'advanced maternal age', 36 - 42 years old, AMH ≤ 2.0 ng/mL, 1st cycle of IVF treatment, and an antral follicle count (AFC) between ≥ 6 and ≤ 19. Mean age unknown. (N = 21) Exclusion criteria: Unknown
Interventions	1. CoQ10 (125 mg/twice daily; Group 2) (N = 12) 2. Placebo (N = 9) Treatment for 3 months prior to IVF
Outcomes	The average number of eggs retrieved maturity, and fertilisation Number of euploid embryos
Notes	Conference abstract Location: Reproductive Endocrinology Associates of Charlotte, Charlotte, NC USA Timeframe: 2015 Trial registration number: NCT02119117 Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: Supported by: Ferring Pharmaceuticals and Theralogix Nutritional Science Conflict of interests: Unknown ITT: Unknown Author email: tyltaylor@gmail.com Email sent to author 30 January 2020 asking for RoB, timeframe, trial registration number and clinical outcomes. Author replied 04 February 2020 giving timeframe, RoB details, trial registration number and that there were no adverse events recorded. Author also replied 11 February 2020 saying that no clinical or live birth data available

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "closed envelopes"

Taylor 2018 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Patient, doctor, embryologist, and PGS lab were all blinded to which supplement the patient received"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number provided, but no live birth or pregnancy outcomes reported
Other bias	Low risk	Unknown other bias

Tunon 2017

Study characteristics	
Methods	Randomised control trial
Participants	Women attending an infertility clinic for ICSI (N = 120) Inclusion criteria: Women meeting the criteria for performing IVF-ICSI treatment, according to the daily clinical practice protocols. Age 18 - 41 years at the time of enrolment, BMI from 18 to 29 kg/m^2, and normal ovulatory cycle of 24 - 35 days Exclusion criteria: Azoospermia; presence of anatomic abnormalities of the reproductive system that could interfere with implantation or pregnancy; other medical conditions causing ovulatory disorders, such as hyperprolactinaemia, hypothyroidism, and adrenal hyperplasia; and hypersensitivity to human gonadotropin preparations or any of the medicines or food supplements used in the study
Interventions	1. Combination antioxidant; Seidivid group. The medication contained 2 g of myo-inositol, 0.975 mg of melatonin, 200 µg of folic acid, and 27.5 µg of selenium (Seidivid), daily oral intake of 2 sachets (breakfast and dinner, before or after meals). Mean age 34.88 ± 4.69 (N = 60) 2. Unknown control, assumed to be no treatment as no mention of placebo. Mean age 34.32 ± 5.85 (N = 60) Treatment for at least 2 months before the ovarian puncture
Outcomes	Number of metaphase II (MII) Number of follicles (≥16 mm on the day of the trigger shot) Number of embryos of good quality, and embryos for vitrification Biochemical and clinical pregnancy rate Miscarriage Live birth
Notes	Location: Human Reproduction Unit, Ginemed, Seville, Spain. 2. DIATROS Clínica de Atención a la Mujer, Barcelona, Spain Timeframe: Unknown Trial registration number: Unknown Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is supported by the funding provided by Laboratorio SEID S.A. Manufactors the product Seidivid

Tunon 2017 *(Continued)*

Conflict of interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article
ITT: Unknown
Author email: rschez.borrego@diatros.com

Emailed authors on 30 January 2020 asking whether the control received a placebo or no treatment. All RoB domains except attrition, Timeframe of trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the first visit, participants were randomized by the nursing staff at a 1:1 ratio into both treatment groups." Comment: Unknown methods
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "A double-blind, randomized, prospective study parallel" Comment: Not sure what the control is. Unclear of who was blinded and no mention of placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "9 patients from the control group and 10 from the Seidivid group were excluded due to noncompliance with the proposed protocol, providing a number of 51 in the control group and 50 in the Seidivid group"
Selective reporting (reporting bias)	Unclear risk	Trial registration number unable to be found. Live birth and clinical pregnancy reported
Other bias	Low risk	No other bias found

Valeri 2015

Study characteristics

Methods	Double-blind randomised controlled trial
Participants	Infertile women aged > 40 years undergoing IVF (N = 358)
Interventions	1. Melatonin 5 mg: 1 tablet a day (N = 178) 2. No treatment (N = 180) Trial ran from July 2009 to December 2013
Outcomes	Oocyte maturity Oxidative stress Antioxidative capacity Progesterone concentration in follicular fluid Embryo grade
Notes	Conducted in Italy, trial ran from July 2009 to Decenber 2013

Valeri 2015 *(Continued)*

	Trial funded by pharmaceutical company Trial registration no: NCT01540747 Email sent to Dr Pacchiarotti regarding the methods of this trial. Dr Pacchiarotti replied 20th March 2017 giving some methods information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number available however clinical pregnancy and live birth not reported
Other bias	Low risk	No other bias found

Westphal 2006

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Infertile women (N = 93). Mean age Treatment group: 35.4; Placebo group 34.8 Inclusion criteria: women aged 24 - 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 start of the trial.
Interventions	1. Fertility blend: capsules containing chaste berry, green tea amino acid, L-arginine, vitamins E, B6 and B12 and folate, iron, magnesium, zinc and selenium. 3 capsules a day for 3 menstrual cycles (N = 53) 2. Placebo (N = 40) Duration of treatment: 3 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

Westphal 2006 *(Continued)*

	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, study dates not reported
	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 when not all women received treatment or placebo in this phase.
	Tried to contact author 25th November 2009 with email, mail and fax, with no reply. Tried to contact author again regarding live birth, no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; mechanism not stated. Quote: "Fertilty 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 clear explanation. Authors contacted regarding this. Placebo control
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts
Selective reporting (reporting bias)	High risk	Trial registration number not available. 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
Other bias	Low risk	No other bias found

Xu 2018

Study characteristics

Methods	Randomised controlled trial

Xu 2018 *(Continued)*

Participants	Subfertile wome attending IVF clinic Inclusion criteria: Poor ovarian reserve and were referred to IVF-ET cycle in our institution were approached. POR was defined according to the ESHRE Bologna criteria. Age < 35 years, anti-Mullerian hormone (AMH) < 1.2 ng/ml, and antral follicle count (AFC) < 5, the parameters that corresponded to a low prognosis group 3 as per the POSEIDON stratification (N = 186) Exclusion criteria: Age ≥ 35 years, history of ovarian surgery, endocrine or autoimmune disease (e.g. diabetes, thyroid disease or presence of anti-thyroid antibodies or PCOS), chromosomal abnormality, uterine malformations, > 3 previous IVF cycles, treatment with cholesterol-lowering drugs, previous treatment with anti-oxidants (last 5 years) or known allergy to CoQ10 or ubiquinol (the water-soluble isoform of CoQ10).
Interventions	1. Oral administration of CoQ10 (GNC Holdings Inc., Pittsburg,PA, USA) 200 mg 3 times a day. The ART treatment (IVF or ICSI) was started in the first menstrual cycle upon completion of CoQ10 treatment. Mean age 32.50 ± 3.3 (N = 93). As analysed N = 76 (16 discontinued intervention and 1 changed decision to have ART) 2. No treatment. The control group began ART (IVF or ICSI) after enrolment without any additional treatment. Mean age 31.92 ± 3.68 (N = 93). As analysed N = 93 Treatment is for a period of 60 days in an open-label fashion
Outcomes	Number of high-quality day-3 embryos generated from 1 stimulation cycle Ovarian response parameters (duration of stimulation, total dose of gonadotrophins, peak E2 level and endometrial thickness on the day of hCG trigger) Embryological parameters (number of oocytes retrieved, fertilisation rate, number of participants with frozen embryos and number of participants who did not achieve embryo transfer) Clinical parameters; miscarriage, clinical pregnancy and live birth rate
Notes	Location: the Reproductive Medical Center of the Peking University Third Hospital, a tertiary university hospital and a centre of excellence in Reproductive Medicine in China Timeframe: The randomisation was performed over the period of 14 months (between 02 June 2015 and 31 July 31 2016) Trial registration number: ChiCTR-IPR-17010945 Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding: This study was supported by National key research and development project (2016YFC1000302) and the scientific research foundation for the returned overseas Ministry of Education (A70538–3). Conflict of interests: The authors declare that they have no competing interests ITT: no Author email: janez2012@sina.com; yushu57200@126.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using the computer generated randomization codes"
Allocation concealment (selection bias)	Low risk	Quote: "randomization codes, which were then placed in the sealed, opaque sequentially numbered envelopes by a third party (nurse practitioner) who was not directly involved in the patient management or in the randomization process".

Xu 2018 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The study participants and the investigators were not blinded to the patient grouping" Quote: "open label fashion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts accounted for, although 18% loss in treatment group and nil in the control
Selective reporting (reporting bias)	Low risk	The study has a trial registration number and reports live birth, clinical pregnancy and miscarriage
Other bias	Low risk	No other bias found

Youssef 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Infertile couples with unexplained infertility seeking ICSI/IVF treatment following at least 3 failed previous IUI cycles (N = 218). Mean age Treatment group: 30.9 years; Control group: 30.6 Inclusion criteria: women aged < 40 years with normal ovulatory cycles, normal baseline; FSH 12 IU/l, thyroid-stimulating hormone, prolactin levels, tubal patency at hysterosalpingography, normal transvaginal ultrasound scan, presence of both ovaries and normal findings at laparoscopy. All male partners had a normal semen analysis by WHO criteria Exclusion criteria: Couples who had received any form of vitamin supplementation for a period of 3 months before start of treatment
Interventions	Women in both groups received a daily dose of 2.5 mg of folic acid. 1. OCTATRON ® NERHADOU INTERNATIONAL (composition; vitamin A 3000 IU; d-alpha tocopheryl acid; (vitamin E) 15 IU; ascorbic acid (vitamin C) 90 mg; Zinc (amino acid-chelated) 11 mg; molybdenum (amino acid chelated) 45 µg; selenium (amino acid chelated) 55 µg, biotin 10 µg and mixed bioflavonoid 100 mg): 1 capsule a day (n= 112) 2. Folic acid 2.5 mg: 1 tablet a day (N = 106) Treatment was for 2½ months 7 women lost from each arm with explanation
Outcomes	The primary outcome was the number of mature oocytes Secondary outcomes were clinical pregnancy rate, defined as appearance of intrauterine gestational sac with fetal heart pulsation at 7 weeks Fertilisation rate Number of embryos transferred and cryopreserved Multiple pregnancy rate Early miscarriage rate Duration of stimulation Amount of FSH

Youssef 2015 *(Continued)*

Notes	Cairo Egypt Trial ran from February 2011 to March 2013 "On pregnancy confirmation, both groups received antioxidant and folic acid supplementation during the first trimester with follow-up in accordance with this canter 's policy. Participants ' compliance with treatment, that is, the intake of supplements was confirmed and recorded on each visit by the caring physicians". This paper is the published version of Aboulfoutouh 2011 in first version of the review Email and letter sent to authors 9th August 2012asking about types of antioxidants used and ITT in the pregnancy outcome. Authors replied with data information. Participants were followed up only to clinical pregnancy, so no live birth data are provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We developed computer generated list for randomization" Comment: from an email received 12th December 2015
Allocation concealment (selection bias)	Low risk	Quote: "used closed opaque envelops for concealment by third party nurse" Comment: from an email received 12th December 2015
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding; control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition explained
Selective reporting (reporting bias)	Low risk	Outcomes reported. Protocol available
Other bias	Low risk	No other bias found

Zadeh Modarres 2018

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Infertile women with PCOS attending an infertility clinic "candidates for IVF" (N = 40) Inclusion criteria: women aged 18 – 40 years with PCOS diagnosis according to the Rotterdam criteria who were IVF candidates Exclusion criteria: pregnant women and women with elevated levels of prolactin, thyroid disorder, and endocrine diseases
Interventions	1. 200-µg selenium per day as selenium. Mean age 31.1 ± 4.7 (N = 20) 2. Placebo Mean age 31.4 ± 3.6 (N = 20). Treatment for 8 weeks

Zadeh Modarres 2018 *(Continued)*

Outcomes	Gene expression of PPAR-γ Glucose transporter 1 (GLUT-1) Gene expression levels of low-density lipoprotein receptor (LDLR) Lipoprotein(a) [LP(a)]
Notes	Location: the Research and Clinical Center for Infertility and the Mahdieh Clinic, Tehran, Iran Timeframe: between April 2017 and July 2017 Trial registration number: IRCT201704245623N113 and?IRCT201701025623N100 (same population, contact names, years and intervention although has metabolic outcomes) or IRCT20170513033941N23 (same population, contact names, years and intervention although has gene expression outcomes outcomes) Informed consent: yes Ethical approval: yes Sample size power calculation: no Funding: This study was founded by a grant from the vice-chancellor for research, Shahid Beheshti, University of Medical Sciences, Tehran, Iran Conflict of interests: The authors declare that they have no conflict of interests ITT: yes Author email: asemi_r@yahoo.com. Emailed Dr Asemi 03 February 2020 asking for methods of allocation concealment. Author replied 03 February 2020 saying "The randomisation was conducted by a trained staff at a different location to the trial".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization assignment was conducted using computer-generated random numbers as blindness by a trained midwife at the clinic".
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was conducted by a trained staff at a different location to the trial"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded. Quote: "Selenium supplement and placebo (cellulose) tablets were identical in colour, shape, size, and packaging and were manufactured by Nature Made (California, USA) and Barij Essence (Kashan, Iran), respectively".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Trial registration number available, but clinical outcomes not reported and title of the trial says "candidates for IVF" so would expect clinical outcomes to be reported
Other bias	Low risk	No other bias found

17B-E2: 17B estradiol; ASRM: American Society for Reproductive Medicine; BMI: body mass index; CC: clomiphene citrate; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ESHRE: European Society of Human Reproduction and Embryology; FSH: follicle stimulating hormone; GnRH: gonadotropin releasing hormone; hCG: human chorionic gonadotropin; HSG: hysterosalpingography; ICSI: intracytoplasmic sperm injection; ITT: intention-to-treat; IVF: in vitro fertilisation; MDA: malondialdehyde; N: number; NAC: *N*-acetylcysteine; OC: oral contraceptive; OHSS: ovarian hyperstimulation syndrome; PCOS: polycystic ovary syndrome; PESA: percutaneous epididymal sperm aspiration; PUFA: poly-unsaturated fatty acid; rFSH: recombinant follicle stimulating hormone; SD: standard deviation; TESE: testicular sperm extraction; VEGF: vascular endothelial growth factor; WHO: World Health Organization

Taylor 2018

Study characteristics	
Methods	Pilot double-blind randomised controlled parallel trial
Participants	Inclusion criteria: Women of 'advanced maternal age', 36 - 42 years old, AMH ≤ 2.0 ng/mL, 1st cycle of IVF treatment, and an antral follicle count (AFC) between ≥ 6 and ≤ 19. Mean age unknown. (N = 21) Exclusion criteria: Unknown
Interventions	1. CoQ10 (125 mg/twice daily; Group 2) (N = 12) 2. Placebo (N = 9) Treatment for 3 months prior to IVF
Outcomes	The average number of eggs retrieved maturity, and fertilisation Number of euploid embryos
Notes	Conference abstract Location: Reproductive Endocrinology Associates of Charlotte, Charlotte, NC USA Timeframe: 2015 Trial registration number: NCT02119117 Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: Supported by: Ferring Pharmaceuticals and Theralogix Nutritional Science Conflict of interests: Unknown ITT: Unknown Author email: tyltaylor@gmail.com Email sent to author 30 January 2020 asking for RoB, timeframe, trial registration number and clinical outcomes. Author replied 04 February 2020 giving timeframe, RoB details, trial registration number and that there were no adverse events recorded. Author also replied 11 February 2020 saying that no clinical or live birth data available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "closed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “Patient, doctor, embryologist, and PGS lab were all blinded to which supplement the patient received”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number provided, but no live birth or pregnancy outcomes reported
Other bias	Low risk	Unknown other bias

Tunon 2017

Study characteristics	
Methods	Randomised control trial
Participants	Women attending an infertility clinic for ICSI (N = 120) Inclusion criteria: Women meeting the criteria for performing IVF-ICSI treatment, according to the daily clinical practice protocols. Age 18 - 41 years at the time of enrolment, BMI from 18 to 29 kg/m^2, and normal ovulatory cycle of 24 - 35 days Exclusion criteria: Azoospermia; presence of anatomic abnormalities of the reproductive system that could interfere with implantation or pregnancy; other medical conditions causing ovulatory disorders, such as hyperprolactinaemia, hypothyroidism, and adrenal hyperplasia; and hypersensitivity to human gonadotropin preparations or any of the medicines or food supplements used in the study
Interventions	1. Combination antioxidant; Seidivid group. The medication contained 2 g of myo-inositol, 0.975 mg of melatonin, 200 µg of folic acid, and 27.5 µg of selenium (Seidivid), daily oral intake of 2 sachets (breakfast and dinner, before or after meals). Mean age 34.88 ± 4.69 (N = 60) 2. Unknown control, assumed to be no treatment as no mention of placebo. Mean age 34.32 ± 5.85 (N = 60) Treatment for at least 2 months before the ovarian puncture
Outcomes	Number of metaphase II (MII) Number of follicles (≥16 mm on the day of the trigger shot) Number of embryos of good quality, and embryos for vitrification Biochemical and clinical pregnancy rate Miscarriage Live birth
Notes	Location: Human Reproduction Unit, Ginemed, Seville, Spain. 2. DIATROS Clínica de Atención a la Mujer, Barcelona, Spain Timeframe: Unknown Trial registration number: Unknown Informed consent: Unknown Ethical approval: Unknown Sample size power calculation: Unknown Funding: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is supported by the funding provided by Laboratorio SEID S.A. Manufactors the product Seidivid Conflict of interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article ITT: Unknown Author email: rschez.borrego@diatros.com Emailed authors on 30 January 2020 asking whether the control received a placebo or no treatment. All RoB domains except attrition, Timeframe of trial.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "At the first visit, participants were randomized by the nursing staff at a 1:1 ratio into both treatment groups." Comment: Unknown methods

Tunon 2017 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "A double-blind, randomized, prospective study parallel" Comment: Not sure what the control is. Unclear of who was blinded and no mention of placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "9 patients from the control group and 10 from the Seidivid group were excluded due to noncompliance with the proposed protocol, providing a number of 51 in the control group and 50 in the Seidivid group"
Selective reporting (reporting bias)	Unclear risk	Trial registration number unable to be found. Live birth and clinical pregnancy reported
Other bias	Low risk	No other bias found

Valeri 2015

Study characteristics	
Methods	Double-blind randomised controlled trial
Participants	Infertile women aged > 40 years undergoing IVF (N = 358)
Interventions	1. Melatonin 5 mg: 1 tablet a day (N = 178) 2. No treatment (N = 180) Trial ran from July 2009 to December 2013
Outcomes	Oocyte maturity Oxidative stress Antioxidative capacity Progesterone concentration in follicular fluid Embryo grade
Notes	Conducted in Italy, trial ran from July 2009 to Decenber 2013 Trial funded by pharmaceutical company Trial registration no: NCT01540747 Email sent to Dr Pacchiarotti regarding the methods of this trial. Dr Pacchiarotti replied 20th March 2017 giving some methods information

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated

Valeri 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unknown
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unknown
Selective reporting (reporting bias)	Unclear risk	Trial registration number available however clinical pregnancy and live birth not reported
Other bias	Low risk	No other bias found

Westphal 2006

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Infertile women (N = 93). Mean age Treatment group: 35.4; Placebo group 34.8 Inclusion criteria: women aged 24 - 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 start of the trial.
Interventions	1. Fertility blend: capsules containing chaste berry, green tea amino acid, L-arginine, vitamins E, B6 and B12 and folate, iron, magnesium, zinc and selenium. 3 capsules a day for 3 menstrual cycles (N = 53) 2. Placebo (N = 40) Duration of treatment: 3 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, study dates not reported Funding stated: David Sen Lin Foundation

Westphal 2006 *(Continued)*

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 when not all women received treatment or placebo in this phase.

Tried to contact author 25th November 2009 with email, mail and fax, with no reply. Tried to contact author again regarding live birth, no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; mechanism not stated. Quote: "Fertilty 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 clear explanation. Authors contacted regarding this. Placebo control
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or dropouts
Selective reporting (reporting bias)	High risk	Trial registration number not available. 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
Other bias	Low risk	No other bias found

Xu 2018

Study characteristics

Methods	Randomised controlled trial
Participants	Subfertile wome attending IVF clinic Inclusion criteria: Poor ovarian reserve and were referred to IVF-ET cycle in our institution were approached. POR was defined according to the ESHRE Bologna criteria. Age < 35 years, anti-Mullerian hormone (AMH) < 1.2 ng/ml, and antral follicle count (AFC) < 5, the parameters that corresponded to a low prognosis group 3 as per the POSEIDON stratification (N = 186) Exclusion criteria: Age ≥ 35 years, history of ovarian surgery, endocrine or autoimmune disease (e.g. diabetes, thyroid disease or presence of anti-thyroid antibodies or PCOS), chromosomal abnormality, uterine malformations, > 3 previous IVF cycles, treatment with cholesterol-lowering drugs, previous treatment with anti-oxidants (last 5 years) or known allergy to CoQ10 or ubiquinol (the water-soluble isoform of CoQ10).

