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Antioxidants for male subfertility (Review)

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de Ligny W, Smits RM, Mackenzie-Proctor R, Jordan V, Fleischer K, de Bruin JP, Showell MG.
Antioxidants for male subfertility.
Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD007411.
DOI: 10.1002/14651858.CD007411.pub5.

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[Intervention Review]

Antioxidants for male subfertility

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 5, 2022.

Citation: de Ligny W, Smits RM, Mackenzie-Proctor R, Jordan V, Fleischer K, de Bruin JP, Showell MG.Antioxidants for male subfertility. *Cochrane Database of Systematic Reviews* 2022, Issue 5. Art. No.: CD007411. DOI: 10.1002/14651858.CD007411.pub5.

ABSTRACT

Background

The inability to have children affects 10% to 15% of couples worldwide. A male factor is estimated to account for up to half of the infertility cases with between 25% to 87% of male subfertility considered to be due to the effect of oxidative stress. Oral supplementation with antioxidants is thought to improve sperm quality by reducing oxidative damage. Antioxidants are widely available and inexpensive when compared to other fertility treatments, however most antioxidants are uncontrolled by regulation and the evidence for their effectiveness is uncertain. We compared the benefits and risks of different antioxidants used for male subfertility.

Objectives

To evaluate the effectiveness and safety of supplementary oral antioxidants in subfertile men.

Search methods

The Cochrane Gynaecology and Fertility (CGF) Group trials register, CENTRAL, MEDLINE, Embase, PsycINFO, AMED, and two trial registers were searched on 15 February 2021, together with reference checking and contact with experts in the field to identify additional trials.

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 subfertile men of a couple attending a reproductive clinic. We excluded studies comparing antioxidants with fertility drugs alone and studies that included men with idiopathic infertility and normal semen parameters or fertile men attending a fertility clinic because of female partner infertility.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. The primary review outcome was live birth. Clinical pregnancy, adverse events and sperm parameters were secondary outcomes.

Main results

We included 90 studies with a total population of 10,303 subfertile men, aged between 18 and 65 years, part of a couple who had been referred to a fertility clinic and some of whom were undergoing medically assisted reproduction (MAR). Investigators compared and combined 20 different oral antioxidants. The evidence was of 'low' to 'very low' certainty: the main limitation was that out of the 67 included

studies in the meta-analysis only 20 studies reported clinical pregnancy, and of those 12 reported on live birth. The evidence is current up to February 2021.

Live birth: antioxidants may lead to increased live birth rates (odds ratio (OR) 1.43, 95% confidence interval (CI) 1.07 to 1.91, P = 0.02, 12 RCTs, 1283 men, I^2 = 44%, very low-certainty evidence). Results in the studies contributing to the analysis of live birth rate suggest that if the baseline chance of live birth following placebo or no treatment is assumed to be 16%, the chance following the use of antioxidants is estimated to be between 17% and 27%. However, this result was based on only 246 live births from 1283 couples in 12 small or medium-sized studies. When studies at high risk of bias were removed from the analysis, there was no evidence of increased live birth (Peto OR 1.22, 95% CI 0.85 to 1.75, 827 men, 8 RCTs, P = 0.27, I^2 = 32%).

Clinical pregnancy rate: antioxidants may lead to increased clinical pregnancy rates (OR 1.89, 95% CI 1.45 to 2.47, P < 0.00001, 20 RCTs, 1706 men, I^2 = 3%, low-certainty evidence) compared with placebo or no treatment. This suggests that, in the studies contributing to the analysis of clinical pregnancy, if the baseline chance of clinical pregnancy following placebo or no treatment is assumed to be 15%, the chance following the use of antioxidants is estimated to be between 20% and 30%. This result was based on 327 clinical pregnancies from 1706 couples in 20 small studies.

Adverse events
Miscarriage: only six studies reported on this outcome and the event rate was very low. No evidence of a difference in miscarriage rate was found between the antioxidant and placebo or no treatment group (OR 1.46, 95% CI 0.75 to 2.83, P = 0.27, 6 RCTs, 664 men, I^2 = 35%, very low-certainty evidence). The findings suggest that in a population of subfertile couples, with male factor infertility, with an expected miscarriage rate of 5%, the risk of miscarriage following the use of an antioxidant would be between 4% and 13%.

Gastrointestinal: antioxidants may lead to an increase in mild gastrointestinal discomfort when compared with placebo or no treatment (OR 2.70, 95% CI 1.46 to 4.99, P = 0.002, 16 RCTs, 1355 men, I^2 = 40%, low-certainty evidence). This suggests that if the chance of gastrointestinal discomfort following placebo or no treatment is assumed to be 2%, the chance following the use of antioxidants is estimated to be between 2% and 7%. However, this result was based on a low event rate of 46 out of 1355 men in 16 small or medium-sized studies, and the certainty of the evidence was rated low and heterogeneity was high.

We were unable to draw conclusions from the antioxidant versus antioxidant comparison as insufficient studies compared the same interventions.

Authors' conclusions

In this review, there is very low-certainty evidence from 12 small or medium-sized randomised controlled trials suggesting that antioxidant supplementation in subfertile males may improve live birth rates for couples attending fertility clinics. Low-certainty evidence suggests that clinical pregnancy rates may increase. There is no evidence of increased risk of miscarriage, however antioxidants may give more mild gastrointestinal discomfort, based on very low-certainty evidence. Subfertile couples should be advised that overall, the current evidence is inconclusive based on serious risk of bias due to poor reporting of methods of randomisation, failure to report on the clinical outcomes live birth rate and clinical pregnancy, often unclear or even high attrition, and also imprecision due to often low event rates and small overall sample sizes. Further large well-designed randomised placebo-controlled trials studying infertile men and reporting on pregnancy and live births are still required to clarify the exact role of antioxidants.

PLAIN LANGUAGE SUMMARY

Antioxidants for male subfertility

Review question
Do supplementary oral antioxidants compared with placebo, no treatment or another antioxidant improve fertility outcomes for subfertile men?

Background
A couple may be considered to have fertility problems if they have been trying to conceive for over a year with no success. Many subfertile men undergoing fertility treatment also take dietary supplements in the hope of improving their fertility. Fertility treatment can be a very stressful time for men and their partners. It is important that these couples have access to high-certainty evidence that will allow them to make informed decisions on whether to take a supplemental antioxidant. This is especially important as most antioxidant supplements are uncontrolled by regulation. This review aimed to assess whether supplements with oral antioxidants, taken by subfertile men, would increase the chances of a couple to achieve a (clinical) pregnancy confirmed by ultrasound and ultimately the birth of a baby (live birth). This review did not examine the use of antioxidants in men with normal sperm.

Study characteristics

Cochrane authors conducted a review including 90 randomised controlled trials comparing 18 different antioxidants with placebo, no treatment or another antioxidant in a total population of 10,303 subfertile men. The age range of the participants was 18 to 65 years; they

were part of a couple who had been referred to a fertility clinic and some were undergoing fertility treatment. The evidence is current to February 2021.

Main results

Antioxidants may be associated with an increased live birth and clinical pregnancy rate. Based on the studied population for live birth, we would expect that out of 100 subfertile men not taking antioxidants, 16 couples would have a baby. In subfertile men taking antioxidants, between 17 and 27 per 100 couples would have a baby. If studies with high risk of bias were removed from the analysis, there was no evidence of increased live birth in the population taking antioxidants. In the people who were studied for clinical pregnancy, we would expect that out of 100 subfertile men not taking antioxidants, 15 couples would have a clinical pregnancy. In subfertile men taking antioxidants, between 20 and 30 per 100 couples would have a clinical pregnancy. Adverse events were poorly reported. Only six studies reported miscarriage. In these studies, miscarriage did not occur more often in the group using antioxidants when compared with the group with placebo or no treatment. However, there is insufficient evidence to draw conclusions about antioxidant use and the risk of miscarriage. The use of antioxidants may be associated with more mild stomach discomfort, with a frequency of 2% in subfertile men not taking antioxidants, and between 2% and 7% in men taking antioxidants. The oral supplements may cause discomforts such as nausea or stomach ache.