Xu 2018 *(Continued)*

Interventions	1. Oral administration of CoQ10 (GNC Holdings Inc., Pittsburg,PA, USA) 200 mg 3 times a day. The ART treatment (IVF or ICSI) was started in the first menstrual cycle upon completion of CoQ10 treatment. Mean age 32.50 ± 3.3 (N = 93). As analysed N = 76 (16 discontinued intervention and 1 changed decision to have ART) 2. No treatment. The control group began ART (IVF or ICSI) after enrolment without any additional treatment. Mean age 31.92 ± 3.68 (N = 93). As analysed N = 93 Treatment is for a period of 60 days in an open-label fashion
Outcomes	Number of high-quality day-3 embryos generated from 1 stimulation cycle Ovarian response parameters (duration of stimulation, total dose of gonadotrophins, peak E2 level and endometrial thickness on the day of hCG trigger) Embryological parameters (number of oocytes retrieved, fertilisation rate, number of participants with frozen embryos and number of participants who did not achieve embryo transfer) Clinical parameters; miscarriage, clinical pregnancy and live birth rate
Notes	Location: the Reproductive Medical Center of the Peking University Third Hospital, a tertiary university hospital and a centre of excellence in Reproductive Medicine in China Timeframe: The randomisation was performed over the period of 14 months (between 02 June 2015 and 31 July 31 2016) Trial registration number: ChiCTR-IPR-17010945 Informed consent: yes Ethical approval: yes Sample size power calculation: yes Funding: This study was supported by National key research and development project (2016YFC1000302) and the scientific research foundation for the returned overseas Ministry of Education (A70538–3). Conflict of interests: The authors declare that they have no competing interests ITT: no Author email: janez2012@sina.com; yushu57200@126.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using the computer generated randomization codes"
Allocation concealment (selection bias)	Low risk	Quote: "randomization codes, which were then placed in the sealed, opaque sequentially numbered envelopes by a third party (nurse practitioner) who was not directly involved in the patient management or in the randomization process".
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: “The study participants and the investigators were not blinded to the patient grouping” Quote: “open label fashion”
Incomplete outcome data (attrition bias) All outcomes	Low risk	All dropouts accounted for, although 18% loss in treatment group and nil in the control
Selective reporting (reporting bias)	Low risk	The study has a trial registration number and reports live birth, clinical pregnancy and miscarriage
Other bias	Low risk	No other bias found

Youssef 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	Infertile couples with unexplained infertility seeking ICSI/IVF treatment following at least 3 failed previous IUI cycles (N = 218). Mean age Treatment group: 30.9 years; Control group: 30.6 Inclusion criteria: women aged < 40 years with normal ovulatory cycles, normal baseline; FSH 12 IU/l, thyroid-stimulating hormone, prolactin levels, tubal patency at hysterosalpingography, normal transvaginal ultrasound scan, presence of both ovaries and normal findings at laparoscopy. All male partners had a normal semen analysis by WHO criteria Exclusion criteria: Couples who had received any form of vitamin supplementation for a period of 3 months before start of treatment
Interventions	Women in both groups received a daily dose of 2.5 mg of folic acid. 1. OCTATRON ® NERHADOU INTERNATIONAL (composition; vitamin A 3000 IU; d-alpha tocopheryl acid; (vitamin E) 15 IU; ascorbic acid (vitamin C) 90 mg; Zinc (amino acid-chelated) 11 mg; molybdenum (amino acid chelated) 45 µg; selenium (amino acid chelated) 55 µg, biotin 10 µg and mixed bioflavonoid 100 mg): 1 capsule a day (n= 112) 2. Folic acid 2.5 mg: 1 tablet a day (N = 106) Treatment was for 2½ months 7 women lost from each arm with explanation
Outcomes	The primary outcome was the number of mature oocytes Secondary outcomes were clinical pregnancy rate, defined as appearance of intrauterine gestational sac with fetal heart pulsation at 7 weeks Fertilisation rate Number of embryos transferred and cryopreserved Multiple pregnancy rate Early miscarriage rate Duration of stimulation Amount of FSH
Notes	Cairo Egypt Trial ran from February 2011 to March 2013 "On pregnancy confirmation, both groups received antioxidant and folic acid supplementation during the first trimester with follow-up in accordance with this canter 's policy. Participants ' compliance with treatment, that is, the intake of supplements was confirmed and recorded on each visit by the caring physicians". This paper is the published version of Aboulfoutouh 2011 in first version of the review Email and letter sent to authors 9th August 2012asking about types of antioxidants used and ITT in the pregnancy outcome. Authors replied with data information. Participants were followed up only to clinical pregnancy, so no live birth data are provided
Risk of bias	

Youssef 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We developed computer generated list for randomization" Comment: from an email received 12th December 2015
Allocation concealment (selection bias)	Low risk	Quote: "used closed opaque envelops for concealment by third party nurse" Comment: from an email received 12th December 2015
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding; control is no treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition explained
Selective reporting (reporting bias)	Low risk	Outcomes reported. Protocol available
Other bias	Low risk	No other bias found

Zadeh Modarres 2018

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Infertile women with PCOS attending an infertility clinic "candidates for IVF" (N = 40) Inclusion criteria: women aged 18 – 40 years with PCOS diagnosis according to the Rotterdam criteria who were IVF candidates Exclusion criteria: pregnant women and women with elevated levels of prolactin, thyroid disorder, and endocrine diseases
Interventions	1. 200-µg selenium per day as selenium. Mean age 31.1 ± 4.7 (N = 20) 2. Placebo Mean age 31.4 ± 3.6 (N = 20). Treatment for 8 weeks
Outcomes	Gene expression of PPAR-γ Glucose transporter 1 (GLUT-1) Gene expression levels of low-density lipoprotein receptor (LDLR) Lipoprotein(a) [LP(a)]
Notes	Location: the Research and Clinical Center for Infertility and the Mahdieh Clinic, Tehran, Iran Timeframe: between April 2017 and July 2017 Trial registration number: IRCT201704245623N113 and?IRCT201701025623N100 (same population, contact names, years and intervention although has metabolic outcomes) or IRCT20170513033941N23 (same population, contact names, years and intervention although has gene expression outcomes outcomes) Informed consent: yes Ethical approval: yes Sample size power calculation: no

Zadeh Modarres 2018 *(Continued)*

Funding: This study was founded by a grant from the vice-chancellor for research, Shahid Beheshti, University of Medical Sciences, Tehran, Iran
Conflict of interests: The authors declare that they have no conflict of interests
ITT: yes
Author email: asemi_r@yahoo.com. Emailed Dr Asemi 03 February 2020 asking for methods of allocation concealment. Author replied 03 February 2020 saying "The randomisation was conducted by a trained staff at a different location to the trial".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization assignment was conducted using computer-generated random numbers as blindness by a trained midwife at the clinic".
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was conducted by a trained staff at a different location to the trial"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded. Quote: "Selenium supplement and placebo (cellulose) tablets were identical in colour, shape, size, and packaging and were manufactured by Nature Made (California, USA) and Barij Essence (Kashan, Iran), respectively".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Trial registration number available, but clinical outcomes not reported and title of the trial says "candidates for IVF" so would expect clinical outcomes to be reported
Other bias	Low risk	No other bias found

17B-E2: 17B estradiol; ASRM: American Society for Reproductive Medicine; BMI: body mass index; CC: clomiphene citrate; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ESHRE: European Society of Human Reproduction and Embryology; FSH: follicle stimulating hormone; GnRH: gonadotropin releasing hormone; hCG: human chorionic gonadotropin; HSG: hysterosalpingography; ICSI: intracytoplasmic sperm injection; ITT: intention-to-treat; IVF: in vitro fertilisation; MDA: malondialdehyde; N: number; NAC: *N*-acetylcysteine; OC: oral contraceptive; OHSS: ovarian hyperstimulation syndrome; PCOS: polycystic ovary syndrome; PESA: percutaneous epididymal sperm aspiration; PUFA: poly-unsaturated fatty acid; rFSH: recombinant follicle stimulating hormone; SD: standard deviation; TESE: testicular sperm extraction; VEGF: vascular endothelial growth factor; WHO: World Health Organization

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

Study	Reason for exclusion
Aflatoonian 2014	Population were vitamin D-deficient
Aksoy 2010	Not a randomised study
Al-Omari 2003	Non-randomised trial. "Forty-two infertile PCOS were divided into three groups".
Alborzi 2007	The intervention pentoxifylline is a prescription drug rather than an antioxidant supplement
Aleyasin 2009	The intervention pentoxifylline is a prescription drug rather than an antioxidant supplement

Study	Reason for exclusion
Ardabili 2012	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Asadi 2014	Vitamin D not given orally but by injection into the muscle
Baillargeon 2004	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Balasch 1997	The intervention pentoxifylline is a prescription drug rather than an antioxidant supplement
Benelli 2016	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Bonakdaran 2012	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Cheang 2008	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Ciotta 2012	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Costantino 2009	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Creus 2008	The intervention pentoxifylline is a prescription drug rather than an antioxidant supplement
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."
Dastorani 2018	Ineligible population. Women enrolled were vitamin D-deficient
Elgindy 2010	Participants were fertile women with infertile male partners.
Elnashar 2007	Interventions *N*-acetyl-cysteine versus metformin
Farzadi 2006	The intervention versus control used in this trial was metformin versus placebo
Fatemi 2017	Ineligible population. 87% of women in the study were vitamin D-deficient
Firouzabadi 2012	83% of the women enrolled were vitamin D-deficient
Genazzani 2008	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore inappropriate for inclusion in this review
Hashim 2010	Interventions *N*-acetylcysteine plus clomiphene citrate versus metformin plus clomiphene citrate
Hebisha 2016	Enrolled women who attended infertility clinic due to male factor issues
Henmi 2003	Described as randomised, but authors confirmed the process of allocation as "alternative treatments". Additionally, 28/46 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
Hernández-Yero 2012	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review

Study	Reason for exclusion
Immediata 2014	Ineligible comparison; Inositol vs metformin
Iuorno 2002	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Jamilian 2016a	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review.
Jamilian 2016b	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore 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
Kermack 2017	Unsuitable comparator i.e. antioxidant drink + olive oil versus antioxidant drink + sunflower oil
Kilicdag 2005	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Le Donne 2012	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Li 2013	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Mokhtari 2016a	Ineligible population. Endometrial tissue samples were taken in a biopsy to measure gene expression, this trial never intended to measure clinical outcomes
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 November 2011
Nestler 1999	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Nestler 2001	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore 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. The population is therefore not suitable for inclusion in this review
Oner 2011	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Pal 2016	A secondary analysis of an RCT measuring ovulation induction (OI) outcomes in women with polycystic ovary syndrome (PCOS).
Papaleo 2007	Not a randomised controlled trial
Papaleo 2008	Interventions myo-inositol plus folic acid versus clomiphene citrate
Pasha 2011	Inappropriate population

Study	Reason for exclusion
Pizzo 2014	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review
Raffone 2010	Interventions myo-inositol plus folic acid versus metformin
Ruder 2014	A secondary analysis of an RCT on the cost effectiveness of fast track to IVF
Salem 2012	Different doses of clomiphene in each arm, i.e. L-carnitine 3 gm plus clomiphene 100 mg (n = 85) versus clomiphene 150 mg (n = 85)
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
Taheri 2015	Population is Vitamin D-deficient
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 January 2012. Letter returned to sender 17 February 2012
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. The population is therefore not suitable for inclusion in this review
Yoon 2010	This trial included women with PCOS, but they were not intending to become pregnant. The population is therefore not suitable for inclusion in this review

PCOS: polycystic ovary syndrome; RCT: randomised controlled trial

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

ChiCTR-IPR-15006369

Study name	The improvement of endometrial receptivity in PCOS patients by Vitamin D3: a prospective randomised controlled clinical trial
Methods	Randomised parallel controlled trial
Participants	Inclusion criteria: • Vitamin deficiency (< 20 ng/mL); • Anovulatory patients with PCOS; • All patients were excluded from other endocrine disorders, and has not used hormone drugs for almost 3 months; Age: 25 - 39 Exclusion criteria: • Malformation of uterus: such as uterus unicornis, uterus bicornis, untreated uterus septus, etc • History of endometrial diseases: such as intrauterine adhesion, uterine cavity tuberculosis, severe dysplasia of endometrium, etc. • Multiple myomata or endometrioma which causes uterus oppression • Multiple and recurrent endometrial polyps • Pelvic tuberculosis, endometriosis

ChiCTR-IPR-15006369 *(Continued)*

	Age minimum: 25; maximum: 39
Interventions	Obesity placebo for 3 months; Vitamin D3: Vitamin D3 for 3 months; Non-obesity-placebo: Placebo for 3 months; Non-obesity-vitamin D3: Vitamin D3 for 3 months;
Outcomes	Primary outcome(s): Clinical pregnancy rate Secondary Outcome(s): Embryo implantation rate; live birth rate; miscarriage rate; preterm birth rate
Starting date	01 January 2016
Contact information	Liang Wu Address: Center for Reproductive Medicine, First Affilited Hospital of Zhengzhou Univercity, 1 Jian-she load, Zhengzhou, Henan, China Telephone: +86 13203813873 Email: rbny@163.com Affiliation: Center for Reproductive Medicine, First Affilited Hospital of Zhengzhou University
Notes	Recruitment status: pending

ChiCTR1800019772

Study name	Effect of omega-3 fatty acids on oocyte quality and early embryo development in elderly infertile women
Methods	Randomised parallel controlled trial
Participants	Inclusion criteria: • Aged 35 - 42 years • Undergo cycle of IVF or ICSI • Short-term ovulation induction • Omega-3 fatty acid were not taken in the past 3 months Exclusion criteria: • Ovarian cyst resection after one-sided ovariectomy in the past • Uterine malformations, such as unilateral uterus, mediastinal uterus, double uterus, double-horned uterus, etc • Abnormal karyotypes (including polymorphism) of the chromosomes of the husband or herself • Suffering from diseases that are not suitable for assisted reproductive technology or for current pregnancy
Interventions	DHA group: DHA treatment for 6 - 8 weeks; ALA group: ALA treatment for 6 - 8 weeks; Placebo group: Placebo treatment for 6 - 8 weeks
Outcomes	Primary outcome(s): DHA and ALA level in serum; DHA and ALA level in follicular fluid; oocyte maturation rate; high-quality embryo rate Secondary outcome(s):

ChiCTR1800019772 *(Continued)*

	Height; weight; waistline; hipline
Starting date	-1 December 2018
Contact information	Ling Geng Address: 157 Jingliu Road, Jinan, Shandong, China Telephone:+86 0531-85651391 Email:gengling@sduivf.com Affiliation: Center for Reproductive Medicine Affiliated to Shandong University Tiantian Zhang Address: 157 Jingliu Road, Jinan, Shandong, China Telephone: +86 17862963456 Email: zhangtiantian@sduivf.com Affiliation: Center for Reproductive Medicine Affiliated to Shandong University
Notes	Recruitment status: recruiting

CTRI/2012/08/002943

Study name	Nutritional supplement for women with polycystic ovary syndrome or subfertility
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: Women between 18 and 38 years of age with PCOS Presence of any 2 of the following parameters: (Rotterdam criteria 2003) • Oligomenorrhoea and/or anovulation • Hyperandrogenism (clinical and/or biochemical) (Ferriman-Gallwey score > 8); biological (luteinising hormone (LH)/FSH ratio > 2) OR • Subfertile women • Sexually active and male partner with potential to produce a child • Polycystic ovaries with exclusion of other aetiologies • Women with normal uterine cavity • Participants with impaired glucose tolerance or insulin resistance • 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
Interventions	Intervention 1: multiple micronutrients supplementation: 1 Formula A tablet + 1 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: 1 tablet after main meal twice a day for 4 months

CTRI/2012/08/002943 *(Continued)*	
	Control intervention 2: placebo tablets for Formula B: 1 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 August 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	Open to recruitment

EUCTR2015-004233-27-IT	
Study name	Vitamin D supplementation on Assisted Reproduction Technology (ART) outcomes: a randomised clinical controlled trial and an investigation of the involved biological mechanisms
Methods	Randomised: single-blind: parallel group: placebo
Participants	Inclusion criteria: • Women with indication for IVF • Age 18 - 39 years • Fewer than 3 previous IVF cycles • BMI 18 - 25 Are the trial participants under 18? no: Number of participants for this age range: 1 F.1.2 Adults (18 - 64 years) yes; F.1.2.1 Number of participants for this age range: 630 F.1.3 Elderly (65+ years): no; F.1.3.1 Number of subjects for this age range Exclusion criteria: • Reduced ovarian reserve (AMH < 0.5 ug/l) • Frozen/thawing cycles • Surgical origin of spermatozoa

EUCTR2015-004233-27-IT *(Continued)*

	• Chronic diseases
Interventions	VITAMIN D3 Placebo
Outcomes	Primary outcome(s): Main objective: the study aims at determining the potential benefits of vitamin D supplementation in improving clinical pregnancy rate in women undergoing ART Primary end point(s): clinical pregnancy rate per oocyte retrieval after the first embryo transfer Secondary objective: to investigate whether vitamin D supplementation might improve clinical and embryological parameters such as: number of cancelled cycles, number of available oocytes, number of good-quality embryos, units of FSH administered per retrieved oocyte, implantation rate of transferred embryos. To investigate the effect of vitamin D supplementation on oocyte and endometrium quality at a molecular level through a comparative analysis between treated and untreated participants based on the analysis af cumulus cells, follicular and endometrial fluids Timepoint(s) of evaluation of this end point: 10 weeks after embryo transfer Secondary outcome(s): Secondary end point(s): delivery rate and obstetric outcome Timepoint(s) of evaluation of this end point: 1 year after embryo transfer
Starting date	23 June 2016
Contact information	U.O.S.D. CENTRO P.M.A. Address: VIA FANTI, N. 6 20122 MILANO Italy Telephone: 0255036582 Email: centrosterilita@policlinico.mi.it Affiliation: FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO
Notes	Authorised-recruitment may be ongoing or finished

IRCT201009131760N9

Study name	Assessment the effect of Ca-Vitamin D and metformin on PCOS
Methods	Randomised, single-blinded

Participants	Inclusion criteria:
	
	• Reproductive age range 18 to 35 years
	• According to the Rotterdam criteria, the presence of 2 of the 3 following characteristics were required for inclusion in the study:
	  * Oligomenorrhea/amenorrhoea;
	  * Chemical or clinical findings of hyperandrogenism;
	  * Polycystic ovaries on transvaginal sonography.
	
	Exclusion criteria:
	Women with systemic diseases such as Cushing's syndrome, hyperparathyroidism or hyperprolactinaemia, androgen secreting tumours, history of abdominal/pelvic surgery, co-existing male-factor infertility, or abnormal hysterosalpingography

Interventions	• Metformin mg/d 1500 for 3 months • Calcium (1000 m) + Vitamin D 400 IU for 3 months • Calcium (1000 m) + Vitamin D 400 IU + metformin mg/d 1500 for three3months
Outcomes	Primary outcomes:

IRCT201009131760N9 *(Continued)*

	Calcium and vitamin D. Timepoint: After 3 months. Method of measurement: Laboratory Follicular growth. Timepoint: After 3 months. Method of measurement: Ultrasound Regulate menstruation. Timepoint: After 3 months. Method of measurement: 35 - 21 day intervals with standard Secondary outcome(s): Pregnancy rate. Timepoint: After 3 months. Method of measurement: Ultrasound
Starting date	23 September 2010
Contact information	Nargess Gholizadeh Pasha Address: Fatemehzahra Fertility & Reproductive Health Research Center - Noshirvani street 4719173716 Babol Iran (Islamic Republic of) Telephone: +98 11 1227 4881 Email: ngh_pa@yahoo.com Affiliation: Fatemehzahra Fertility & Reproductive Health Research Center Seddigheh Esmaeilzadeh Address: Fatemehzahra Fertility & Reproductive Health Research, Noshirvani street 4719173716 Babol Iran (Islamic Republic of) Telephone: +98 11 1227 4881 Email: Sesmael@yahoo.com Affiliation: Fatemehzahra Fertility & Reproductive Health Research Center
Notes	Recruitment status: complete

IRCT201112148408N1

Study name	Evaluation of the effects of calcium-vitamin D supplement on ovulation and fertility outcomes of patients with polycystic ovary syndrome referring to Infertility Clinic of Imam Khomeini Hospital in 2011 and 2012 for in vitro fertilisation
Methods	Randomisation: randomised. Blinding: double-blind. Placebo: used
Participants	Abnormal menstrual cycles (oligomenorrhoea or amenorrhoea); sonographically-confirmed poly-cystic ovary; hyperandrogenism
Interventions	Intervention 1: Control group participants do not receive routine administration of calcium-D combinations Intervention 2: Intervention group, supplementary tablets of 1000 mg calcium combined with 400 IU vitamin D are administered (orally) twice a day for 3 months
Outcomes	Pregnancy. Timepoint: 2 and 12 weeks. Method of measurement: sonography and biochemistry
Starting date	21 January 2012
Contact information	Azadeh Mahdian Department of Obstetrics and Gynecology, Vali-e- Asr Hospital, Imam Khomeini Hospital Complex, Keshavarz Blv Tehran, Iran mahdian@razi.tums.ac.ir
Notes	

IRCT201207156420N11

Study name	Treatment of vitamin D deficiency in assisted reproductive cycles
Methods	Randomised
Participants	Inclusion criteria: • Women who want to transfer cryopreserved embryos Exclusion criteria: • > 40 years old • < 20 years old • History of endocrine disorder • Severe endometriosis • Systemic disease; • Repeated implantation failure • Repeated abortion • Congenital or acquired uterine anomaly with or without operation • Donation-recepient cycles
Interventions	50,000 units vitamin D orally every week for 8 - 10 weeks before starting embryo transfer cycle versus no treatment
Outcomes	Primary outcome(s): Chemical pregnancy. Timepoint: 14 days after embryo transfer. Method of measurement: Serum B-hcg Secondary outcome(s); Clinical pregnancy. Timepoint: 28 days after embryo transfer. Method of measurement: vaginal sonography
Starting date	25 September 2013
Contact information	Abbas Aflatoonian Address: Bouali Avenue, Safayeh Yazd Iran (Islamic Republic of) Telephone: +98 35 1824 7085 Email: Abbas_aflatoonian@yahoo.com Affiliation: Yazd research center for infertility Maryam Eftekhar Address: Bouali Avenue, Safayeh Yazd Iran (Islamic Republic of) Telephone: +98 35 1824 7085 Email: eftekhar@ssu.ac.ir Affiliation: Yazd Research and Clinical Center for Infertility
Notes	Complete en.irct.ir/trial/6868

IRCT2012120311430N2

Study name	The efficacy of vitD3 in patients with ART (Assisted Reproductive Technique) failure
Methods	Randomised, double-blinded

IRCT2012120311430N2 *(Continued)*

Participants	Inclusion criteria: • Infertile women 20 - 35 years old with 2 or more previous IVF failure, without using vitamin D and Calcium from 3 months before Exclusion criteria: • Untreated medical disorders • Endometriosis • Poor responders • Hydrosalpinx in ultrasonography • Abnormal semen analysis (abnormal form > 96%, A+B = 32%) • Use of drugs that affect immune system • Thrombophilia (homozygote PAI-I, homozygote C677T, homozygote A1908C, heterozygote A1908C-C977T) • Hormonal disorder (FSH > 12, PCO) • Anatomical disorders • Genetic disorders • Infective disorders
Interventions	Control Group: Tablet of Ca twice a day Intervention 1: Tablet Ca-vitamin D twice a day
Outcomes	Abortion rate. Timepoint: every 2 months. Method of measurement: ßhCG and ultrasonography Pregnancy rate. Timepoint: 14 days after embryo transfer. Method of measurement: ßhCG,14 days after embryo transfer
Starting date	21 April 2013
Contact information	Dr Zafardoost Simin Address: Shariati-Yakhchal 194191133194 Tehran Iran (Islamic Republic of) Telephone: +98 21 2264 4701 Email: siminzafardoost@yahoo.com; s.zafardoost@avicenna.ac.ir Affiliation: Infertility and recurrent pregnancy loss center
Notes	Complete en.irct.ir/trial/11701

IRCT201306115942N2

Study name	Effects of antioxidative treatments on pregnancy results
Methods	Randomised, unblinded, no placebo, parallel assignment
Participants	Inclusion criteria: Normal hormonal analysis; infertile women candidates for IUI method; age at least 25 years old and < 40years old; BMI minimum 19 kg/m^2 and < 30 kg/m^2; at least 1 open fallopian tube in hysterosalpingography; the absence of cervicitis or clinical cervical lesion; SDF (Sperm DNA Fragmentation) < 30%; the absence of infection in accessory glands; lack of drug addiction and smoking; the absence of varicocoele Exclusion criteria:

IRCT201306115942N2 *(Continued)*

	Irregular menstruation; galactorrhoea; abnormal hysterosalpingography; obstruction in fallopian; adhesion of fallopian; past medical peritoneal surgery; infection in accessory glands Age minimum: 25 years; maximum: 40 years
Interventions	Intervention 1: Vitamin C orally administered daily with 1000 mg dosage for 2 months Intervention 2: Control group without any treatment Intervention 3: Zinc supplement orally administered daily with 30 mg dosage for 2 months Intervention 4: Vitamin E orally administered daily with 400 mg dosage for 2 months Intervention 5: W3 supplement orally administered daily with1000 mg dosage for 2 months
Outcomes	Primary outcome(s): Sperm DNA fragmentation. Timepoint: Before interposition, 2 months after interposition. Method of measurement: Observation with optic microscope Secondary outcome(s): Pregnancy outcomes. Timepoint: 2 weeks after IUI. Method of measurement: Pregnancy occurrence after positive blood HCG assay
Starting date	10 June 2013
Contact information	Aliye Ghasemzadeh Address: Al-Zahra Hospital, Bagshomal Crossroad, Southern Artesh St., Tabriz Tabriz Iran (Islamic Republic of) Telephone: +98 914 340 7313 Email: gasemzadeha@tbzmed.ac.ir Affiliation: Tabriz University of Medical Sciences Aliye Ghasemzadeh Address: Al-Zahra Hospital, Bagshomal Crossroad, Southern Artesh St., Tabriz Tabriz Iran (Islamic Republic of) Telephone: +98 914 340 7313 Email: gasemzadeha@tbzmed.ac.ir Affiliation: Tabriz University of Medical Sciences
Notes	Complete

IRCT20150831023831N2

Study name	Effect of N-acetyl cysteine on expression of oxidation-reduction genes during implantation window in women with recurrent implantation failure
Methods	Randomised, double-blinded, placebo-controlled, parallel assignment Purpose: Health service research Randomisation description: permuted block randomisation Blinding description: participant and assessor are blinded
Participants	Inclusion criteria: • Age between 20 and 40 years • At least twice implantation failure • BMI in the normal range • Participants prescribed drugs such as folic acid, iron, multivitamins, and supplements generally equal status Exclusion criteria:

IRCT20150831023831N2 *(Continued)*

	• Irregular menstrual cycle • Taking hormonal drugs except thyroid medication • Women with abnormal karyotype or chromosomal disorders • Women who have coagulation problems Age minimum: 20 years; maximum: 40 years Gender: Female
Interventions	Intervention group: administer 1200 mg of effervescent tablets of N-acetyl cysteine (NAC) daily for about 6 weeks Control group: administer 1200 mg of effervescent tablets of placebo daily for about 6 weeks
Outcomes	Primary outcome(s): Gene expression related to implantation. Timepoint: 9 weeks after intervention. Method of measurement: Real-time PCR Secondary outcome(s): Clinical pregnancy. Timepoint: 2 weeks after embryo transfer. Method of measurement: Measurement of quantitative serum ß-hCG
Starting date	22 May 2015
Contact information	Dr.Parvaneh Afsharian Address: Eastern Hafez street, Bani Hashem square, Resalat Highway 16635148 Tehran Iran (Islamic Republic of) Telephone: +98 21 2356 2674 Email: pafshar@royaninstitute.org Affiliation: Royan Institute
Notes	Complete

IRCT201510266917N3

Study name	Effect of thiamine tablet (B1) on general health and treatment success in infertile women with polycystic ovary syndrome
Methods	Randomised, triple-blinded, placebo-controlled, parallel assignment Purpose: Treatment Other design features: randomised study using blocking
Participants	Inclusion criteria: • Women with PCOS according to Rotterdam criteria • age 18 - 40 years • Agree to take part in the study • Do not use alcohol • Do not use psychological drugs • Non-addict or a history of addiction; • No underlying illnesses • Did not use B1 in the last month • Did not use complementary drug in the last month • at least 3-period treatment for infertility Exclusion criteria:

IRCT2015102669l7N3 *(Continued)*

	• Does not agree to continue in the study • Allergic symptoms • Incorrect drug usage • Discontinued treatment of infertility Gender: Female
Interventions	Intervention group 1: 300 mg vitamin B1 tablets (product HAKIM Pharmaceutical Company) once in the morning for a period of 4 weeks Intervention 2: Control group: Placebo tablets 300 mg (product HAKIM Pharmaceutical Company)
Outcomes	Primary outcome(s): General health. Timepoint: before and after intervention. Method of measurement: standard questionnaire Successful treatment. Timepoint: before and after intervention. Method of measurement: positive pregnancy test Secondary outcome(s): B-HCG. Timepoint: Before and after of experiment. Method of measurement: hormone assay
Starting date	22 December 2015
Contact information	Leila Amini Address: Valiasr street Tehran Iran (Islamic Republic of) Telephone: +98 21 8820 8159 Email: l-amini@tums.ac.ir Affiliation: Iran Nursing and Midwifery School Mahtab moti Address: Valiasr street Tehran Iran (Islamic Republic of) Telephone: +98 21 8820 8159 Email: mahtab_moti@gmail.com Affiliation: Iran Nursing and Midwifry School
Notes	Complete

IRCT20160228216l3N5

Study name	Assessing the effect of adding vitamin D and vitamin E to metformin with dydrogesterone regimen in the treatment of infertile women with polycystic ovary syndrome
Methods	Randomised controlled trial
Participants	Inclusion criteria: • Infertile women with polycystic ovary syndrome (PCOS) ; which had no pregnancy history after 12 months of unprotected intercourse Exclusion criteria: • Women with other causes of infertility such as endometriosis • Internal and surgical diseases • Women who do not have polycystic ovary syndrome (PCOS) criteria
Interventions	Intervention group 1: Metformin plus dydrogesterone plus vitamin E Intervention group 2: Metformin plus dydrogesterone plus vitamin D

IRCT20160228216533N5 (Continued)	
	Control group: Metformin plus dydrogesterone
Outcomes	Endometrial thickness. Timepoint: Before intervention and 3 months after intervention. Method of measurement: sonography Follicle size. Timepoint: Before intervention and 3 months after intervention. Method of measurement: sonography Menstural discipline. Timepoint: Before intervention and 3 months after intervention. Method of measurement: sonography. Pregnancy. Timepoint: Before intervention and 3 months after intervention. Method of measurement: BHCG Weight. Timepoint: Before intervention and 3 months after intervention. Method of measurement: Scale
Starting date	21 June 2016
Contact information	Fatemeh Kargarfard Address: Alley 5. Fard asadi avenue 7416653134 Jahrom Iran (Islamic Republic of) Telephone: +7 1330990 Email: fatemehkargarfard@yahoo.com Affiliation: Jahrom University of Medical Sience Dr Kavous Solhjo Address: Jahrom University of Medical Sience, Motahari Boulevard Jahrom Iran (Islamic Republic of) Telephone:+98 71 5444 0821 Email: sohjo@jums.ac.ir Affiliation: Jahrom University of Medical Sience
Notes	Complete

IRCT20160410027311N6	
Study name	The effect of selenium and vit E supplementation on oogenesis improvement in infertile women with occult premature ovarian insufficiency: a randomised controlled clinical trial
Methods	Randomised, triple-blinded, placebo-controlled, parallel-assignment Purpose: Treatment Randomisation description: Participants will be randomly assigned 1 to 1 using the 4 and 6 block method right before the intervention begins Blinding description: Blinding the allocation by a non-trafficker is done in the sampling; the received intervention (drug or placebo) is placed in the numbered blank opaque glasses, thus identifying the placement of the individuals. Glasses will be numbered from 1 to 70. The first person will be given the number-one glass, and this will continue until the end of the sampling
Participants	Inclusion criteria: • Providing informed written consent • Women aged 20 to 40 years • Menstrual cycle • Having both ovaries • No evidence of endocrine disorders (diabetes, thyroid disorders, Addison's disease, etc.) by asking the woman and checking out the results of previous tests • Occult POI (hormone AMH < 1 ng/ml, reduced ovarian reserve, < 5 antral follicles, reduced ovarian volume to < 2.5 cubic centimeters, or all 3 cases)

IRCT20160410027311N6 *(Continued)*

	• BMI < 30, the weight and height in this study will be measured by the researcher and the BMI will be calculated according to the formula BMI = WEIGHT (kg)/HEIGHT (m^2) Exclusion criteria: • Drug addiction and smoking • Tendency to use donated eggs • Evidence of OVERT POI (FSH > 15 or amenorrhoea for > 3 months) • Supplementation of selenium and vitamin E 3 months before the onset of intervention • History of radiotherapy and chemotherapy • Use of anticoagulants (co-administration of vitamin E with these drugs increases the risk of bleeding) Age minimum: 20 years; maximum: 40 years Gender: Female
Interventions	The intervention group will receive 1 tablet of selenium 200 micrograms daily and 1 vitamin E 400 units per day for 90 days Control group: Placebo of selenium and vitamin E for 90 days
Outcomes	Primary outcome(s): Concentration of anti-mullerian hormone (AMH). Timepoint: Before the intervention begins and 12 months after the intervention. Method of measurement: Blood sampling from the brachial vein on the day of referral and tested with ELISA kit Number of ovarian antral follicles. Timepoint: Before the intervention begins and 12 months after the intervention. Method of measurement: Transvaginal ultrasonography of the ovary on the 3rd day of the menstrual cycle, performed by a radiologist Secondary outcome(s) Ovarian volume. Timepoint: Before the intervention begins and 12 months after the intervention. Method of measurement: Ovarian volume with the same ultrasound on the 3rd day of menstruation using the following formula: ovarian volume = length × height × width × p/6, calculated for each ovary separately The incidence of side effects of selenium and vitamin E and their placebo. Timepoint: After the end of the intervention. Method of measurement: Checklist given during supplements or placebo Secondary ID(s)
Starting date	04 May 2018
Contact information	Behnaz Sadeghzadeh Oskouei Address: Faculty of Nursing & Midwifery, South Shariati Street 5138947977 Tabriz Iran (Islamic Republic of) Telephone: +98 41 3479 0364 Email: sadeghzadehb@tbzmed.ac.ir Affiliation: Tabriz University of Medical Sciences Safiyeh Farhadi Dizaji Address: Midwifery Department, Nursing and Midwifery Faculty, South Shariati Street,Tabriz, Iran 5138947977 Tabriz Iran (Islamic Republic of) Telephone: +98 41 3479 6770 Email: s63farhad i@gmail.com Affiliation: Tabriz University of Medical Sciences
Notes	Recruiting

ISRCTN23488518

Study name	A randomised controlled trial to compare conception rates for preconceptional folic acid 400 mg daily versus Pregnacare Plus in assisted conception
Methods	Randomised controlled trial
Participants	Inclusion criteria: • Sub-fertile women scheduled for IVF or IUI • Aged < 35 years • Infertility lasting for > 6 months Exclusion criteria: • Aged > 35 years • General medical conditions that make a woman unsuitable for assisted conception (e.g. morbid obesity) • Women whose understanding of English is insufficient to consent to participate
Interventions	Folic acid (400 mcg) versus Pregnacare Plus (contains folic acid 400 mcg and 17 other micronutrients) given for 10 weeks prior to assisted conception and follow-up to 20 weeks in those that become pregnant. Participants will also be monitored for nutritional status
Outcomes	Primary outcome(s) Survival of assisted conception pregnancy to 20 weeks, or failure to conceive and failure of pregnancy to survive to 20 weeks Secondary outcome(s) Length of pregnancy Birth weight (expressed as percentile birth weight in relation to length of pregnancy) Abdominal circumference Head circumference
Starting date	01 November 2007
Contact information	John Nichols Address: 60 Manor Way Onslow Village GU2 7RR Guildford United Kingdom Telephone: +44 (0)1483 564967 Email: drjaan@ntlworld.com
Notes	Complete

JPRN-UMIN000016992

Study name	Double-blinded randomised controlled trial to evaluate the effect of dietary supplements, Propolis, royal jelly and resveratrol for infertility treatment of aging women
Methods	Parallel randomised
Participants	Inclusion criteria: • Infertile women undergoing IVF-ET treatment • > 38 years of age and < 48 years of age when we receive written informed consent • Outpatients in our hospital • Women giving written informed consent after explanation of this clinical study Exclusion criteria:

JPRN-UMIN000016992 *(Continued)*

	• Women with ingestion of other dietary supplements within 1 menstrual cycle prior to the initiation of study • Women deemed unsuitable for this study by physicians Age minimum: 38 years; maximum: 48 years Gender: Female
Interventions	Duration of ingestion: 6 months 1. Propolis or placebo: 2 tablets after every meal, 3 times a day Combined therapy: 1 FSH/hMG injection (150 - 300 IU) a day until maturation of follicles, 1 hCG injection (5000 - 10,000 IU) a day when follicles mature Perform several IVFs during 6 months including at the end of 6 months ingestion Perform blood test, follicular fluid test, and cytological analyses in ovarian cells at the time of oocyte retrieval Duration of ingestion: 6 months 2. Royal jelly or placebo: 2 tablets after every meal, 3 times a day Combined therapy: 1 FSH/hMG injection (150 - 300 IU) a day until maturation of follicles, 1 hCG injection (5000 - 10,000 IU) a day when follicles mature Perform several IVFs during 6 months including at the end of 6 months ingestion Perform blood test, follicular fluid test, and cytological analyses in ovarian cells at the time of oocyte retrieval Duration of ingestion: 6 months 3. Resveratrol or placebo: 1 tablet after morning meal, once a day Combined therapy: 1 FSH/hMG injection (150 - 300 IU) a day until maturation of follicles, 1 hCG injection (5000 - 10,000 IU) a day when follicles mature Perform several IVFs during 6 months including at the end of 6 months ingestion Perform blood test, follicular fluid test, and cytological analyses in ovarian cells at the time of oocyte retrieval
Outcomes	Primary outcome(s) Using Veeck criteria for the classification of embryos with their morphology that reflect the oocyte quality, we score the quality of day 2 or 3 embryo obtained under IVF cycles during 6 months of the dietary supplement treatment and compare their values with those in placebo controls Secondary outcome(s) We compare the proportions of fertilisation (fertilised oocytes/retrieved oocytes), pregnancy (pregnant cycles/embryo transfer cycles), abortion (abortion cycles/pregnant cycles) between dietary supplement treatment and placebo groups. We also compare the concentration of makers for oxidative stress and immune-related factors (inflammatory cytokines and auto-antibodies)
Starting date	31 March 2015
Contact information	Kazuhiro Kawamura Address: 2-16-1 Sugao, Miyamaeku, Kawasakishi, Kanagawa Japan Telephone: 044-977-8111(ext.3332) Email: kazuhironanami@gmail.com Affiliation: St. Marianna University School of Medicine Obstetrics and Gynecology
Notes	Recruitment status: recruiting

NCT01019785

Study name	Vitamin D during In Vitro Fertilisation (IVF) - a prospective randomised trial delivery
Methods	Randomised double-blind trial
Participants	Target sample size: 1000 women > 18 years of age initiating IVF treatment in Sweden

NCT01019785 *(Continued)*

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	clinicaltrials.gov/ct2/show/NCT01019785?term=NCT01019785&rank=1

NCT01267604

Study name	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 - 39 years undergoing assisted reproductive techniques (ART) because of male infertility BMI 18 - 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

NCT01267604 *(Continued)*

	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 7th August 2012

NCT01659788

Study name	Co Enzyme Q10 Improves IVF outcome in women of advanced reproductive age
Methods	Randomised, parallel assignment, double-blind (participant, investigator)
Participants	Women having IVF of advanced reproductive age Age: 38 to 43 years
Interventions	Coenzyme Q10 concomitant treatment vs placebo
Outcomes	Level of ATP production Steriodogenesis-associated enzymatic activity Ovarian response Embryo quality Cumulative pregnancy rate per retrieval Cumulative live birth rate per retrieval
Starting date	September 2012
Contact information	Hadassah Medical Organization
Notes	Status: unknown status

NCT01665547

Study name	Adding L-carnitine in clomiphene-resistant polycystic ovary improves the quality of ovulation and the pregnancy outcome
Methods	Single-group assignment. Masking: quadruple (participant, care provider, investigator, outcomes assessor)

NCT01665547 *(Continued)*

Participants	Wome with PCOS Age: 18 to 35 years
Interventions	L-carnitine
Outcomes	Ovulation induction Pregnancy
Starting date	July 2012
Contact information	Woman's Health University Hospital, Egypt
Notes	Status: unknown

NCT01782911

Study name	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, Madrid 91 180 2900 mailto:israel.ortega%40ivi.es?subject=NCT01782911, MAD-IO-01-2013-01, Effect of Resveratrol on Metabolic Parameters and Oocyte Quality in PCOS Patients
Notes	Not yet recruiting

NCT01896492

Study name	Clomiphene plus N-acetylcysteine for induction of ovulation in newly-diagnosed PCOS
Methods	Randomised, single-group assignment, triple-blind (participant, care provider, investigator)
Participants	Women with PCOS Age: 18 to 35 years
Interventions	Intervention: Clomiphene citrate plus N-acetylcysteine Control group: Clomiphene citrate
Outcomes	Ovulation rate

NCT01896492 *(Continued)*

	Include PR Number of follicles of ≥ 18 mm Serum E2 concentration, serum P Endometrial thickness
Starting date	January 2011
Contact information	Woman's Health University Hospital, Egypt
Notes	Status: completed

NCT02058212

Study name	Use of antioxidant in endometriotic women to improve intracytoplasmic sperm injection (ICSI) (ROS) Official title: Does antioxidant supplementation to endometriotic women undergoing ICSI alter re-active oxygen species (ROS) levels and affect pregnancy outcome
Methods	Randomised, parallel-assignment, single-blind (participant)
Participants	Women with endometriosis undergoing IVF, 20 - 40 years
Interventions	Drug: ascorbate 1000 mg, vitamin E 400, zinc and selenium
Outcomes	Pregnancy
Starting date	March 2013
Contact information	Olfat Nouh Riad, Assisstant Professor, Cairo University Egyptian Centre for IVF Maadi, Egypt, 11451
Notes	ClinicalTrials.gov Identifier: NCT02058212