Authors' conclusion and certainty of the evidence

Antioxidant supplementation taken by subfertile males of a couple attending a fertility clinic may increase the chance of a live birth, however the overall certainty of evidence was very low from only 12 small to medium-sized randomised controlled trials. Low-certainty evidence suggests that clinical pregnancy rates may increase. Overall, there is no evidence of increased risk of miscarriage. Evidence of low certainty suggests that antioxidants may be associated with more gastrointestinal discomfort. Subfertile couples should be advised that overall the current evidence is inconclusive due to the poor reporting of methods, failure to report on live birth and clinical pregnancy rate, imprecision due to low event rates, high number of dropouts and small study group sizes. Large well-designed randomised placebo-controlled trials studying infertile men and reporting on pregnancy and live births are still required to clarify the exact role of antioxidants.

SUMMARY OF FINDINGS

Summary of findings 1. Antioxidants compared to placebo or no treatment for patients with male subfertility

Antioxidants compared to placebo or no treatment for patients with male subfertility

Patient or population: patients with male subfertility
Setting: clinic
Intervention: antioxidants
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with antioxidants				
Live birth rate per couple randomised	162 per 1000	216 per 1000 (171 to 269)	OR 1.43 (1.07 to 1.91)	1283 (12 RCTs)	⊕⊝⊝⊝ VERY LOW [1 2 3]	
Clinical pregnancy rate per couple randomised	146 per 1000	245 per 1000 (199 to 297)	OR 1.89 (1.45 to 2.47)	1706 (20 RCTs)	⊕⊕⊝⊝ LOW [1 3]	
Adverse events - Miscarriage	48 per 1000	68 per 1000 (36 to 125)	OR 1.46 (0.75 to 2.83)	664 (6 RCTs)	⊕⊝⊝⊝ VERY LOW [1 3 4]	
Adverse events - Gastrointestinal	15 per 1000	39 per 1000 (22 to 71)	OR 2.70 (1.46 to 4.99)	1355 (16 RCTs)	⊕⊕⊝⊝ LOW [1 3]	

*__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:** Peto 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.

1 Downgraded one level for serious risk of bias: lack of blinding and incomplete accounting of patients and outcome events
2 Downgraded one level for suspected publication bias based on the funnel plot
3 Downgraded one level for serious imprecision: less than 400 events
4 Downgraded one level for serious imprecision: crossing the line of no effect

BACKGROUND

Description of the condition

It is believed that 48.5 to 186 million people worldwide are affected by the inability to have children (Boivin 2007; Inhorn 2015; Mascarenhas 2012), with delayed conception affecting 10% to 15% of couples trying to conceive (Evers 2002). The International Glossary on Infertility and Fertility Care (Zegers-Hochschild 2017) defines *infertility* as a disease characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected intercourse and is used interchangeably with the term *subfertility* (Zegers-Hochschild 2017). Subfertility generally describes any form or grade of reduced fertility in couples trying to conceive (Gnoth 2005).

In 2010, it was stated in a World Health Organization (WHO) report, based on data from 190 countries (Mascarenhas 2012), that worldwide 1.9% of women trying to conceive were unable to have a first live birth (primary infertility) and 10.5% with a prior live birth were unable to have an additional live birth (secondary infertility). However, the distribution of male and female causes of infertility has not been well-defined. Based on a WHO multicentre study from the 1980s, it is suggested that 20% of cases are solely attributed to the male, 38% to the female, 27% to both, and 15% not clearly to either (Comhaire 1987).

In the literature, it is suggested that a male factor is indeed involved in up to 50% of infertility cases (Irvine 1998; Winters 2014). An epidemiological study in the USA showed a mean prevalence of 17.1% of isolated male factor infertility (infertility exclusively caused by a male factor) and 34.6% of total male factor infertility (infertility exclusively or partially caused by a male factor) (Odisho 2014). The true extent of male infertility is likely to be underestimated due to the lack of male evaluation in infertile couples and the heterogeneity of studies (Barratt 2017; Eisenberg 2013). Oxidative stress (OS) has been commonly investigated and found to play a role in 25% to 87% of male factor subfertility (Aitken 1987; Aitken 1989; Aitken 1992; Iwasaki 1992; Mazzilli 1994; Shekarriz 1995; Zini 1993).

In all cells using oxygen to survive, toxins are produced as a consequence. These toxic end-products are better known as free radicals. Some free radicals are characterised by having higher reactive activity than molecular oxygen, and are therefore called reactive oxygen species (ROS). Excessive production of ROS can lead to cell damage. Therefore, the human body has developed a defence system in which antioxidants play an important role. Antioxidants are capable of reducing the production of free radicals, slowing or preventing the oxidation, and repairing the damage (Mirończuk-Chodakowska 2018).

The increased levels of ROS are thought to be due to either exogenous or endogenous factors. Exogenous factors could be environmental such as high temperatures, pesticides and pollution, or related to lifestyle such as alcohol consumption, smoking, poor nutrition, and obesity. Endogenous factors are infections, chronic disease, autoimmune disease, and in the male reproductive tract the occurrence of leukocytes (white blood cells) and immature spermatozoa, and varicocele (Alvarez 2003; Tremellen 2008).

Spermatozoa are especially vulnerable to ROS due to the lack of cytoplasm containing antioxidants (Aitken 1994; Ebisch 2007). Also, spermatozoal membranes are rich in polyunsaturated fatty acids (PUFAs) which makes them susceptible for lipid peroxidation by ROS, resulting in decreased flexibility of the sperm membrane and reduction of tail motion (Jones 1973).

This means that OS can lead to impaired male fertility firstly by damaging the sperm membrane, thus affecting the sperm motility and ability to break down the oocyte membrane, and secondly by apoptosis and direct alteration of the sperm DNA (Kodama 1997; Lewis 2013). Deceivingly, men with sperm DNA damage can still have normal seminal parameters but have a poor chance of natural conception (Aktan 2013; Intasqui 2015). Sperm DNA damage or integrity can be measured in several ways, either direct or indirect (Agarwal 2017). Direct tests measure the actual DNA strand breaks, and indirect tests measure the susceptibility of the damaged DNA to denaturation or fragmentation.

The most current sperm DNA fragmentation (SDF) tests used are the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL) test, the comet assay, and the sperm chromatin structure assay (SCSA). Other options are measurement of 8-hydroxydeoxyguanosine (8-OHdG), a by-product of DNA oxidation, or chemoluminescence assays.

Multiple studies and meta-analyses show an association between low SDF and clinical pregnancy and live birth rate after intrauterine insemination (IUI), in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment (Bungum 2004; Sugihara 2020; Collins 2008; Evenson 2006; Li 2006; Osman 2015; Zhang 2015; Zhao 2018). However, Cissen and colleagues found that this association does not imply that SDF tests have a predictive value (Cissen 2016). The test used in these studies are heterogenic and most of them are expensive, complex and lack standardisation and validation (Borini 2017; Cissen 2016).

All the above suggests a leading role of OS in the evaluation and management of male factor infertility. Agarwal and colleagues have even proposed the introduction of a novel condition that comprises subfertile men with abnormal semen characteristics and seminal OS: Male Oxidative Stress Infertility (MOSI) (Agarwal 2019). There are also studies suggesting that sperm DNA damage and OS do not exist in male idiopathic infertility (Hughes 1996; Verit 2006).