NCT02239107

Study name	N-acetylcysteine for ovulation Induction in clomiphene citrate-resistant polycystic ovary syndrome
Methods	Randomised, parallel assignment, open-label. Primary purpose: Treatment
Participants	Wome with PCOS Age: 18 to 39 years
Interventions	N-Acetylcysteine
Outcomes	Ovulation rate

NCT02239107 *(Continued)*	
	Pregnancy rate
Starting date	January 2012
Contact information	Assiut University (Egypt)
Notes	Status: completed

NCT02993588	
Study name	Impact of melatonin on IVF/ICSI outcomes in prospective poor responders
Methods	Randomised, parallel assignment, double-blind (participant, care provider). Primary purpose: Treatment
Participants	Female Age: 30 to 42 years IVF. poor ovarian Response
Interventions	Melatonin, placebo
Outcomes	Total number of retrieved mature oocytes
Starting date	December 2016
Contact information	Osama Abdalmageed, Assiut University, Egypt
Notes	ClinicalTrials.gov/show/NCT02993588

NCT03023514	
Study name	Lipoic acid supplementation in IVF
Methods	Allocation: randomised
Participants	Women with infertility - aged 30 to 50 years
Interventions	Dietary supplement: oral lipoic acid Drug: vaginal progesterone
Outcomes	Number of implants per cycle Number of biochemical pregnancies per group Number of clinical pregnancies per group Number of live births per group Number of miscarriages per group
Starting date	2015

NCT03023514 *(Continued)*

Contact information	Lo.Li.Pharma s.r.l
Notes	ClinicalTrials.gov/show/NCT03023514

NCT03085030

Study name	Can antioxidants affect pregnancy rate in patients with expected low number of egg retrieval in IVF cycles?
Methods	Randomised, parallel assignment, quadruple-blinded (participant, care provider, investigator, outcomes assessor) Primary purpose: Treatment
Participants	Women with infertility Age: 20 to 40 years
Interventions	Antioxidant formula vs placebo
Outcomes	Pregnancy rate Number oocytes retrieved Number of good-quality eggs Number of grade 1 and 2 embryos
Starting date	01 April 2017
Contact information	Department of Obstetrics and Gynecology, Kasr Al-Ainy hospital, Cairo, Greater Cairo, Egypt
Notes	ClinicalTrials.gov/show/NCT03085030

NCT03117725

Study name	Melatonin study between diminished and normal responder in IVF
Methods	Randomised, cross-over assignment, double-blind (participant, investigator) Primary purpose: Supportive care
Participants	Women with infertility, aged 20 to 40 years
Interventions	Melatonin vs placebo
Outcomes	Oocyte quality Embryo quality Biochemical pregnancy rate Clinical pregnancy rate Acquired oocyte numbers Fertilisation rate

NCT03117725 *(Continued)*	
	Comparing Pittsburgh Sleep Quality Index Marker (melatonin level, receptor, 8-OHdg) in serum, follicular fluid and endometrium during IVF
Starting date	12 May 2017
Contact information	Bundang CHA Medical Center, Seongnam si, Gyeonggi Do, Korea, Republic of
Notes	Enrolling by invitation ClinicalTrials.gov/show/NCT03117725

NCT03306745	
Study name	Micronutrient supplementation in PCO-syndrome
Methods	Randomised, parallel assignment, double-blind (participant, investigator)
Participants	PCOS Women with infertility Micronutrient deficiency
Interventions	Dietary supplement: Profertil female Dietary supplement: Folic acid 400 mg
Outcomes	Anti-mullerian hormone (AMH), testosterone, androstenedione
Starting date	02 June 2017
Contact information	Medical University of Vienna, Clinical Division of Gynecologic Endocrinology and Reproductive Medicine, Vienna, Austria
Notes	Completed ClinicalTrials.gov/show/NCT03306745

NCT03396380	
Study name	Effect of vitamin D supplement in induction of ovulation in overweight women with polycystic ovary syndrome
Methods	Randomised, parallel assignment, triple-blind (participant, care provider, outcomes assessor) Primary purpose: Treatment
Participants	Women aged 25 to 35 years
Interventions	Vitamin D with calcium and clomiphene citrate Placebo Oral Tablet with calcium and clomiphene citrate
Outcomes	Rate of ovulation

NCT03396380 *(Continued)*

	Number of growing follicles Endometrial thickness Pregnancy rates Adverse effects
Starting date	01 July 2017
Contact information	AinShams University Maternity Hospital, Cairo, Abbassya, Egypt
Notes	ClinicalTrials.gov/show/NCT03396380

NCT03476564

Study name	Effects of pentoxifylline and vitamin E on pregnancy rate in infertile women treated by ICSI
Methods	Randomised, parallel assignment, single-blind (participant) Primary purpose: Supportive Care
Participants	Women with infertility aged 20 to 39 years
Interventions	Pentoxifylline and Vitamin E
Outcomes	Clinical pregnancy rate
Starting date	2018
Contact information	El Galaa Teaching Hosptial, Cairo, Ghamra, Egypt
Notes	Status: Not yet recruiting ClinicalTrials.gov/show/NCT03476564

NCT04019899

Study name	Myo-inositol and Vitamin D3 during IVF
Methods	Randomised, parallel assignment, open-label
Participants	Inclusion criteria: • Infertile women undergoing IVF • BMI (kg/m^2): 18.5 - 24.9 • Basal FSH on day 3 < 15 mIU/ml Exclusion criteria: • Presence of insulin resistance (IR) • Hyperglycaemia, hyperprolactinaemia, hypothyroidism or androgen excess • Diagnosis of PCOS (according to Rotterdam ESHRE-ASRM Sponsored PCOS consensus workshop group) • intake of hormones or drugs that can potentially influence ovulation

NCT04019899 *(Continued)*

	• FSH > 15 on day 3
Interventions	1. 2 g Myo-Inositol, 50 mg Alpha-Lactalbumin and 200 µg folic acid (1 sachet/day in the morning): from the first day of the menstrual cycle until 14 days after embryo transfer. If pregnancy occurs, until the 12th week of gestation 2. 600 mg Myo-Inositol, 200 µg folic acid, 1 mg melatonin (1 soft capsule/day in the evening): from the first day of the menstrual cycle until hCG administration. If pregnancy occurs, until the 12th week of gestation 3. 600 mg Myo-Inositol, 200 µg folic acid, 1 mg melatonin, 50 µg vitamin D3 as cholecalciferol (1 soft capsule/day in the evening) substitutes the previous treatment at hCG administration and lasting until 14 days after embryo transfer. If pregnancy occurs, until the 12th week of gestation
Outcomes	Implantation rate at 6 weeks of pregnancy Number of gestational sacs observed at ecographic screening divided by the number of embryos transferred Oocyte and embryo quality 12 days and 15 days after the beginning of Controlled Ovarian Hyper-stimulation Classification of the morphological aspects under the optical microscope Clinical pregnancy at 14 days from embryo transfer Positive beta-hCG test after embryo transfer
Starting date	02 May 2018
Contact information	Italy, Clinica Alma Res, Roma, RM, Italy, 00198 Responsible Party: Lo.Li.Pharma s.r.l Other Study ID Numbers:000153
Notes	Study completion date: 31 May 2019

PACTR201902584533870

Study name	Could L-carnitine help poor responders to ovarian stimulation?
Methods	Randomised (permuted block randomisation, sealed opaque envelopes)
Participants	Inclusion criteria: • Infertile women resistant to stimulation Exclusion criteria: • Any other causes of infertility
Interventions	L carnitine Placebo
Outcomes	Clinical pregnancy Response to ovulation
Starting date	28 February 2019
Contact information	Elsayedamr Basma Address: 30 Garden City Smouha 21615 Alexandria Egypt Telephone:00201223106023 Email: elsayedamr@yahoo.com

PACTR201902584533870 *(Continued)*

	Affiliation: Patient Information Manager Eman Abdelfattah Address: 514 Elhoryaa Road Elwezara Bolkely 21531 Alexandria Egypt Telephone: 00201284374180 Email: Eman0eman0eman7@gmail.com Affiliation: Assistant Professor of Obstetrics and Gynaecology Faculty of Medicine University of Alexandria
Notes	Pending

TCTR20171109001

Study name	Effect of 1000 mg supplement of ascorbic acid during ovarian stimulation on the rate of fertilization: double-blind randomised controlled trial
Methods	Randomised controlled trial
Participants	Inclusion criteria: • infertile women Exclusion criteria: • Smoking, alcohol drinking or drug abuse • Vitamin C supplement within 3 months • Inflammatory bowel syndromes or malabsorption syndrome • Chronic kidney disease • Contraindication for vitamin C intake: haemochromatosis, allergy
Interventions	Vitamin C (ascorbic acid) 500 mg twice a day Placebo
Outcomes	Primary Outcome(s): Fertilisation rate 1½ years, by microscopy Secondary Outcome(s): Total antioxidant capacity 1½ years, by ELISA test
Starting date	01December 2017
Contact information	Kingkaew Mingsuttiporn Address: 111/159 Manthana praram 5 village, Mahasawa, Bangkruai Nonthaburi 11130 11130 Nonthaburi Thailand Telephone: 66896150509 Email: kingkaew.msp@gmail.com Affiliation: Siriraj hospital
Notes	Recruitment status: pending (Not yet recruiting)

ALA; aminolevulinic acid; BMI: body mass index; DHA: docosahexenoiic acid; ELISA: enzyme-linked immunosorbent acid; PCOS: polycystic ovary syndrome; PCR: polymerase chain reaction

DATA AND ANALYSES

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

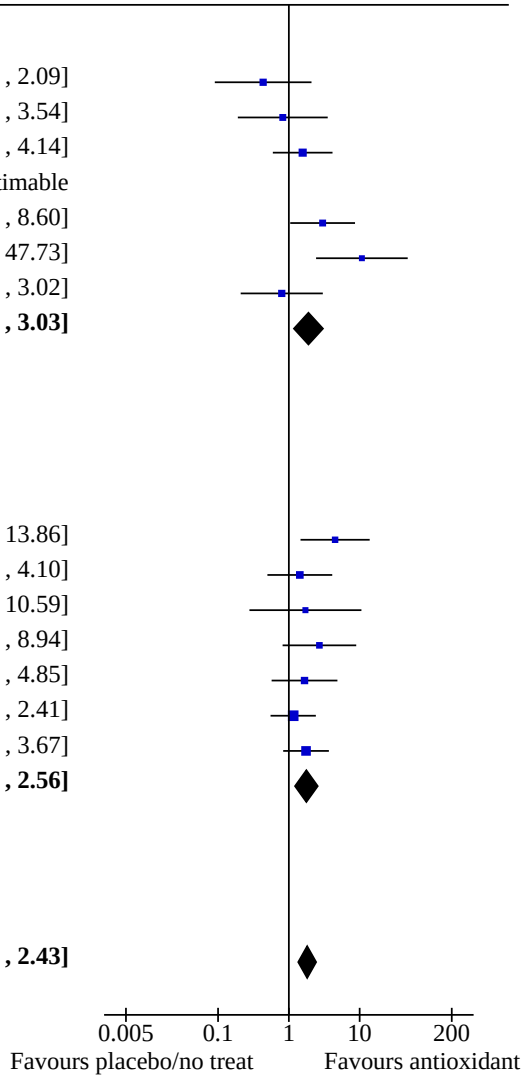
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	13	1227	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.36, 2.43]
1.1.1 Placebo	7	628	Odds Ratio (M-H, Fixed, 95% CI)	1.89 [1.18, 3.03]
1.1.2 No treatment	6	599	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.22, 2.56]
1.2 Live birth; type of antioxidant	13	1227	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [1.36, 2.43]
1.2.1 N-acetyl-cysteine	1	60	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [1.05, 8.60]
1.2.2 L-arginine	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.09, 2.09]
1.2.3 CoQ10	2	225	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.78, 2.88]
1.2.4 Vitamin D	1	52	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.21, 3.02]
1.2.5 Vitamin B complex	1	102	Odds Ratio (M-H, Fixed, 95% CI)	2.07 [0.93, 4.57]
1.2.6 Combined antioxidants	3	378	Odds Ratio (M-H, Fixed, 95% CI)	2.59 [1.52, 4.40]
1.2.7 Vitamin E	1	103	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.50, 4.10]
1.2.8 Melatonin	3	270	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.68, 3.76]
1.3 Live birth; indications for subfertility	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 Polycystic ovary syndrome	3	362	Odds Ratio (M-H, Fixed, 95% CI)	3.34 [1.90, 5.86]
1.3.2 Tubal subfertility	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.09, 2.09]
1.3.3 Varying indications	3	338	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [1.02, 2.83]
1.3.4 Unexplained subfertility	2	133	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.60, 3.72]
1.3.5 Poor ovarian reserve	2	266	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [0.83, 3.67]
1.4 Live birth; IVF/ICSI	9	806	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.96, 1.93]
1.5 Clinical pregnancy; antioxidants vs placebo or no treatment/standard treatment (natural conceptions and undergoing fertility treatments)	35	5165	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [1.43, 1.89]
1.5.1 Placebo	17	3292	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [1.42, 2.05]
1.5.2 No treatment/standard treatment	19	1873	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [1.28, 1.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Clinical pregnancy; type of antioxidant	35	5165	Odds Ratio (M-H, Fixed, 95% CI)	1.65 [1.43, 1.89]
1.6.1 N-acetylcysteine	8	1590	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [1.05, 1.77]
1.6.2 Combined antioxidants	5	689	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.33, 2.70]
1.6.3 Melatonin	7	678	Odds Ratio (M-H, Fixed, 95% CI)	1.66 [1.12, 2.47]
1.6.4 Vitamin E	1	103	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.50, 4.10]
1.6.5 Ascorbic acid	2	899	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.66, 1.25]
1.6.6 L-arginine	2	71	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.32, 3.46]
1.6.7 Myo-inositol plus folic acid	1	94	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.06]
1.6.8 CoQ10	4	397	Odds Ratio (M-H, Fixed, 95% CI)	2.49 [1.50, 4.13]
1.6.9 L-carnitine	2	450	Odds Ratio (M-H, Fixed, 95% CI)	11.14 [5.70, 21.81]
1.6.10 Vitamin D	2	92	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.25, 2.76]
1.6.11 Vitamin B complex	1	102	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [0.82, 4.58]
1.7 Clinical pregnancy; indications for subfertility	31		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Polycystic ovary syndrome	15	1908	Odds Ratio (M-H, Fixed, 95% CI)	4.24 [3.23, 5.56]
1.7.2 Unexplained	4	997	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.61, 1.16]
1.7.3 Tubal subfertility	2	71	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.32, 3.46]
1.7.4 Varying indications	6	1135	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.85, 1.52]
1.7.5 Poor responders	1	65	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.64, 5.47]
1.7.6 Poor ovarian reserve	2	266	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.86, 3.37]
1.7.7 Endometriosis	1	280	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.71, 1.98]
1.8 Clinical pregnancy; IVF/ICSI	18	2341	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.95, 1.40]
1.9 Adverse events	27		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 Miscarriage	24	3229	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.82, 1.55]
1.9.2 Multiple pregnancy	9	1886	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.63, 1.56]
1.9.3 Gastrointestinal disturbances	3	343	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.47, 5.10]
1.9.4 Ectopic pregnancy	4	404	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.27, 7.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.5 Headache	2	330	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.75]
1.9.6 Congenital (missing kidney)	1	160	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.04, 25.46]
1.9.7 Low birth weight < 2.500 g	1	160	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.00, 2.74]
1.9.8 Preterm birth	2	220	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.17, 9.93]
1.9.9 Placenta praevia	1	160	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.04, 25.46]
1.9.10 Pre-eclampsia	1	160	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.08, 36.35]
1.9.11 Fatigue	1	160	Odds Ratio (M-H, Fixed, 95% CI)	1.86 [0.75, 4.62]
1.9.12 Ovarian hyperstimulation syndrome (OHSS)	1	150	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

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)

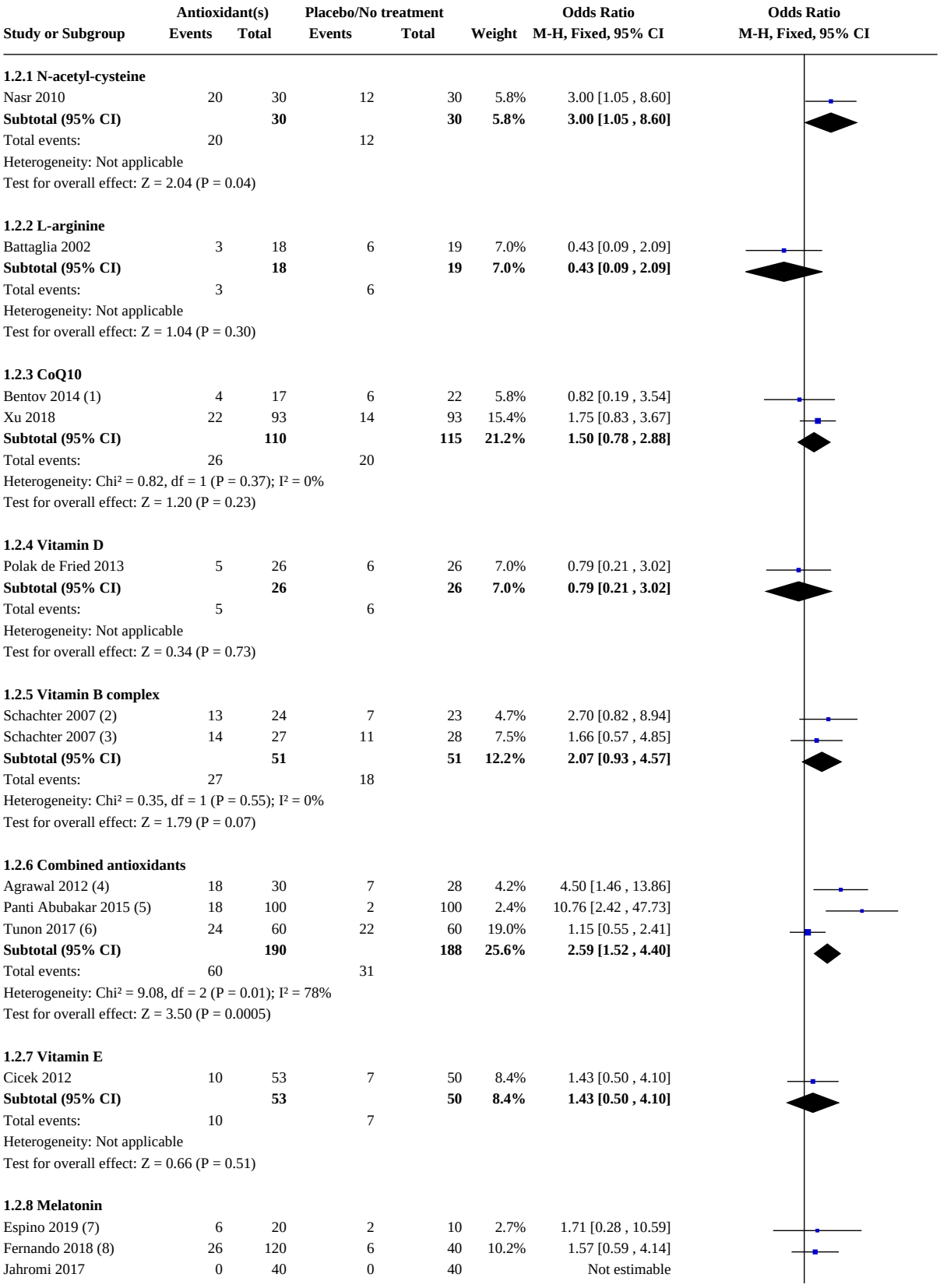
Study or Subgroup	Antioxidant Events	Antioxidant Total	Placebo/No treatment Events	Placebo/No treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Placebo						
Battaglia 2002 (1)	3	18	6	19	7.0%	0.43 [0.09 , 2.09]
Bentov 2014 (2)	4	17	6	22	5.8%	0.82 [0.19 , 3.54]
Fernando 2018 (3)	26	120	6	40	10.2%	1.57 [0.59 , 4.14]
Jahromi 2017	0	40	0	40		Not estimable
Nasr 2010 (4)	20	30	12	30	5.8%	3.00 [1.05 , 8.60]
Panti Abubakar 2015	18	100	2	100	2.4%	10.76 [2.42 , 47.73]
Polak de Fried 2013	5	26	6	26	7.0%	0.79 [0.21 , 3.02]
Subtotal (95% CI)		**351**		**277**	**38.1%**	**1.89 [1.18 , 3.03]**
Total events:	76		38			
Heterogeneity: Chi² = 12.36, df = 5 (P = 0.03); I² = 60%						
Test for overall effect: Z = 2.65 (P = 0.008)						
1.1.2 No treatment						
Agrawal 2012 (5)	18	30	7	28	4.2%	4.50 [1.46 , 13.86]
Cicek 2012 (6)	10	53	7	50	8.4%	1.43 [0.50 , 4.10]
Espino 2019 (7)	6	20	2	10	2.7%	1.71 [0.28 , 10.59]
Schachter 2007 (8)	13	24	7	23	4.7%	2.70 [0.82 , 8.94]
Schachter 2007 (9)	14	27	11	28	7.5%	1.66 [0.57 , 4.85]
Tunon 2017 (10)	24	60	22	60	19.0%	1.15 [0.55 , 2.41]
Xu 2018	22	93	14	93	15.4%	1.75 [0.83 , 3.67]
Subtotal (95% CI)		**307**		**292**	**61.9%**	**1.77 [1.22 , 2.56]**
Total events:	107		70			
Heterogeneity: Chi² = 4.60, df = 6 (P = 0.60); I² = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**658**		**569**	**100.0%**	**1.81 [1.36 , 2.43]**
Total events:	183		108			
Heterogeneity: Chi² = 16.86, df = 12 (P = 0.15); I² = 29%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