Description of the intervention

Antioxidants are substances that inhibit or delay the oxidation of biologically-relevant molecules, either by directly scavenging free radicals or by chelation of redox metals (Valko 2006). However, the definition is very general and does not specify how a compound may act as an antioxidant (Huang 2018). Antioxidants can be categorised as enzymatic and non-enzymatic. Enzymatic antioxidants prevent the reaction of ROS with bodily substances and repair cellular damage. Non-enzymatic antioxidants, which include exogenous or dietary antioxidants, act to modify or deactivate ROS (Mirończuk-Chodakowska 2018).

The predominant supplementary antioxidants that are studied in male subfertility clinical trials are carnitines, carotenoids, coenzyme Q10 (ubiquinol), cysteine, the micronutrients folate, selenium and zinc, vitamin C, and vitamin E (Eskenazi 2005; Majzoub 2017). Antioxidants can be administered orally as a

single or combined supplement. They are widely available and inexpensive when compared to other fertility treatments. However, cost-benefit analysis is beyond the scope of this review.

Substances with direct antioxidant action

Arginine
Arginine, or L-arginine, is an amino acid that is required for normal spermatogenesis. It plays a role in the inflammatory response and directly protects against oxidative damage by being a free radical scavenger. Arginine can be derived from meat products, dairy, nuts and seeds. Significant adverse events have not been observed, however arginine is contraindicated for people with a history of genital or oral herpes, asthma or cancer (Appleton 2002).

Carnitines
Carnitine is an antioxidant, with the two most important isomers being called l-carnitine (LC) and its active form l-acetylcarnitine (LAC). In the male genital tract carnitines are found in the epididymis, seminal plasma and in spermatozoa (Bøhmer 1978). Carnitines assist sperm metabolism by positively affecting sperm motility and maturation. There might be an association between the concentration of LAC and male fertility (Agarwal 2004a). Animal products like meat, fish, poultry and dairy are the best sources for carnitines. Doses above 3 g/day can give gastrointestinal side effects and malodorous effects (Annals of the New York Academy of Science 2004).

Carotenoids
Carotenoids are pigments found in plants. One of the most important carotenoids is β-carotene (Ross 2006), a provitamin A, which can directly scavenge ROS. Other carotenoids found in food are lycopene, lutein, and zeaxanthin, however these are not converted into vitamin A. Both in vivo and in vitro, β-carotene has been shown to protect isolated lipid membranes from peroxidation (Bendich 1989). Healthy young men with a higher carotenoid intake have higher sperm motility, and higher lycopene intake is associated with better sperm morphology (Zareba 2013). However, a review by Grune and colleagues (Grune 2010) stated that there are conflicting results whether β-carotene has antioxidant properties. Carotenoids come from leafy green vegetables, fruits, and some vegetable oils (Ross 2006). Excess intake of preformed vitamin A can lead to toxicity (hypervitaminosis A). However, excessive ingestion of provitamins such as carotenoids are not associated with vitamin A toxicity, the only side effect is carotenaemia (yellow-tinged skin).

Coenzyme Q10
Coenzyme Q10 (CoQ10) is a fat-soluble antioxidant synthesised endogenously and an essential component of the mitochondrial energy metabolism. In its reduced form, CoQH2, ubiquinol, it inhibits protein and DNA oxidation and lipid peroxidation (Littarru 2007). CoQ10 seminal fluid levels are significantly correlated to sperm count and motility, except in men with varicocele (Mancini 1994). Meat, fish, nuts and some oils are the most important dietary sources of CoQ10 due to their relatively high level of fats and mitochondria (Pravst 2010). Reported side effects are mild gastrointestinal symptoms (Bhagavan 2006).

Cysteine
Cysteine plays an important role in glutathione synthesis. N-acetylcysteine (NAC) is a precursor of the amino acid cysteine and a direct scavenger of ROS. Glutathione becomes depleted when there is OS, and this can be reversed by NAC supplementation (Atkuri 2007). NAC is less toxic and less susceptible to oxidation compared to cysteine itself. Oral administration of NAC up to 8000 mg/day is not known to cause significant adverse events (Atkuri 2007). Less is known about ethylcysteine, however in vivo and animal studies have shown anti-oxidative effects (Hsia 2016).