Footnotes

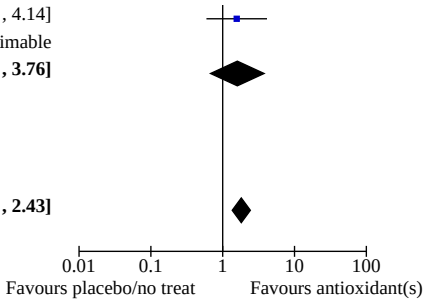
(1) Women are also undergoing IVF/ICSI
(2) Study terminated due to embryo safety reasons before reaching target number of enrolled women
(3) 3 active arms; the numbers for the active groups have been combined
(4) Women are also undergoing laparoscopic ovarian drilling
(5) Ongoing pregnancy rate
(6) Ongoing pregnancy rate. Women undergoing IUI
(7) Considered high risk as no blinding (low risk for the head-to-head comparison where there is blinding). 3-armed trial; treatment groups were combined
(8) Ongoing pregnancy rate. 84 of these women underwent IVF/ICSI and 18 ovulation induction.
(9) Ongoing pregnancy rate. 82 of these women underwent IVF/ICSI and 18 ovulation induction
(10) Combined antioxidants

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



Analysis 1.2. (Continued)

Fernando 2018 (8)	26	120	6	40	10.2%	1.57 [0.59 , 4.14]
Jahromi 2017	0	40	0	40		Not estimable
Subtotal (95% CI)		**180**		**90**	**12.9%**	**1.60 [0.68 , 3.76]**
Total events:	32		8			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**658**		**569**	**100.0%**	**1.81 [1.36 , 2.43]**
Total events:	183		108			
Heterogeneity: Chi² = 16.86, df = 12 (P = 0.15); I² = 29%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Test for subgroup differences: Chi² = 7.96, df = 7 (P = 0.34), I² = 12.0%						

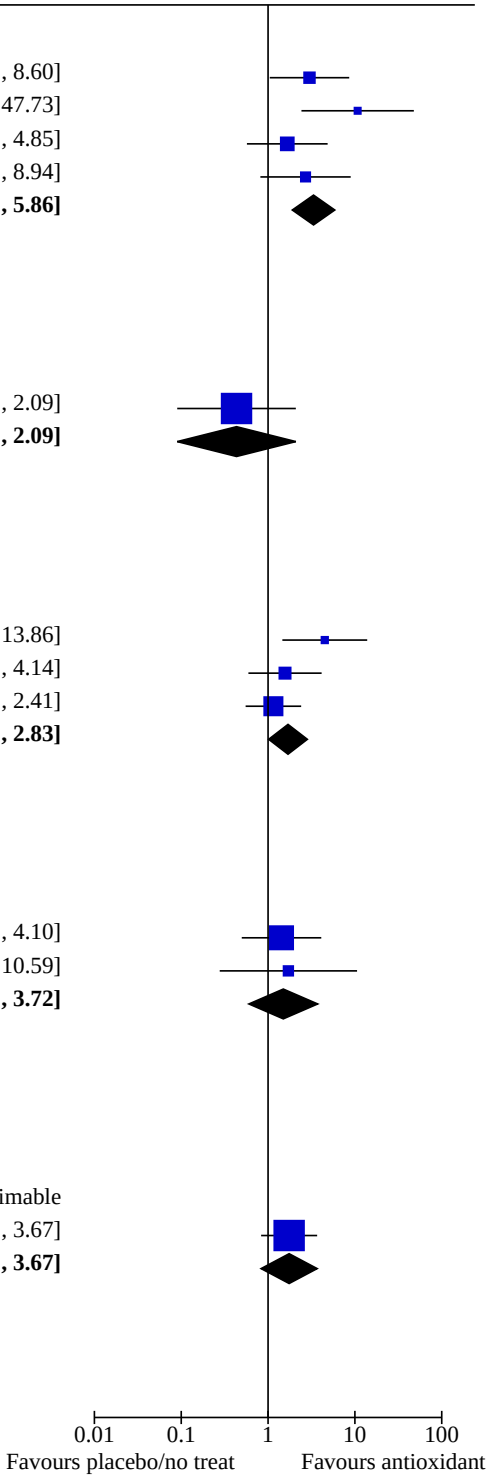


Footnotes

(1) Study terminated due to embryo safety reasons before reaching target number of enrolled women
(2) Vitamin B complex versus no treatment
(3) Vitamin B complex plus metformin versus metformin (no treatment)
(4) Multiple micronutrients (MMN)
(5) Vitacap
(6) Seidivid
(7) 3-armed trial; treatment groups were combined
(8) 3 active arms, the events and total numbers for the active groups have been combined

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

Study or Subgroup	Antioxidant(s) Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Polycystic ovary syndrome						
Nasr 2010	20	30	12	30	28.3%	3.00 [1.05 , 8.60]
Panti Abubakar 2015	18	100	2	100	11.6%	10.76 [2.42 , 47.73]
Schachter 2007	14	27	11	28	36.8%	1.66 [0.57 , 4.85]
Schachter 2007	13	24	7	23	23.2%	2.70 [0.82 , 8.94]
Subtotal (95% CI)		**181**		**181**	**100.0%**	**3.34 [1.90 , 5.86]**
Total events:	65		32			
Heterogeneity: Chi² = 4.15, df = 3 (P = 0.25); I² = 28%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
1.3.2 Tubal subfertility						
Battaglia 2002	3	18	6	19	100.0%	0.43 [0.09 , 2.09]
Subtotal (95% CI)		**18**		**19**	**100.0%**	**0.43 [0.09 , 2.09]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.3.3 Varying indications						
Agrawal 2012	18	30	7	28	12.5%	4.50 [1.46 , 13.86]
Fernando 2018 (1)	26	120	6	40	30.5%	1.57 [0.59 , 4.14]
Tunon 2017	24	60	22	60	57.0%	1.15 [0.55 , 2.41]
Subtotal (95% CI)		**210**		**128**	**100.0%**	**1.70 [1.02 , 2.83]**
Total events:	68		35			
Heterogeneity: Chi² = 3.98, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.3.4 Unexplained subfertility						
Cicek 2012	10	53	7	50	75.8%	1.43 [0.50 , 4.10]
Espino 2019 (2)	6	20	2	10	24.2%	1.71 [0.28 , 10.59]
Subtotal (95% CI)		**73**		**60**	**100.0%**	**1.50 [0.60 , 3.72]**
Total events:	16		9			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
1.3.5 Poor ovarian reserve						
Jahromi 2017	0	40	0	40		Not estimable
Xu 2018	22	93	14	93	100.0%	1.75 [0.83 , 3.67]
Subtotal (95% CI)		**133**		**133**	**100.0%**	**1.75 [0.83 , 3.67]**
Total events:	22		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						



Footnotes

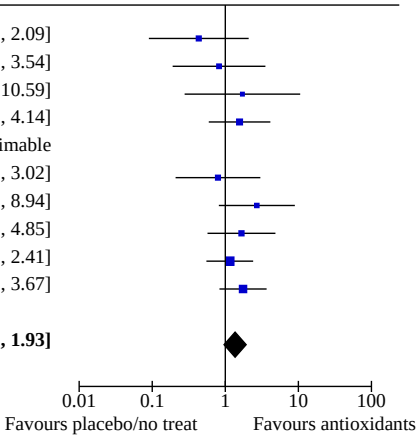
(1) 3 active arms; the events and total numbers for the active groups have been combined

(2) 3-armed trial; treatment groups were combined

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

Study or Subgroup	Antioxidant(s) Events	Antioxidant(s) Total	Placebo/No treatment Events	Placebo/No treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Battaglia 2002	3	18	6	19	8.8%	0.43 [0.09 , 2.09]
Bentov 2014	4	17	6	22	7.3%	0.82 [0.19 , 3.54]
Espino 2019 (1)	6	20	2	10	3.4%	1.71 [0.28 , 10.59]
Fernando 2018 (2)	26	120	6	40	12.8%	1.57 [0.59 , 4.14]
Jahromi 2017	0	40	0	40		Not estimable
Polak de Fried 2013	5	26	6	26	8.8%	0.79 [0.21 , 3.02]
Schachter 2007	13	24	7	23	6.0%	2.70 [0.82 , 8.94]
Schachter 2007	14	27	11	28	9.5%	1.66 [0.57 , 4.85]
Tunon 2017	24	60	22	60	24.0%	1.15 [0.55 , 2.41]
Xu 2018	22	93	14	93	19.4%	1.75 [0.83 , 3.67]
Total (95% CI)		**445**		**361**	**100.0%**	**1.36 [0.96 , 1.93]**
Total events:	117		80			

Heterogeneity: Chi² = 5.29, df = 8 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Not applicable

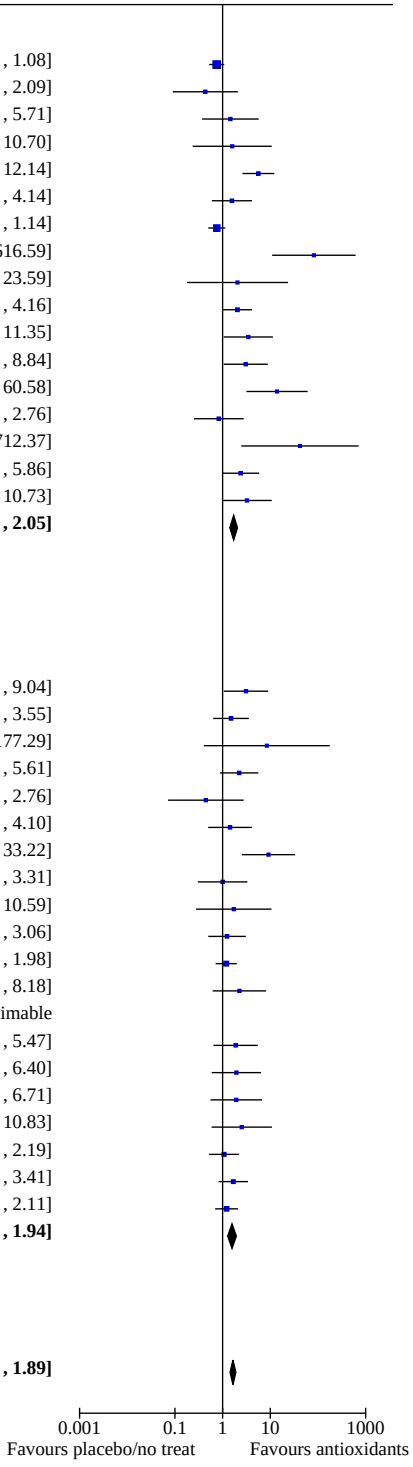


Footnotes

(1) 3-armed trial; treatment groups were combined
(2) 3 active arms; the numbers for the active groups have been combined

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)

Study or Subgroup	Antioxidant(s) Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Placebo						
Badawy 2006	63	404	79	400	21.0%	0.75 [0.52 , 1.08]
Battaglia 2002	3	18	6	19	1.5%	0.43 [0.09 , 2.09]
Bentov 2014 (1)	6	17	6	22	1.1%	1.45 [0.37 , 5.71]
Cheraghi 2016	3	20	2	20	0.5%	1.59 [0.24 , 10.70]
El Sharkwy 2019b (2)	39	140	9	140	2.0%	5.62 [2.60 , 12.14]
Fernando 2018 (3)	26	120	6	40	2.2%	1.57 [0.59 , 4.14]
Griesinger 2002 (4)	104	461	44	158	15.9%	0.75 [0.50 , 1.14]
Ismail 2014 (5)	42	85	1	85	0.2%	82.05 [10.92 , 616.59]
Jahromi 2017	2	40	1	40	0.3%	2.05 [0.18 , 23.59]
Mokhtari 2019 (6)	26	98	15	100	3.4%	2.05 [1.01 , 4.16]
Mostajeran 2018 (7)	12	65	4	65	1.0%	3.45 [1.05 , 11.35]
Nasr 2010	21	30	13	30	1.2%	3.05 [1.05 , 8.84]
Panti Abubakar 2015	22	100	2	100	0.5%	13.82 [3.15 , 60.58]
Polak de Fried 2013	7	26	8	26	1.8%	0.83 [0.25 , 2.76]
Rizk 2005 (8)	16	75	0	75	0.1%	41.87 [2.46 , 712.37]
Salehpour 2012 (9)	17	90	8	90	2.0%	2.39 [0.97 , 5.86]
Westphal 2006 (10)	14	53	4	40	1.1%	3.23 [0.97 , 10.73]
Subtotal (95% CI)		**1842**		**1450**	**56.0%**	**1.70 [1.42 , 2.05]**
Total events:	423		208			
Heterogeneity: Chi² = 79.33, df = 16 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 5.65 (P < 0.00001)						
1.5.2 No treatment/standard treatment						
Agrawal 2012 (11)	20	30	11	28	1.2%	3.09 [1.06 , 9.04]
Batioglu 2012	20	40	18	45	2.7%	1.50 [0.63 , 3.55]
Battaglia 1999	3	17	0	17	0.1%	8.45 [0.40 , 177.29]
Behrouzi 2017	16	52	9	54	1.9%	2.22 [0.88 , 5.61]
Cheraghi 2016 (12)	2	20	4	20	1.1%	0.44 [0.07 , 2.76]
Cicek 2012 (13)	10	53	7	50	1.8%	1.43 [0.50 , 4.10]
El Refaeey 2014 (14)	19	55	3	55	0.6%	9.15 [2.52 , 33.22]
Eryilmaz 2011	7	30	7	30	1.7%	1.00 [0.30 , 3.31]
Espino 2019 (15)	6	20	2	10	0.6%	1.71 [0.28 , 10.59]
Lisi 2012	14	47	12	47	2.6%	1.24 [0.50 , 3.06]
Lu 2018	54	160	36	120	8.6%	1.19 [0.71 , 1.98]
Maged 2015 (16)	8	40	4	40	1.0%	2.25 [0.62 , 8.18]
Rashidi 2009 (17)	0	20	0	20		Not estimable
Rizzo 2010	12	32	8	33	1.5%	1.88 [0.64 , 5.47]
Schachter 2007 (18)	21	27	18	28	1.2%	1.94 [0.59 , 6.40]
Schachter 2007 (19)	18	24	14	23	1.1%	1.93 [0.55 , 6.71]
Sen Sharma 2017 (20)	7	32	3	30	0.8%	2.52 [0.59 , 10.83]
Tunon 2017	28	60	27	60	4.5%	1.07 [0.52 , 2.19]
Xu 2018	24	93	16	93	3.7%	1.67 [0.82 , 3.41]
Youssef 2015	43	112	36	106	7.2%	1.21 [0.70 , 2.11]
Subtotal (95% CI)		**964**		**909**	**44.0%**	**1.57 [1.28 , 1.94]**
Total events:	332		235			
Heterogeneity: Chi² = 17.28, df = 18 (P = 0.50); I² = 0%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
Total (95% CI)		**2806**		**2359**	**100.0%**	**1.65 [1.43 , 1.89]**
Total events:	755		443			
Heterogeneity: Chi² = 95.61, df = 35 (P < 0.00001); I² = 63%						
Test for overall effect: Z = 7.05 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%						



Footnotes

(1) Study terminated due to embryo safety reasons

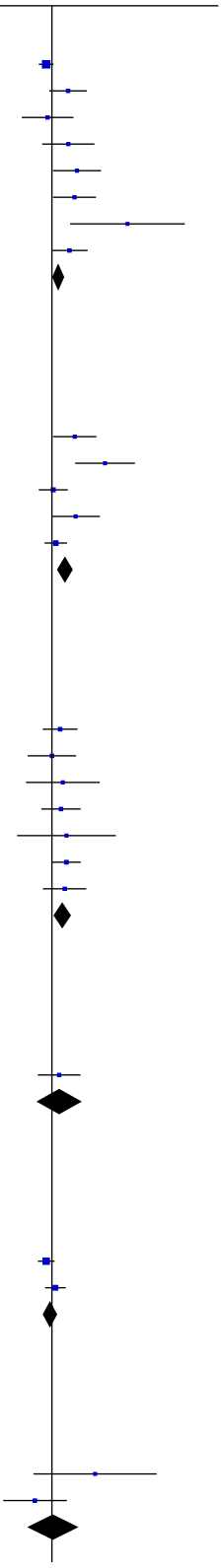
Analysis 1.5. (Continued)

Footnotes

(1) Study terminated due to embryo safety reasons
(2) CC plus metformin and L-carnitine versus CC plus metformin and placebo
(3) 3 active arms; the numbers for the active groups have been combined
(4) The 3 active arms versus placebo of this trial have been combined
(5) timed intercourse PCOS clomiphene + carnitine vs clomiphene + placebo
(6) Women with PCOS undergoing IUI
(7) Timed intercourse with ovulation induction. Letrozole + NAC vs letrozole + placebo
(8) N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate
(9) NAC + clomiphene vs placebo + clomiphene
(10) Women are conceiving naturally. Only first 3 months data used
(11) Agrawal 2012 and Lisi 2012 use folic acid 400 mcg (standard care) as control
(12) 4-armed trial; NAC plus metformin versus metformin
(13) Women undergoing IUI
(14) Data per woman over 2 cycles of timed intercourse. CoQ10 + clomiphene versus clomiphene
(15) 3-armed trial; treatment groups were combined
(16) N-acetylcysteine plus clomiphene citrate versus no treatment + clomiphene citrate
(17) Natural conception
(18) Vitamin B complex plus metformin vs metformin alone. Cumulative pregnancy rate over 3 months
(19) Cumulative pregnancy rate over 3 cycles
(20) Co-enzyme Q10 + clomiphene citrate versus clomiphene citrate. Timed intercourse

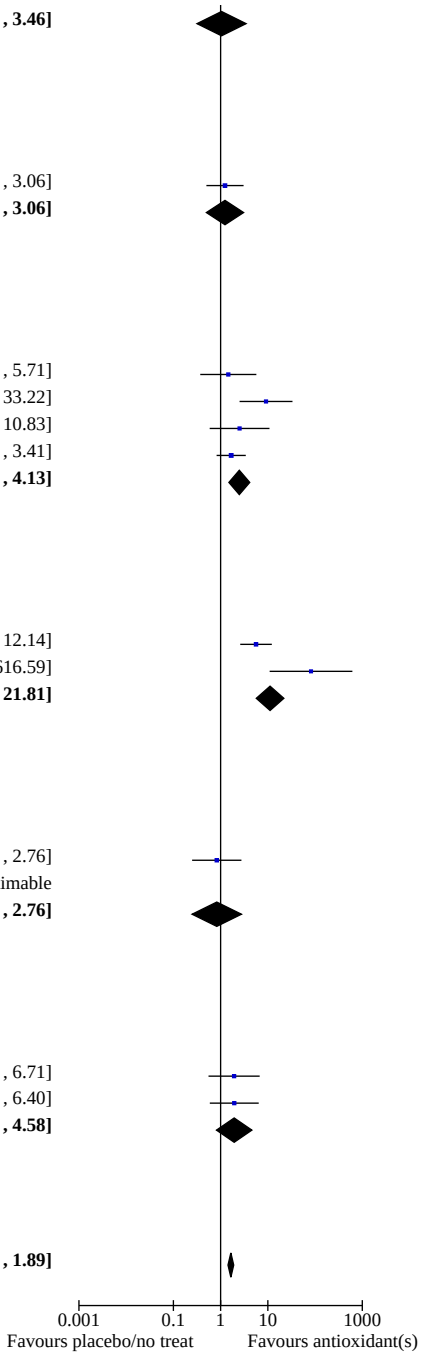
Analysis 1.6. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 6: Clinical pregnancy; type of antioxidant

Study or Subgroup	Antioxidant(s) Events	Antioxidant(s) Total	Placebo/No treatment Events	Placebo/No treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 N-acetylcysteine						
Badawy 2006 (1)	63	404	79	400	21.0%	0.75 [0.52 , 1.08]
Behrouzi 2017	16	52	9	54	1.9%	2.22 [0.88 , 5.61]
Cheraghi 2016 (2)	5	40	6	40	1.6%	0.81 [0.23 , 2.90]
Maged 2015 (3)	8	40	4	40	1.0%	2.25 [0.62 , 8.18]
Mostajeran 2018 (4)	12	65	4	65	1.0%	3.45 [1.05 , 11.35]
Nasr 2010 (5)	21	30	13	30	1.2%	3.05 [1.05 , 8.84]
Rizk 2005 (1)	16	75	0	75	0.1%	41.87 [2.46 , 712.37]
Salehpour 2012	17	90	8	90	2.0%	2.39 [0.97 , 5.86]
Subtotal (95% CI)		**796**		**794**	**30.0%**	**1.36 [1.05 , 1.77]**
Total events:	158		123			
Heterogeneity: Chi² = 24.24, df = 7 (P = 0.001); I² = 71%						
Test for overall effect: Z = 2.31 (P = 0.02)						
1.6.2 Combined antioxidants						
Agrawal 2012	20	30	11	28	1.2%	3.09 [1.06 , 9.04]
Panti Abubakar 2015	22	100	2	100	0.5%	13.82 [3.15 , 60.58]
Tunon 2017	28	60	27	60	4.5%	1.07 [0.52 , 2.19]
Westphal 2006	14	53	4	40	1.1%	3.23 [0.97 , 10.73]
Youssef 2015	43	112	36	106	7.2%	1.21 [0.70 , 2.11]
Subtotal (95% CI)		**355**		**334**	**14.4%**	**1.90 [1.33 , 2.70]**
Total events:	127		80			
Heterogeneity: Chi² = 13.46, df = 4 (P = 0.009); I² = 70%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
1.6.3 Melatonin						
Batioglu 2012	20	40	18	45	2.7%	1.50 [0.63 , 3.55]
Eryilmaz 2011	7	30	7	30	1.7%	1.00 [0.30 , 3.31]
Espino 2019 (6)	6	20	2	10	0.6%	1.71 [0.28 , 10.59]
Fernando 2018 (7)	26	120	6	40	2.2%	1.57 [0.59 , 4.14]
Jahromi 2017	2	40	1	40	0.3%	2.05 [0.18 , 23.59]
Mokhtari 2019	26	98	15	100	3.4%	2.05 [1.01 , 4.16]
Rizzo 2010	12	32	8	33	1.5%	1.88 [0.64 , 5.47]
Subtotal (95% CI)		**380**		**298**	**12.4%**	**1.66 [1.12 , 2.47]**
Total events:	99		57			
Heterogeneity: Chi² = 1.17, df = 6 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.54 (P = 0.01)						
1.6.4 Vitamin E						
Cicek 2012	10	53	7	50	1.8%	1.43 [0.50 , 4.10]
Subtotal (95% CI)		**53**		**50**	**1.8%**	**1.43 [0.50 , 4.10]**
Total events:	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.6.5 Ascorbic acid						
Griesinger 2002 (8)	104	461	44	158	15.9%	0.75 [0.50 , 1.14]
Lu 2018	54	160	36	120	8.6%	1.19 [0.71 , 1.98]
Subtotal (95% CI)		**621**		**278**	**24.5%**	**0.91 [0.66 , 1.25]**
Total events:	158		80			
Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.6.6 L-arginine						
Battaglia 1999	3	17	0	17	0.1%	8.45 [0.40 , 177.29]
Battaglia 2002	3	18	6	19	1.5%	0.43 [0.09 , 2.09]
Subtotal (95% CI)		**35**		**36**	**1.7%**	**1.05 [0.32 , 3.46]**
Total events:	6		6			



Analysis 1.6. (Continued)

Subtotal (95% CI)		**35**		**36**	**1.7%**	**1.05 [0.32 , 3.46]**
Total events:	6		6			
Heterogeneity: Chi² = 3.02, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 0.07 (P = 0.94)						
1.6.7 Myo-inositol plus folic acid						
Lisi 2012	14	47	12	47	2.6%	1.24 [0.50 , 3.06]
Subtotal (95% CI)		**47**		**47**	**2.6%**	**1.24 [0.50 , 3.06]**
Total events:	14		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
1.6.8 CoQ10						
Bentov 2014 (9)	6	17	6	22	1.1%	1.45 [0.37 , 5.71]
El Refaeey 2014 (10)	19	55	3	55	0.6%	9.15 [2.52 , 33.22]
Sen Sharma 2017	7	32	3	30	0.8%	2.52 [0.59 , 10.83]
Xu 2018	24	93	16	93	3.7%	1.67 [0.82 , 3.41]
Subtotal (95% CI)		**197**		**200**	**6.2%**	**2.49 [1.50 , 4.13]**
Total events:	56		28			
Heterogeneity: Chi² = 5.70, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 3.52 (P = 0.0004)						
1.6.9 L-carnitine						
El Sharkwy 2019b	39	140	9	140	2.0%	5.62 [2.60 , 12.14]
Ismail 2014	42	85	1	85	0.2%	82.05 [10.92 , 616.59]
Subtotal (95% CI)		**225**		**225**	**2.2%**	**11.14 [5.70 , 21.81]**
Total events:	81		10			
Heterogeneity: Chi² = 6.80, df = 1 (P = 0.009); I² = 85%						
Test for overall effect: Z = 7.04 (P < 0.00001)						
1.6.10 Vitamin D						
Polak de Fried 2013	7	26	8	26	1.8%	0.83 [0.25 , 2.76]
Rashidi 2009 (11)	0	20	0	20		Not estimable
Subtotal (95% CI)		**46**		**46**	**1.8%**	**0.83 [0.25 , 2.76]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.6.11 Vitamin B complex						
Schachter 2007 (12)	18	24	14	23	1.1%	1.93 [0.55 , 6.71]
Schachter 2007 (13)	21	27	18	28	1.2%	1.94 [0.59 , 6.40]
Subtotal (95% CI)		**51**		**51**	**2.4%**	**1.94 [0.82 , 4.58]**
Total events:	39		32			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						
Total (95% CI)		**2806**		**2359**	**100.0%**	**1.65 [1.43 , 1.89]**
Total events:	755		443			
Heterogeneity: Chi² = 94.83, df = 34 (P < 0.00001); I² = 64%						
Test for overall effect: Z = 7.05 (P < 0.00001)						
Test for subgroup differences: Chi² = 51.55, df = 10 (P < 0.00001), I² = 80.6%						



Footnotes

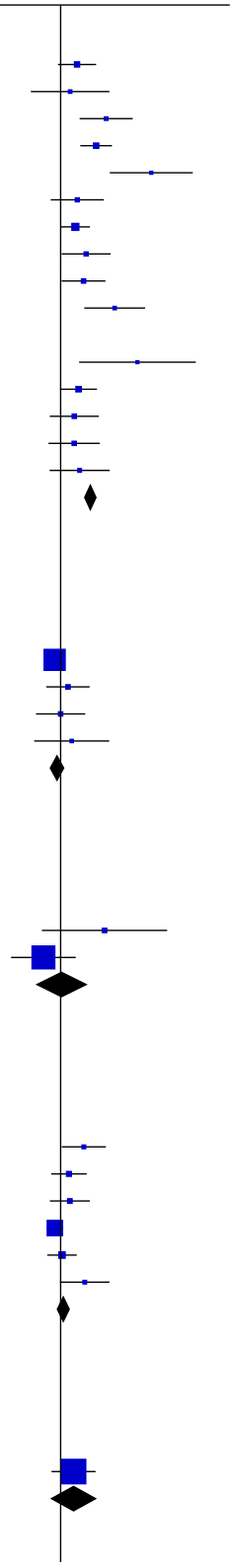
(1) N-acetyl-cysteine plus clomiphene citrate versus placebo plus clomiphene citrate
(2) 2 active arms pooled here
(3) N-acetyl-cysteine plus clomiphene citrate versus clomiphene citrate
(4) 1200 mg NAC plus 5 mg leterozole versus 5 mg leterozole plus placebo
(5) Both groups had laparoscopic ovarian drilling
(6) 3-armed trial; treatment groups were combined
(7) 3 active arms; numbers for the active groups have been combined
(8) 3 active arms have been pooled

Analysis 1.6. (Continued)

(7) 3 active arms; numbers for the active groups have been combined
(8) 3 active arms have been pooled
(9) Study terminated due to embryo safety reasons
(10) Data per women over 2 cycles, timed intercourse
(11) Vitamin D and calcium + metformin versus metformin
(12) Cumulative pregnancy rate over 3 months.
(13) Vitamin B complex plus metformin versus metformin. Cumulative pregnancy rate over 3 months

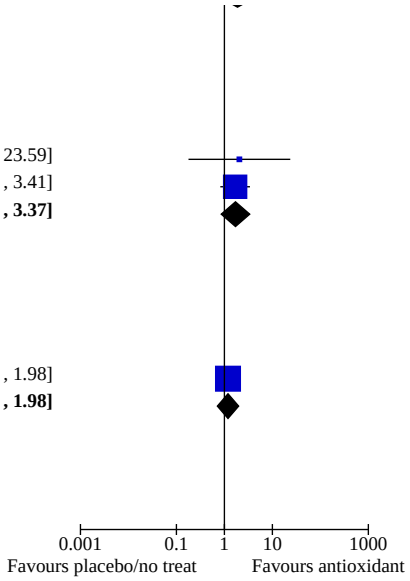
Analysis 1.7. Comparison 1: Antioxidant(s) versus placebo or no treatment/standard treatment, Outcome 7: Clinical pregnancy; indications for subfertility

Study or Subgroup	Antioxidant(s) Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Polycystic ovary syndrome						
Behrouzi 2017	16	52	9	54	10.8%	2.22 [0.88 , 5.61]
Cheraghi 2016	3	20	2	20	3.0%	1.59 [0.24 , 10.70]
El Refaeey 2014 (1)	19	55	3	55	3.5%	9.15 [2.52 , 33.22]
El Sharkwy 2019b	39	140	9	140	11.5%	5.62 [2.60 , 12.14]
Ismail 2014 (2)	42	85	1	85	0.9%	82.05 [10.92 , 616.59]
Maged 2015	8	40	4	40	5.7%	2.25 [0.62 , 8.18]
Mokhtari 2019	26	98	15	100	19.3%	2.05 [1.01 , 4.16]
Mostajeran 2018	12	65	4	65	5.8%	3.45 [1.05 , 11.35]
Nasr 2010	21	30	13	30	6.9%	3.05 [1.05 , 8.84]
Panti Abubakar 2015	22	100	2	100	2.8%	13.82 [3.15 , 60.58]
Rashidi 2009	0	20	0	20		Not estimable
Rizk 2005 (3)	16	75	0	75	0.7%	41.87 [2.46 , 712.37]
Salehpour 2012	17	90	8	90	11.5%	2.39 [0.97 , 5.86]
Schachter 2007 (4)	21	27	18	28	7.0%	1.94 [0.59 , 6.40]
Schachter 2007 (4)	18	24	14	23	6.3%	1.93 [0.55 , 6.71]
Sen Sharma 2017	7	32	3	30	4.3%	2.52 [0.59 , 10.83]
Subtotal (95% CI)		**953**		**955**	**100.0%**	**4.24 [3.23 , 5.56]**
Total events:	287		105			
Heterogeneity: Chi² = 28.71, df = 14 (P = 0.01); I² = 51%						
Test for overall effect: Z = 10.39 (P < 0.00001)						
1.7.2 Unexplained						
Badawy 2006	63	404	79	400	83.7%	0.75 [0.52 , 1.08]
Cicek 2012	10	53	7	50	7.3%	1.43 [0.50 , 4.10]
Eryilmaz 2011	7	30	7	30	6.7%	1.00 [0.30 , 3.31]
Espino 2019 (5)	6	20	2	10	2.3%	1.71 [0.28 , 10.59]
Subtotal (95% CI)		**507**		**490**	**100.0%**	**0.84 [0.61 , 1.16]**
Total events:	86		95			
Heterogeneity: Chi² = 2.01, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.7.3 Tubal subfertility						
Battaglia 1999	3	17	0	17	7.6%	8.45 [0.40 , 177.29]
Battaglia 2002	3	18	6	19	92.4%	0.43 [0.09 , 2.09]
Subtotal (95% CI)		**35**		**36**	**100.0%**	**1.05 [0.32 , 3.46]**
Total events:	6		6			
Heterogeneity: Chi² = 3.02, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 0.07 (P = 0.94)						
1.7.4 Varying indications						
Agrawal 2012	20	30	11	28	4.3%	3.09 [1.06 , 9.04]
Batioglu 2012	20	40	18	45	9.6%	1.50 [0.63 , 3.55]
Fernando 2018 (6)	26	120	6	40	8.0%	1.57 [0.59 , 4.14]
Griesinger 2002	104	461	44	158	57.8%	0.75 [0.50 , 1.14]
Tunon 2017	28	60	27	60	16.4%	1.07 [0.52 , 2.19]
Westphal 2006	14	53	4	40	3.8%	3.23 [0.97 , 10.73]
Subtotal (95% CI)		**764**		**371**	**100.0%**	**1.14 [0.85 , 1.52]**
Total events:	212		110			
Heterogeneity: Chi² = 10.92, df = 5 (P = 0.05); I² = 54%						
Test for overall effect: Z = 0.89 (P = 0.38)						
1.7.5 Poor responders						
Rizzo 2010	12	32	8	33	100.0%	1.88 [0.64 , 5.47]
Subtotal (95% CI)		**32**		**33**	**100.0%**	**1.88 [0.64 , 5.47]**
Total events:	12		8			
Heterogeneity: Not applicable						



Analysis 1.7. (Continued)

Total events:	12		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.7.6 Poor ovarian reserve						
Jahromi 2017	2	40	1	40	7.4%	2.05 [0.18 , 23.59]
Xu 2018	24	93	16	93	92.6%	1.67 [0.82 , 3.41]
Subtotal (95% CI)		**133**		**133**	**100.0%**	**1.70 [0.86 , 3.37]**
Total events:	26		17			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.53 (P = 0.13)						
1.7.7 Endometriosis						
Lu 2018	54	160	36	120	100.0%	1.19 [0.71 , 1.98]
Subtotal (95% CI)		**160**		**120**	**100.0%**	**1.19 [0.71 , 1.98]**
Total events:	54		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						



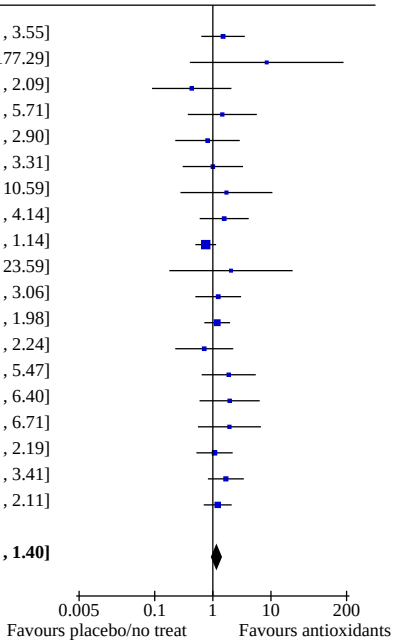
Footnotes

(1) Data per woman over 2 cycles, timed intercourse. COQ10 + clomiphene vs clomiphene
(2) Timed intercourse
(3) Antioxidant plus clomiphene citrate versus placebo plus clomiphene citrate
(4) Cumulative pregnancy rate
(5) 3-armed trial; treatment groups were combined
(6) 3 active arms; total numbers have been combined

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

Study or Subgroup	Favours placebo/no treat Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Batioglu 2012	20	40	18	45	4.4%	1.50 [0.63 , 3.55]
Battaglia 1999	3	17	0	17	0.2%	8.45 [0.40 , 177.29]
Battaglia 2002	3	18	6	19	2.5%	0.43 [0.09 , 2.09]
Bentov 2014 (1)	6	17	6	22	1.8%	1.45 [0.37 , 5.71]
Cheraghi 2016 (2)	5	40	6	40	2.7%	0.81 [0.23 , 2.90]
Eryilmaz 2011	7	30	7	30	2.8%	1.00 [0.30 , 3.31]
Espino 2019 (3)	6	20	2	10	1.0%	1.71 [0.28 , 10.59]
Fernando 2018 (4)	26	120	6	40	3.7%	1.57 [0.59 , 4.14]
Griesinger 2002 (5)	104	461	44	158	26.4%	0.75 [0.50 , 1.14]
Jahromi 2017	2	40	1	40	0.5%	2.05 [0.18 , 23.59]
Lisi 2012	14	47	12	47	4.4%	1.24 [0.50 , 3.06]
Lu 2018	54	160	36	120	14.2%	1.19 [0.71 , 1.98]
Polak de Fried 2013	8	26	10	26	3.6%	0.71 [0.23 , 2.24]
Rizzo 2010	12	32	8	33	2.6%	1.88 [0.64 , 5.47]
Schachter 2007 (6)	21	27	18	28	2.0%	1.94 [0.59 , 6.40]
Schachter 2007 (7)	18	24	14	23	1.9%	1.93 [0.55 , 6.71]
Tunon 2017	28	60	27	60	7.5%	1.07 [0.52 , 2.19]
Xu 2018	24	93	16	93	6.2%	1.67 [0.82 , 3.41]
Youssef 2015	43	112	36	106	11.8%	1.21 [0.70 , 2.11]
Total (95% CI)		**1384**		**957**	**100.0%**	**1.15 [0.95 , 1.40]**
Total events:	404		273			

Odds Ratio M-H, Fixed, 95% CI



Heterogeneity: Chi² = 12.85, df = 18 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)
Test for subgroup differences: Not applicable

Footnotes

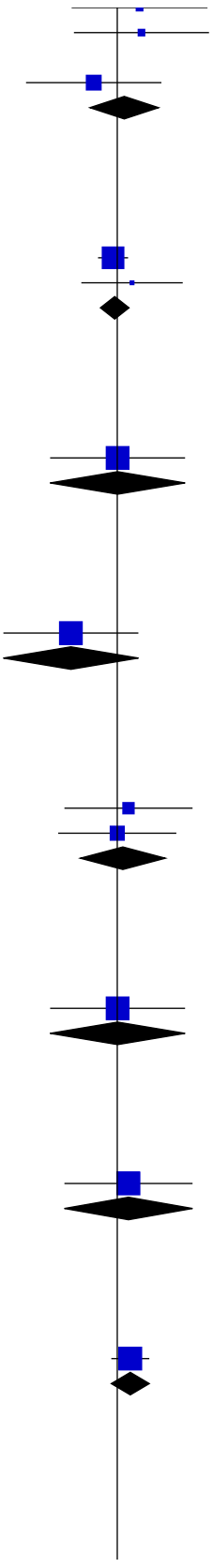
(1) Study terminated due to embryo safety reasons
(2) 2 active and control arms were pooled
(3) "Women subjected to second cycle of IVF". 3-armed trial; treatment groups were combined
(4) 3 active arms; numbers for the active groups have been combined
(5) 3 active arms of this trial have been combined
(6) Vitamin B complex + metformin versus metformin
(7) Cumulative clinical pregnancy rate over 3 cycles. 84 women from 102 underwent IVF, 18 had ovulation induction

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

Study or Subgroup	Antioxidant(s) Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.9.1 Miscarriage						
Agrawal 2012	1	30	4	28	5.6%	0.21 [0.02 , 1.98]
Badawy 2006	27	404	29	400	37.8%	0.92 [0.53 , 1.58]
Battaglia 1999	3	17	0	17	0.6%	8.45 [0.40 , 177.29]
Battaglia 2002	0	18	0	19		Not estimable
Behrouzi 2017	1	52	0	54	0.7%	3.17 [0.13 , 79.71]
Bentov 2014	2	17	0	22	0.5%	7.26 [0.33 , 161.84]
Cicek 2012	0	53	1	50	2.1%	0.31 [0.01 , 7.75]
El Refaeey 2014	2	55	0	55	0.7%	5.19 [0.24 , 110.57]
El Sharkwy 2019b	7	140	2	140	2.6%	3.63 [0.74 , 17.80]
Eryilmaz 2011	1	30	1	30	1.3%	1.00 [0.06 , 16.76]
Espino 2019	0	20	0	10		Not estimable
Fernando 2018	0	120	0	40		Not estimable
Ismail 2014	2	85	4	85	5.4%	0.49 [0.09 , 2.74]
Jahromi 2017	2	40	0	40	0.7%	5.26 [0.24 , 113.11]
Nasr 2010	2	30	4	30	5.2%	0.46 [0.08 , 2.75]
Panti Abubakar 2015	4	100	0	100	0.7%	9.37 [0.50 , 176.43]
Polak de Fried 2013	2	26	2	26	2.6%	1.00 [0.13 , 7.69]
Rizzo 2010	2	32	2	33	2.6%	1.03 [0.14 , 7.81]
Schachter 2007 (1)	7	27	7	28	7.1%	1.05 [0.31 , 3.53]
Schachter 2007 (2)	5	24	7	23	7.9%	0.60 [0.16 , 2.27]
Sen Sharma 2017	1	32	1	30	1.4%	0.94 [0.06 , 15.66]
Tunon 2017	4	60	5	60	6.5%	0.79 [0.20 , 3.08]
Westphal 2006	3	53	1	40	1.5%	2.34 [0.23 , 23.38]
Xu 2018	2	93	2	93	2.7%	1.00 [0.14 , 7.25]
Youssef 2015	5	112	3	106	4.1%	1.60 [0.37 , 6.89]
Subtotal (95% CI)		**1670**		**1559**	**100.0%**	**1.13 [0.82 , 1.55]**
Total events:	85		75			
Heterogeneity: Chi² = 16.48, df = 21 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.9.2 Multiple pregnancy						
Badawy 2006	8	404	12	400	31.1%	0.65 [0.26 , 1.62]
Behrouzi 2017	1	52	0	54	1.3%	3.17 [0.13 , 79.71]
El Refaeey 2014	1	55	0	55	1.3%	3.06 [0.12 , 76.64]
Ismail 2014	5	85	0	85	1.2%	11.68 [0.64 , 214.68]
Nasr 2010	0	30	0	30		Not estimable
Polak de Fried 2013	3	26	1	26	2.3%	3.26 [0.32 , 33.61]
Salehpour 2012	1	90	2	90	5.2%	0.49 [0.04 , 5.55]
Xu 2018	4	93	3	93	7.6%	1.35 [0.29 , 6.20]
Youssef 2015	18	112	22	106	50.0%	0.73 [0.37 , 1.46]
Subtotal (95% CI)		**947**		**939**	**100.0%**	**1.00 [0.63 , 1.56]**
Total events:	41		40			
Heterogeneity: Chi² = 6.78, df = 7 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
1.9.3 Gastrointestinal disturbances						
Ismail 2014	4	85	2	85	42.7%	2.05 [0.37 , 11.50]
Maged 2015	0	40	1	40	33.2%	0.33 [0.01 , 8.22]
Westphal 2006	3	53	1	40	24.1%	2.34 [0.23 , 23.38]
Subtotal (95% CI)		**178**		**165**	**100.0%**	**1.55 [0.47 , 5.10]**
Total events:	7		4			
Heterogeneity: Chi² = 1.12, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.9.4 Ectopic pregnancy						
Agrawal 2012	1	30	0	28	20.1%	2.90 [0.11 , 74.13]
Behrouzi 2017	1	52	0	54	19.5%	3.17 [0.13 , 79.71]
Fernando 2018 (3)	0	120	0	40		Not estimable