Micronutrients (folate, selenium, zinc)
Folate, also known as vitamin B9, is a micronutrient important for the synthesis of DNA, transfer RNA and the amino acids cysteine and methionine. Folic acid, the synthetic form, can scavenge oxidising free radicals, and it inhibits lipid peroxidation (Joshi 2001). Folate is present in green-leafy vegetables, liver, bread, yeast and fruits (Ebisch 2007). Folic acid doses of 5 mg/day and over can cause abdominal cramps, diarrhoea and rash. Higher doses can even cause altered sleep patterns, irritability, confusion, exacerbation of seizures and nausea (Rogovik 2009).

Zinc is involved as a cofactor in DNA transcription and protein synthesis and has extensive antioxidants properties (Ebisch 2007). Zinc has an important role in testes development, sperm physiological functions and decrease of zinc in seminal plasma is associated with sperm quality (Colagar 2009a). Zinc, like selenium, is absorbed from the soil into plants. Dietary sources rich of zinc are meat products, wheat and seeds.

Magnesium and selenium are different from other antioxidant nutrients because they are involved in the mechanisms of cellular antioxidant defence by increasing the activity of the antioxidant enzyme glutathione peroxidase, and not by directly reacting with oxidant molecules (Burk 2002; Yavuz 2013). It is suggested that both magnesium and selenium deficiency would make humans more susceptible to oxidative injury. Selenium is furthermore essential for normal spermatogenesis (Boitani 2008). Selenium is derived from fish, meat products, dairy, and soil absorption by plants (Navarro-Alarcon 2008). Early indicators of excess intake are a garlic odour in the breath and a metallic taste in the mouth. The most common clinical signs of chronically high selenium intakes are gastrointestinal symptoms, fatigue, hair loss, joint pain, and nail problems (MacFarquhar 2010). Magnesium is derived from green leafy vegetables, nuts, beans, and cereals (McNeill 1985).

Vitamin E
Vitamin E, also known as the bioactive form α-tocopherol, has a principal role by being the first defence against oxidant-induced membrane injury (Traber 2007). Vitamin E is found in vegetable oils and there is a given upper daily limit based on the possible increased bleeding risk (Institute of Medicine 2000).

Vitamin C
Vitamin C, also known as ascorbic acid, is able to diminish DNA damage directly by scavenging free radicals and decreasing formation of lipid hydroperoxides (Padayatty 2003). Ascorbic acid concentrations are 10-fold higher in seminal plasma compared to blood plasma. Low levels of seminal plasma ascorbic acid are directly related to decreased number of spermatozoa with normal morphology and increased sperm DNA damage (Colagar 2009). Vitamin C is mainly found in fruits and vegetables.

Substances with antioxidant properties

Myo-inositol
Inositol is a polyalcohol, naturally occurring as nine stereoisomers including myo-inositol. Myo-inositol, a "pseudovitamin" and

previously known as vitamin B8, plays an important role in cell membrane formation and lipid synthesis. The highest concentration in the genital tract is within the seminiferous tubules. Myo-inositol is produced by Sertoli cells in response to follicle-stimulating hormone (FSH) (Lewin 1976). Myo-inositol is a precursor for the phosphatidyl-inositol signalling pathway and directly involved in regulation of sperm motility, capacitation and acrosome reaction (Bevilacqua 2015). Myo-inositol has a role as a possible antioxidant agent by increasing endogenous antioxidant enzymes and directly affecting the mitochondria leading to an increase of the membrane potential (Colone 2010; Condorelli 2017). Corns, beans, fruits, and nuts are the main dietary sources of myo-inositol (Vazquez-Levin 2020)