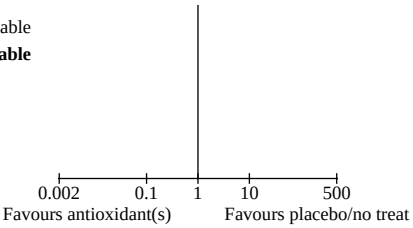
Analysis 1.9. (Continued)

Behrouzi 2017	1	52	0	54	19.5%	3.17 [0.13 , 79.71]	
Fernando 2018 (3)	0	120	0	40		Not estimable	
Jahromi 2017	0	40	1	40	60.5%	0.33 [0.01 , 8.22]	
Subtotal (95% CI)		**242**		**162**	**100.0%**	**1.40 [0.27 , 7.20]**	
Total events:	2		1				
Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.40 (P = 0.69)							
1.9.5 Headache							
Fernando 2018	54	120	20	40	94.4%	0.82 [0.40 , 1.68]	
Ismail 2014	2	85	1	85	5.6%	2.02 [0.18 , 22.75]	
Subtotal (95% CI)		**205**		**125**	**100.0%**	**0.89 [0.45 , 1.75]**	
Total events:	56		21				
Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
1.9.6 Congenital (missing kidney)							
Fernando 2018 (4)	1	120	0	40	100.0%	1.02 [0.04 , 25.46]	
Subtotal (95% CI)		**120**		**40**	**100.0%**	**1.02 [0.04 , 25.46]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.01 (P = 0.99)							
1.9.7 Low birth weight < 2.500 g							
Fernando 2018 (3)	0	120	1	40	100.0%	0.11 [0.00 , 2.74]	
Subtotal (95% CI)		**120**		**40**	**100.0%**	**0.11 [0.00 , 2.74]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
1.9.8 Preterm birth							
Fernando 2018 (5)	2	120	0	40	43.1%	1.71 [0.08 , 36.35]	
Nasr 2010	1	30	1	30	56.9%	1.00 [0.06 , 16.76]	
Subtotal (95% CI)		**150**		**70**	**100.0%**	**1.31 [0.17 , 9.93]**	
Total events:	3		1				
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%							
Test for overall effect: Z = 0.26 (P = 0.80)							
1.9.9 Placenta praevia							
Fernando 2018 (6)	1	120	0	40	100.0%	1.02 [0.04 , 25.46]	
Subtotal (95% CI)		**120**		**40**	**100.0%**	**1.02 [0.04 , 25.46]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.01 (P = 0.99)							
1.9.10 Pre-eclampsia							
Fernando 2018 (7)	2	120	0	40	100.0%	1.71 [0.08 , 36.35]	
Subtotal (95% CI)		**120**		**40**	**100.0%**	**1.71 [0.08 , 36.35]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
1.9.11 Fatigue							
Fernando 2018	34	120	7	40	100.0%	1.86 [0.75 , 4.62]	
Subtotal (95% CI)		**120**		**40**	**100.0%**	**1.86 [0.75 , 4.62]**	
Total events:	34		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
1.9.12 Ovarian hyperstimulation syndrome (OHSS)							
Rizk 2005	0	75	0	75		Not estimable	
Subtotal (95% CI)		**75**		**75**		**Not estimable**	



Analysis 1.9. (Continued)

Rizk 2005	0	75	0	75	Not estimable
Subtotal (95% CI)		**75**		**75**	**Not estimable**
Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Footnotes

(1) Vitamin B complex plus metformin versus metformin (no treatment)
(2) Vitamin B complex versus no treatment
(3) 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups and the placebo have been combined
(4) The missing kidney was in the 2 mg melatonin group. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active gro
(5) Births between 34 and 37 weeks were in the 2 mg and 8 mg melatonin group. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total nu
(6) Placenta praevia was in the 2 mg melatonin group. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active groups
(7) Pre-eclampsia was in the 4 mg and 8 mg melatonin arms. 3 active arms; melatonin 2 mg, 4 mg, 8 mg arms versus placebo, the events and total numbers for the active

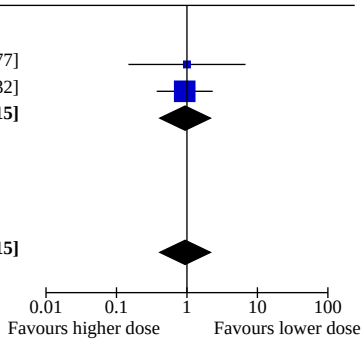
Comparison 2. Head-to-head antioxidants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth; type of antioxidant (natural conceptions and undergoing fertility treatments)	2	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.15]
2.1.1 Melatonin lower dose versus melatonin higher dose	2	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.15]
2.2 Live Birth; indications for subfertility	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 Unexplained subfertility	1	20	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.77]
2.2.2 Varying Indications	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.32]
2.3 Live Birth; IVF/ICSI	2	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.15]
2.4 Clinical pregnancy; type of antioxidant (natural conceptions and undergoing fertility treatments)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 N-acetylcysteine versus L-carnitine	1	164	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.33, 2.00]
2.4.2 Melatonin lower dose versus melatonin higher dose	2	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.15]
2.5 Clinical pregnancy; indications for subfertility	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.5.1 Polycystic ovary syndrome	1	164	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.33, 2.00]
2.5.2 Unexplained subfertility	1	20	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.77]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.5.3 Varying indications	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.32]
2.6 Clinical pregnancy; IVF/ICSI	2	140	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.41, 2.15]
2.7 Adverse events	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 Miscarriage	3	304	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.42, 5.67]
2.7.2 Ectopic pregnancy	1	120	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.7.3 Congenital (missing kidney)	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.06, 38.36]
2.7.4 Low birth weight < 2.500 g	1	120	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.7.5 Birth between 34 and 37 weeks	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.03, 8.10]
2.7.6 Placenta praevia	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.06, 38.36]
2.7.7 Pre-eclampsia	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.03, 8.10]

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

Study or Subgroup	Melatonin lower dose Events	Total	Melatonin higher dose Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Melatonin lower dose versus melatonin higher dose						
Espino 2019 (1)	3	10	3	10	18.2%	1.00 [0.15 , 6.77]
Fernando 2018 (2)	17	80	9	40	81.8%	0.93 [0.37 , 2.32]
Subtotal (95% CI)		**90**		**50**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	20		12			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**90**		**50**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	20		12			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Not applicable						



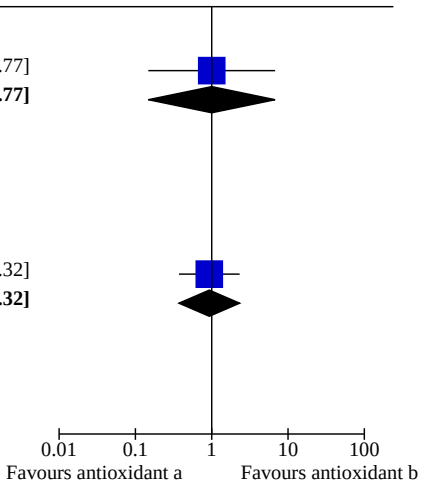
Footnotes

(1) 3mg melatonin vs 6mg. Low risk for blinding here but high risk for the melatonin vs no treatment comparison

(2) Numbers in the melatonin arms 2mg and 4mg were combined versus 8mg

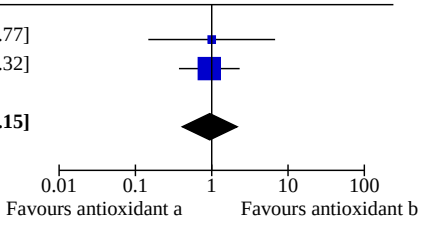
Analysis 2.2. Comparison 2: Head-to-head antioxidants, Outcome 2: Live Birth; indications for subfertility

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Unexplained subfertility						
Espino 2019	3	10	3	10	100.0%	1.00 [0.15 , 6.77]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**1.00 [0.15 , 6.77]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.2.2 Varying Indications						
Fernando 2018	17	80	9	40	100.0%	0.93 [0.37 , 2.32]
Subtotal (95% CI)		**80**		**40**	**100.0%**	**0.93 [0.37 , 2.32]**
Total events:	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



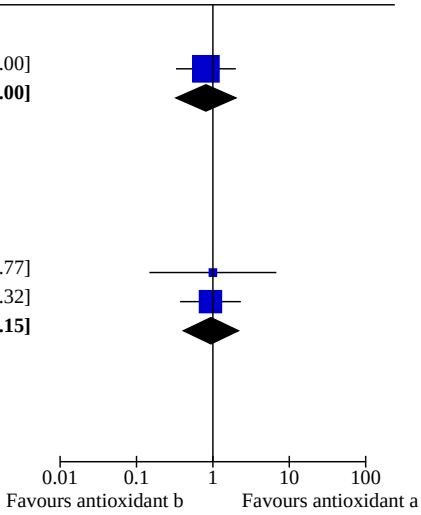
Analysis 2.3. Comparison 2: Head-to-head antioxidants, Outcome 3: Live Birth; IVF/ICSI

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Espino 2019	3	10	3	10	18.2%	1.00 [0.15 , 6.77]
Fernando 2018	17	80	9	40	81.8%	0.93 [0.37 , 2.32]
Total (95% CI)		**90**		**50**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	20		12			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
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)

Study or Subgroup	Antioxidant a Events	Total	Antioxidant b Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 N-acetylcysteine versus L-carnitine						
El Sharkwy 2019a (1)	10	82	12	82	100.0%	0.81 [0.33 , 2.00]
Subtotal (95% CI)		**82**		**82**	**100.0%**	**0.81 [0.33 , 2.00]**
Total events:	10		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
2.4.2 Melatonin lower dose versus melatonin higher dose						
Espino 2019 (2)	3	10	3	10	18.2%	1.00 [0.15 , 6.77]
Fernando 2018 (3)	17	80	9	40	81.8%	0.93 [0.37 , 2.32]
Subtotal (95% CI)		**90**		**50**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	20		12			
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.81), I^2 = 0%						



Footnotes

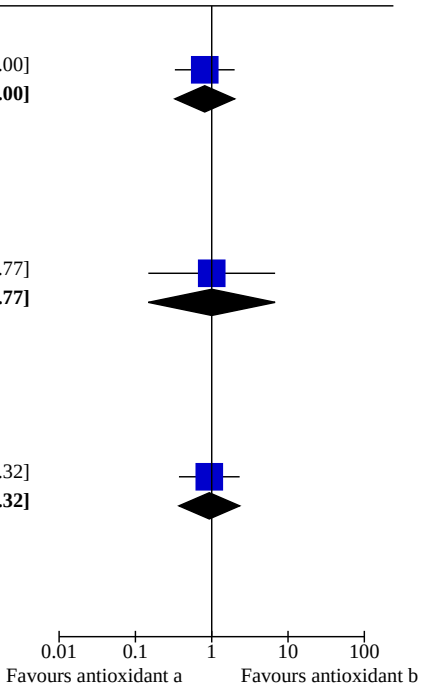
(1) CC plus 600 mg N-acetylcysteine + placebo versus CC plus 3 g of oral l-carnitine + placebo (OI)

(2) Melatonin 3 mg versus 6 mg

(3) Numbers in the melatonin arms 2 mg and 4 mg were combined versus 8 mg

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

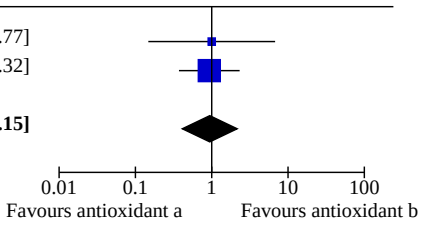
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.5.1 Polycystic ovary syndrome						
El Sharkwy 2019a	10	82	12	82	100.0%	0.81 [0.33 , 2.00]
Subtotal (95% CI)		**82**		**82**	**100.0%**	**0.81 [0.33 , 2.00]**
Total events:	10		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
2.5.2 Unexplained subfertility						
Espino 2019	3	10	3	10	100.0%	1.00 [0.15 , 6.77]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**1.00 [0.15 , 6.77]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.5.3 Varying indications						
Fernando 2018	17	80	9	40	100.0%	0.93 [0.37 , 2.32]
Subtotal (95% CI)		**80**		**40**	**100.0%**	**0.93 [0.37 , 2.32]**
Total events:	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Chi^2 = 0.06, df = 2 (P = 0.97), I^2 = 0%						



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

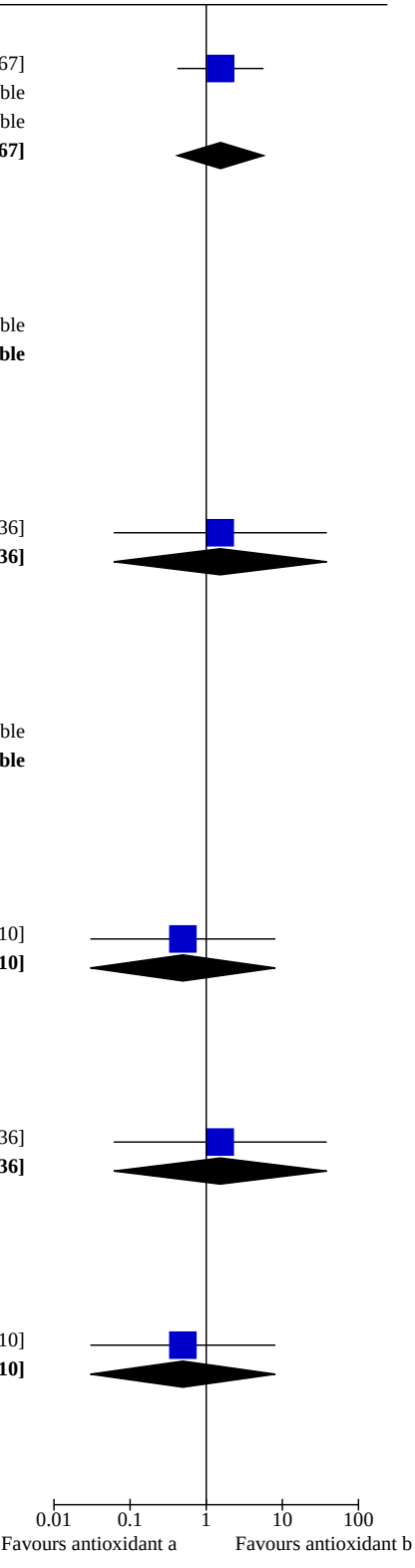
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Espino 2019	3	10	3	10	18.2%	1.00 [0.15 , 6.77]
Fernando 2018	17	80	9	40	81.8%	0.93 [0.37 , 2.32]
Total (95% CI)		**90**		**50**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	20		12			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



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

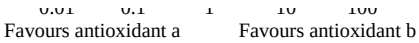
Study or Subgroup	Antioxidant a Events	Total	Antioxidant b Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.7.1 Miscarriage						
El Sharkwy 2019a (1)	6	82	4	82	100.0%	1.54 [0.42 , 5.67]
Espino 2019 (2)	0	10	0	10		Not estimable
Fernando 2018 (3)	0	80	0	40		Not estimable
Subtotal (95% CI)		**172**		**132**	**100.0%**	**1.54 [0.42 , 5.67]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.7.2 Ectopic pregnancy						
Fernando 2018	0	80	0	40		Not estimable
Subtotal (95% CI)		**80**		**40**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.7.3 Congenital (missing kidney)						
Fernando 2018	1	80	0	40	100.0%	1.53 [0.06 , 38.36]
Subtotal (95% CI)		**80**		**40**	**100.0%**	**1.53 [0.06 , 38.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.7.4 Low birth weight < 2.500 g						
Fernando 2018	0	80	0	40		Not estimable
Subtotal (95% CI)		**80**		**40**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.7.5 Birth between 34 and 37 weeks						
Fernando 2018	1	80	1	40	100.0%	0.49 [0.03 , 8.10]
Subtotal (95% CI)		**80**		**40**	**100.0%**	**0.49 [0.03 , 8.10]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
2.7.6 Placenta praevia						
Fernando 2018	1	80	0	40	100.0%	1.53 [0.06 , 38.36]
Subtotal (95% CI)		**80**		**40**	**100.0%**	**1.53 [0.06 , 38.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.7.7 Pre-eclampsia						
Fernando 2018	1	80	1	40	100.0%	0.49 [0.03 , 8.10]
Subtotal (95% CI)		**80**		**40**	**100.0%**	**0.49 [0.03 , 8.10]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						



Footnotes

(1) Antioxidant 'a' is NAC versus Antioxidant 'b' L-carnitine

Analysis 2.7. (Continued)



Footnotes
(1) Antioxidant 'a' is NAC versus Antioxidant 'b' L-carnitine
(2) Melatonin 3 mg versus 6 mg
(3) Numbers in the melatonin arms 2mg and 4mg combined versus melatonin 8mg

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 92 women enrolled in this trial declared a desire to become pregnant
Clinical pregnancy rate; folic acid + placebo	1/19	-
Miscarriage rate; myo-inositol + folic acid	Miscarriage reported, but unknown whether 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
Mier-Cabrera 2008	0/16 (vitamins C + E), at follow-up over 9 months 3/16	0/18 (placebo), at follow-up over 9 months 2/18
Mohammadbeigi 2012	9/22 (vitamin D)	7/22 (placebo)
Razavi 2015	6/32 (selenium)	1/32 (placebo)
Al-Alousi 2018	20/60 (omega)	15/58 (placebo)
Ghomian 2019	7/33 (NAC + CC)	5/33 (CC)
Heidar 2019	6/20 (selenium)	5/20 (placebo)
Siavashani 2018	5/20 (chromium)	4/20 (placebo)
Schillaci 2012	0/6 (myo-inositol + 200 µg folic acid twice a day)	0/6 (400 µg folic acid once a day)

CC: clomiphene citrate; NAC: *N*-acetylcysteine

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register search strategy

PROCITE platform

Searched 12 September 2019

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"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"

(529 records)

Appendix 2. Cochrane CENTRAL Register of Studies Online (CRSO)

Web platform

Searched 12 September 2019

#1 MESH DESCRIPTOR Antioxidants EXPLODE ALL TREES 14668
#2 MESH DESCRIPTOR free radical scavengers EXPLODE ALL TREES 4969
#3 (antioxidant* or radical scavenger*):TI,AB,KY 11407
#4 MESH DESCRIPTOR Vitamins EXPLODE ALL TREES 17099
#5 MESH DESCRIPTOR Ascorbic Acid EXPLODE ALL TREES 2104
#6 vitamin*:TI,AB,KY 27018
#7 (zinc or selenium):TI,AB,KY 8015
#8 (Glutathione* or folate):TI,AB,KY 5278
#9 (ubiquin* or folic acid):TI,AB,KY 4764
#10 (coenzyme q10):TI,AB,KY 795
#11 MESH DESCRIPTOR Acetylcarnitine EXPLODE ALL TREES 119
#12 MESH DESCRIPTOR Carnitine EXPLODE ALL TREES 586
#13 (carnitine* or carotenoid):TI,AB,KY 2146
#14 (astaxanthin* or lycopene):TI,AB,KY 736
#15 multivitamin*:TI,AB,KY 1083
#16 (ascorbic acid):TI,AB,KY 3505
#17 n-acetylcysteine:TI,AB,KY 1464
#18 MESH DESCRIPTOR Acetylcysteine EXPLODE ALL TREES 959
#19 MESH DESCRIPTOR alpha-Tocopherol EXPLODE ALL TREES 546
#20 alpha-tocopherol:TI,AB,KY 2320
#21 (fish adj2 oil*):TI,AB,KY 2718
#22 omega:TI,AB,KY 5664
#23 MESH DESCRIPTOR Fish Oils EXPLODE ALL TREES 3136
#24 (fatty acid*):TI,AB,KY 15640
#25 l-arginine:TI,AB,KY 1345
#26 (n acetyl cysteine):TI,AB,KY 372
#27 melatonin:TI,AB,KY 2372
#28 (dietary supplement*):TI,AB,KY 12103
#29 MESH DESCRIPTOR Dietary Supplements EXPLODE ALL TREES 11121
#30 (nutritional supplement*):TI,AB,KY 2241
#31 micronutrient*:TI,AB,KY 2343
#32 Nutraceutical*:TI,AB,KY 507
#33 (myoinositol or mesoinositol or Inositol):TI,AB,KY 706