Polyunsaturated fatty acids (PUFAs)
Polyunsaturated fatty acids (PUFAs) are subdivided into omega-3 (docosahexaenoic acid, DHA), omega-6 and omega-9. Omega-9 is synthesised by animals, but omegas-3 and -6 needs to be supplemented in the diet. The main sources of these are vegetables and fish oils (Wathes 2007). PUFAs increase the plasma fluidity of the sperm membrane. However, this fluidity makes the sperm susceptible to ROS and lipid peroxidation that can damage the sperm. Wathes and colleagues state that "It appears that PUFAs are a two-edged sword - some are essential, but too many are potentially harmful" (Wathes 2007, page 198). It seems to be that PUFAs have a pro-oxidant rather than a direct antioxidant effect. Although it is suggested that omega 3 might have a free radical-scavenging potential (Giordano 2014; Richard 2008).

Resveratrol
Resveratrol is a natural phytoalexin with antioxidant properties. Several *in vitro* studies with human cryopreserved sperm and *in vivo* studies in animal models suggest that resveratrol improves sperm motility and enhances antioxidant defences (Branco 2010; Collodel 2011; Ourique 2013). It is naturally found in our diet in the form of grapes, berries, several nuts, and wine (Ourique 2013). Worldwide, resveratrol is better known from research on the effect of daily intake of red wine, "the Mediterranean diet", in cardiovascular disease (Bertelli 2009). Reversible gastrointestinal side effects are reported, however evidence on side effects is limited (Hausenblas 2014).

Vitamin B (complex)
Vitamin B is a water-soluble vitamin and consists of several precursors and coenzymes such as thiamine (B1), riboflavin (B2) and cobalamin (B12). Vitamin B plays an important role in the homocysteine metabolism. It is suggested that total plasma homocysteine may have a pro-oxidant effect and may play a role in the release of ROS (Hankey 1999). Increased intake of vitamin B has a homocysteine-lowering effect, with folate (also known as vitamin B9) shown to have the strongest effect, however vitamins B6, B12, and B2 have all been shown to be independently predictive of plasma homocysteine (Hankey 1999). Vitamin B is mainly found in meat products, other food sources are beans, potatoes, bananas, and mushrooms.

Vitamin D
Vitamin D is a fat-soluble vitamin, with the natural main source being dermal synthesis (sunlight). The active form of vitamin D is 1,25-dihydroxyvitamin D, also called vitamin D3. Halicka and colleagues suggest that vitamin D3 has antioxidant activity, mainly by inducing the antioxidant protein superoxide dismutase (Halicka 2012). However, there are no other studies about the antioxidant properties of vitamin D in male fertility. Clearly, vitamin D plays an important role in male fertility and serum levels of vitamin D are positively associated with semen quality (de Angelis 2017). However, most of the studies do not mention the antioxidant properties of vitamin D, but rather relate the effect to the synthesis of sex steroids or the regulation of calcium.

How the intervention might work

It must be noted that a low production of reactive oxygen species (ROS) is physiological and required for adequate sperm function by supporting capacitation, maturation and hyperactivation (Aitken 1994; Du Plessis 2015). However, OS occurs when the balance between ROS production and antioxidant defence is disturbed. This applies to sperm cells in particular.

If OS at the heart of the increased sperm DNA damage and the decrease of pregnancy and live birth rates, then supporting the antioxidant defence system with exogenous antioxidants would seem logical. An extra dietary intake of antioxidants or a healthy diet in general has shown to be strongly associated with semen quality in healthy men (Eskenazi 2005; Irvine 1998; Lewis 1997; Mendiola 2010; Pasqualotto 2001; Salas-Huetos 2017; Zareba 2013). In conclusion, there is a fine balance between preventing OS by antioxidants, removing excessive amounts of ROS, and maintaining a small amount of ROS for their physiological effect on sperm functions. Since "reductive stress" as a rebound effect of antioxidants has been reported, large or high doses of antioxidants might better be avoided (Dattilo 2016; Ghyczy 2001; Henkel 2019).

Why it is important to do this review

In an effort to enhance