#34 MESH DESCRIPTOR Inositol EXPLODE ALL TREES 413
#35 MESH DESCRIPTOR Pentoxifylline EXPLODE ALL TREES 535
#36 Pentoxifylline:TI,AB,KY 1133
#37 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 85690
#38 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 1058
#39 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 1997
#40 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES 525
#41 (embryo* adj2 transfer*):TI,AB,KY 3717
#42 (vitro fertili?ation):TI,AB,KY 3231
#43 ivf:TI,AB,KY 5281
#44 icsi:TI,AB,KY 2536
#45 (intracytoplasmic sperm injection*):TI,AB,KY 1833
#46 (blastocyst* adj2 transfer*):TI,AB,KY 379
#47 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 3062
#48 (assisted reproduct*):TI,AB,KY 1349
#49 (artificial insemination):TI,AB,KY 242
#50 MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES 358
#51 IUI:TI,AB,KY 839
#52 (intrauterine insemination*):TI,AB,KY 952
#53 (ovulation induc*):TI,AB,KY 2494
#54 (ovar* adj2 stimulat*):TI,AB,KY 2106
#55 superovulat*:TI,AB,KY 213
#56 (ovarian hyperstimulation):TI,AB,KY 1345
#57 COH:TI,AB,KY 385
#58 infertil*:TI,AB,KY 7867
#59 subfertil*:TI,AB,KY 888
#60 (ovar* adj2 induction):TI,AB,KY 231
#61 #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 14082
#62 #37 AND #61 798

Appendix 3. MEDLINE search strategy

OVID platform

Searched from 1946 to 12 September 2019

1 exp antioxidants/ or free radical scavengers/ (450779)
2 (antioxidant$ or radical scavengers).tw. (187413)
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/ (333915)
4 vitamin$.tw. (199584)
5 exp Zinc/ (58586)
6 (zinc or selenium).tw. (133593)
7 exp Selenium/ (20073)
8 exp Glutathione Peroxidase/ or exp folic acid/ (55638)
9 (Glutathione$ or folate).tw. (145559)
10 exp Ubiquinone/ (8918)
11 (ubiquin$ or folic acid).tw. (27862)
12 coenzyme q10.tw. (3284)
13 exp Carnitine/ (9416)
14 (carnitine$ or carotenoid$).tw. (33590)
15 (astaxanthin$ or lycopene$).tw. (6542)
16 multivitamin$.tw. (3648)
17 (betacarotene$ or beta carotene$).tw. (13423)
18 ascorbic acid.tw. (30335)
19 n-acetylcysteine.tw. (10906)
20 exp Acetylcysteine/ (12772)
21 alpha-tocopherol$.tw. (15310)
22 (fish adj2 oil$).tw. (10343)
23 omega$.tw. (49466)
24 exp fatty acids/ or exp fish oils/ or exp cod liver oil/ or exp fatty acids, omega-3/ or exp plant oils/ (472246)

25 fatty acid$.tw. (203789)
26 (plant adj4 oil$).tw. (2856)
27 l-arginine$.tw. (33412)
28 (flavonoid$ or Quercetin).tw. (48080)
29 exp Flavonoids/ (107908)
30 riboflavin$.tw. (9909)
31 pycnogenol$.tw. (384)
32 lutein$.tw. (37948)
33 lipoic acid$.tw. (4356)
34 n acetyl cysteine.tw. (3417)
35 melatonin.tw. (23152)
36 dietary supplement$.tw. (17596)
37 nutritional supplement$.tw. (5939)
38 micronutrient$.tw. (14121)
39 Nutraceuticals$.tw. (2640)
40 exp Chromium/ or chromium.tw. or chromax.tw. (34790)
41 (myoinositol or mesoinositol or Inositol).tw. (36790)
42 exp Inositol/ (22811)
43 exp Pentoxifylline/ or Pentoxifylline$.tw. (5203)
44 or/1-43 (1789053)
45 exp Infertility, Female/ (27850)
46 female$ subfertil$.tw. (83)
47 female$ infertilit$.tw. (1599)
48 (subfertil$ adj5 women).tw. (585)
49 (infertil$ adj5 women).tw. (8464)
50 female$ fertility.tw. (2144)
51 (in vitro fertilisation or intracytoplasmic sperm injection$).tw. (8444)
52 intrauterine insemination$.tw. (2418)
53 (ivf or icsi or iui).tw. (27383)
54 in vitro fertilization.tw. (20500)
55 ART.tw. (93602)
56 Assisted reproducti$.tw. (14069)
57 ovulation induction.tw. (3491)
58 ovarian hyperstimulation.tw. (4914)
59 or/45-58 (165914)
60 randomized controlled trial.pt. (489083)
61 controlled clinical trial.pt. (93275)
62 randomized.ab. (454403)
63 placebo.tw. (206202)
64 clinical trials as topic.sh. (188281)
65 randomly.ab. (318000)
66 trial.ti. (204626)
67 (crossover or cross-over or cross over).tw. (81635)
68 or/60-67 (1267341)
69 (animals not (humans and animals)).sh. (4584154)
70 68 not 69 (1164369)
71 44 and 59 and 70 (865)

Appendix 4. Embase search strategy

OVID platform

Searched from 1980 to 12 September 2019

1 exp antioxidants/ or free radical scavengers/ (201452)
2 (antioxidant$ or radical scavengers).tw. (244217)
3 vitamin$.tw. (237423)
4 exp vitamin/ or exp ascorbic acid/ or exp carotenoid/ or exp tocopherol/ (573159)
5 exp Zinc/ (100860)
6 (zinc or selenium).tw. (147362)
7 exp Selenium/ (35153)
8 exp chromium picolinate/ or Chromium.tw. or chromax.tw. (25942)
9 exp Glutathione Peroxidase/ or exp folic acid/ (93347)

10 (Glutathione$ or folate).tw. (168513)
11 exp Ubiquinone/ (7145)
12 (ubiquin$ or folic acid).tw. (31265)
13 coenzyme q10.tw. (4641)
14 exp Carnitine/ (14458)
15 (carnitine$ or carotenoid$).tw. (37897)
16 (astaxanthin$ or lycopene$).tw. (7735)
17 multivitamin$.tw. (4983)
18 (betacarotene$ or beta carotene$).tw. (15246)
19 ascorbic acid.tw. (31529)
20 n-acetylcysteine.tw. (14087)
21 exp acetylcysteine/ (34238)
22 n-acetyl-cysteine.tw. (4679)
23 alpha-tocopherol$.tw. (16240)
24 (fish adj2 oil$).tw. (13130)
25 omega$.tw. (50193)
26 fatty acid$.tw. (226006)
27 exp edible oil/ or exp castor oil/ or exp cod liver oil/ or exp fish oil/ or exp lyprinol/ or exp olive oil/ or exp safflower oil/ or exp fatty acid/ or exp essential fatty acid/ or exp arachidonic acid/ or exp linoleic acid/ or exp linolenic acid/ or exp gamma linolenic acid/ or exp unsaturated fatty acid/ or exp omega 3 fatty acid/ or exp omega 6 fatty acid/ or exp polyunsaturated fatty acid/ (553010)
28 (plant adj4 oil$).tw. (3955)
29 l-arginine$.tw. (37405)
30 (flavonoid$ or Quercetin).tw. (67755)
31 riboflavin$.tw. (9540)
32 pycnogenol$.tw. (491)
33 lipoic acid$.tw. (5383)
34 melatonin.tw. (28312)
35 dietary supplement$.tw. (21900)
36 micronutrient$.tw. (18636)
37 nutritional supplement$.tw. (8229)
38 Nutraceutical$.tw. (7566)
39 exp inositol/ (10942)
40 (Inositol or mesoinositol or myoinositol).tw. (39887)
41 exp Pentoxifylline/ or Pentoxifylline$.tw. (13513)
42 or/1-41 (1914706)
43 exp Infertility, Female/ (41066)
44 (female$ adj2 subfertil$).tw. (219)
45 (female$ adj2 infertilit$).tw. (2861)
46 (subfertil$ adj2 women).tw. (741)
47 (infertil$ adj2 women).tw. (9098)
48 (female$ adj2 fertility).tw. (3341)
49 (vitro fertilisation or intracytoplasmic sperm injection$).tw. (11556)
50 (intrauterine adj3 insemination$).tw. (3737)
51 (ivf or icsi or iui).tw. (47478)
52 vitro fertilization.tw. (26672)
53 Artificial reproduc$ technique$.tw. (204)
54 Assisted reproducti$.tw. (21695)
55 exp artificial insemination/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ or exp intrauterine insemination/ (77680)
56 exp Superovulation/ (2788)
57 Superovulation.tw. (2305)
58 or/43-57 (144258)
59 Clinical Trial/ (952533)
60 Randomized Controlled Trial/ (565068)
61 exp randomization/ (84159)
62 Single Blind Procedure/ (36462)
63 Double Blind Procedure/ (162252)
64 Crossover Procedure/ (60492)
65 Placebo/ (327459)
66 Randomi?ed controlled trial$.tw. (210783)
67 Rct.tw. (33803)
68 random allocation.tw. (1909)

69 randomly allocated.tw. (33204)
70 allocated randomly.tw. (2474)
71 (allocated adj2 random).tw. (809)
72 Single blind$.tw. (23300)
73 Double blind$.tw. (195064)
74 ((treble or triple) adj blind$).tw. (1005)
75 placebo$.tw. (290276)
76 prospective study/ (548416)
77 or/59-76 (2077888)
78 case study/ (64016)
79 case report.tw. (380889)
80 abstract report/ or letter/ (1072000)
81 or/78-80 (1507016)
82 77 not 81 (2026320)
83 42 and 58 and 82 (1562)

Appendix 5. PsycINFO search strategy

OVID platform

Searched from 1806 to 12 September 2019

1 exp Antioxidants/ (2646)
2 (antioxidant$ or radical scavengers).tw. (5404)
3 exp Vitamins/ (4662)
4 vitamin$.tw. (7099)
5 exp Zinc/ (816)
6 (zinc or selenium).tw. (2421)
7 (Glutathione$ or folate).tw. (3760)
8 (ubiquin$ or folic acid).tw. (870)
9 (coenzyme q10 or chromium).tw. (328)
10 (carnitine$ or carotenoid$).tw. (791)
11 multivitamin$.tw. (241)
12 (betacarotene$ or beta carotene$).tw. (146)
13 ascorbic acid.tw. (428)
14 n-acetylcysteine.tw. (417)
15 alpha-tocopherol$.tw. (226)
16 (fish adj2 oil$).tw. (307)
17 omega$.tw. (2730)
18 exp Fatty Acids/ (4830)
19 fatty acid$.tw. (4449)
20 l-arginine$.tw. (1109)
21 melatonin.tw. (4582)
22 dietary supplement$.tw. (991)
23 nutritional supplement$.tw. (579)
24 micronutrient$.tw. (626)
25 Nutraceuticals$.tw. (107)
26 (Pentoxifylline or myoinositol or inositol).tw. (1693)
27 or/1-26 (34273)
28 exp Infertility/ (2093)
29 (female$ adj2 subfertil$).tw. (2)
30 (female$ adj2 infertil$).tw. (210)
31 (subfertil$ adj2 women).tw. (8)
32 (infertil$ adj2 women).tw. (464)
33 female$ fertility.tw. (151)
34 (vitro fertilisation or intracytoplasmic sperm injection$).tw. (165)
35 intrauterine insemination$.tw. (27)
36 (ivf or icsi or iui).tw. (604)
37 vitro fertilization.tw. (654)
38 Artificial reproduc$ technique$.tw. (15)
39 Assisted reproducti$.tw. (925)
40 or/28-39 (3533)
41 27 and 40 (31)

Appendix 6. AMED search strategy

OVID platform

Searched from 1985 to 12 September 2019

1 exp Antioxidants/ or exp Free radicals/ (2511)
2 (antioxidant$ or radical scavengers).tw. (3507)
3 exp Vitamins/ or exp Dietary supplements/ (4384)
4 exp Ascorbic acid/ (308)
5 vitamin$.tw. (2623)
6 exp Zinc/ (126)
7 (zinc or selenium).tw. (505)
8 (Glutathione$ or folate).tw. (877)
9 exp Selenium/ (106)
10 (ubiquin$ or folic acid).tw. (190)
11 coenzyme q10.tw. (88)
12 exp Carnitine/ (20)
13 chromium.tw. (91)
14 (carnitine$ or carotenoid$).tw. (237)
15 multivitamin$.tw. (70)
16 ascorbic acid.tw. (519)
17 n-acetylcysteine.tw. (35)
18 Acetylcysteine.tw. (37)
19 alpha-tocopherol$.tw. (91)
20 (fish adj2 oil$).tw. (193)
21 omega$.tw. (280)
22 exp Fatty acids/ (651)
23 exp Fish oils/ (118)
24 fatty acid$.tw. (977)
25 (plant adj4 oil$).tw. (1089)
26 l-arginine$.tw. (142)
27 (flavonoid$ or Quercetin).tw. (1920)
28 riboflavin$.tw. (24)
29 pycnogenol$.tw. (18)
30 micronutrient$.tw. (126)
31 nutriceutical$.tw. (10)
32 dietary supplement$.tw. (1841)
33 Pentoxifylline$.tw. (12)
34 (myoinositol or inositol).tw. (58)
35 melatonin.tw. (119)
36 or/1-35 (11918)
37 exp Infertility female/ (203)
38 (female$ adj3 subfertil$).tw. (0)
39 (female$ adj3 infertil$).tw. (211)
40 (subfertil$ adj3 women).tw. (2)
41 (infertil$ adj3 women).tw. (41)
42 female$ fertility.tw. (8)
43 (vitro fertilisation or intracytoplasmic sperm injection$).tw. (24)
44 intrauterine insemination$.tw. (7)
45 (ivf or icsi or iui).tw. (50)
46 in vitro fertilization.tw. (28)
47 assisted reproduct$ techn$.tw. (23)
48 or/37-47 (264)
49 36 and 48 (5)

Appendix 7. CINAHL search strategy

EBSCO platform

Searched from 1961 to 12 September 2019

S63 S50 AND S62 96

S62 S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 1,348,929
S61 TX allocat* random* 10,957
S60 (MH "Quantitative Studies") 23,242
S59 (MH "Placebos") 11,447
S58 TX placebo* 58,990
S57 TX random* allocat* 10,957
S56 (MH "Random Assignment") 56,426
S55 TX randomi* control* trial* 174,871
S54 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*)) 1,031,287
S53 TX clinic* n1 trial* 250,249
S52 PT Clinical trial 86,854
S51 (MH "Clinical Trials+") 266,333
S50 S26 AND S49 375
S49 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 15,649
S48 TX intra-uterine insemination 29
S47 TX natural cycle* 363
S46 TX timed intercourse 38
S45 TX (ovari* N2 induction) 34
S44 TX COH 232
S43 TX ovarian hyperstimulation 808
S42 TX superovulat* 82
S41 TX ovulation induc* 1,720
S40 TX intrauterine insemination 461
S39 TX IUI 335
S38 TX artificial insemination 769
S37 TX assisted reproduct* 3,692
S36 (MM "Insemination, Artificial") 428
S35 (MM "Reproduction Techniques+") 8,754
S34 TX intracytoplasmic sperm injection* 864
S33 TX embryo* N3 transfer* 2,981
S32 TX ovar* N3 hyperstimulat* 813
S31 TX ovari* N3 stimulat* 968
S30 TX IVF or TX ICSI 4,829
S29 (MM "Fertilization in Vitro") 3,357
S28 TX vitro fertilization 6,786
S27 TX vitro fertilisation 6,786
S26 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 160,786
S25 TX Nutraceutical* 1,625
S24 TX micronutrient* 6,074
S23 TX nutritional supplement* 2,855
S22 TX dietary supplement* 39,500
S21 TX melatonin 3,042
S20 TX n acetyl cysteine 472
S19 TX l-arginine 1,681
S18 TX (fish N2 oil*) 4,039
S17 (MH "Acetylcysteine") 1,450
S16 TX n-acetylcysteine 1,204
S15 TX ascorbic acid 5,628
S14 TX multivitamin* 1,563
S13 TX(astaxanthin* or lycopene*) 1,286
S12 TX (carnitine* or carotenoid*) 4,485
S11 (MM "Carnitine") 665
S10 TX coenzyme q10 645
S9 TX (ubiquin* or folic acid) 8,278
S8 TX (zinc or selenium) 10,413
S7 TX omega$ 2,692
S6 TX fatty acid* 27,131
S5 (MH "Fatty Acids, Omega 3") OR (MH "Fatty Acids, Unsaturated+") 23,362
S4 TX vitamin* 53,224

S3 (MH "Vitamins+") 47,086
S2 TX antioxidant* 27,638
S1 (MM "Antioxidants+") 9,064

Appendix 8. Search strategies for The WHO portal (ICTRP), clinicaltrials.gov, Google, DARE, Web of Knowledge and OpenGrey

Web platforms

Searched 12 September 2019

'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'

WHAT'S NEW

Date	Event	Description
28 May 2020	New search has been performed	We have removed from the review studies looking at myo-inositol for women with polycystic ovary syndrome, as they are now included in another published Cochrane Review (Showell 2018) (Ciotta 2012; Papaleo 2008; Raffone 2010). We moved four formerly-included pentoxifylline studies to excluded studies, as pentoxifylline is a prescription drug rather than an over-the-counter antioxidant supplement (Alborzi 2007; Aleyasin 2009; Balasch 1997; Creus 2008).
28 May 2020	New citation required and conclusions have changed	The removal of pentoxifylline studies, and those of myo-inositol in women with polycystic ovary syndrome, and the addition of new studies has led to a change in the conclusions of this review.

HISTORY

Protocol first published: Issue 2, 2009
Review first published: Issue 8, 2013

Date	Event	Description
16 October 2017	Amended	Some references updated and corrected
28 June 2017	New citation required and conclusions have changed	With the addition of new studies data now show an association between the use of antioxidants and live birth and clinical pregnancy.
28 June 2017	New search has been performed	Updated. Twenty-three new trials added, making a total of 50 trials now included in this updated review. New studies added:Battaglia 1999; Bentov 2014; Brusco 2013; Carlomagno 2012; Cheraghi 2016; Choi 2012; Colazingari 2013; Daneshbodi 2013; Deeba 2015; El Refaeey 2014; Ismail 2014; Keikha 2010; Lesoine 2016; Maged 2015; Mohammadbeigi 2012; Pacchiarotti 2016; Panti Abubakar 2015; Polak de Fried 2013; Razavi 2015; Rosalbino 2012; Salehpour 2012; Schachter 2007; Valeri 2015.

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.

Rebecca Mackenzie-Proctor assisted with assessing the trials for inclusion, extracted the data, assisted with the data analysis and helped with the writing of the updated review.

Vanessa Jordan assisted with the methodology in the updated review and commented on the drafts.

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

DECLARATIONS OF INTEREST

Roger Hart is the Medical Director of Fertility Specialists of WA and a shareholder in Western IVF. He has received educational sponsorship from Merck Serono and Ferring pharmaceuticals, and is on the medical advisory board of MSD and Ferring Pharmaceuticals.

Rebecca Mackenzie-Proctor: no conflict of interest to declare

Vanessa Jordan: no conflict of interest to declare

Marian Showell: no conflict of interest to declare

SOURCES OF SUPPORT

Internal sources

- NZ GOVT MOH, New Zealand

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After publication of the protocol:

- two of the five protocol authors (Agarwal A, Gupta S) withdrew from involvement in the review.
- we have removed the secondary outcome of stillbirth rate per woman.
- we have removed the exclusion criterion 'Trials that exclusively reported on women who have previously had chemotherapy' as not clinically relevant to this review.
- we have expanded the inclusion criteria for participants to include women undergoing ART. Exclusion criteria now cover trials that enrol exclusively fertile women attending a fertility clinic because of male partner infertility, and women who are Vitamin D-deficient.
- exclusion criteria for interventions now cover 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.
- we have created a separate comparison for pentoxifylline, as we had concerns that this medicine does not have purely antioxidant capabilities.
- we have updated the search strategy.
- we have added two 'Summary of findings' tables.
- where we had data from multi-armed trials, we have pooled the intervention arms versus the control arm. This differs from the protocol, where we said that we would divide the intervention arms. This was done on the advice of a statistician.
- we decided, with clinical advice, that we would treat trials using folic acid (< 1 mg) as a control as assessing standard treatment, and would include them in the 'no treatment' subgroup.

For the 2017 update:

- we have analysed trials that used an antioxidant plus an antioxidant versus the same antioxidants plus placebo/no treatment or standard treatment in the 'Antioxidants versus no treatment' comparison, whereas in the original review they were considered as head-to-head.
- prior to the 2017 update, the effect estimate used was the Peto odds ratio. As this is not recommended as a default approach for meta-analysis unless intervention effects are small (odds ratios close to one) and events are not particularly common (Higgins 2019), we have used the Mantel-Haenszel odds ratio for the 2017 update.

For the 2020 update:

- We removed pentoxifylline from the inclusion criteria on clinical advice, as it was deemed to be a medicine rather than an over-the-counter supplement, and those formerly included trials were excluded.
- The trials that used inositol for subfertile women with polycystic ovary syndrome were removed, as they are now included in a new Cochrane Review on this topic (Showell 2018).
- We have also expanded the exclusion criterion from only vitamin D-deficient women to any vitamin deficiency.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [epidemiology]; Administration, Oral; Antioxidants [*administration & dosage] [adverse effects]; Infertility, Female [*drug therapy]; Live Birth [epidemiology]; Oxidative Stress; Pentoxifylline [adverse effects] [therapeutic use]; Pregnancy Rate; Pregnancy, Multiple; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy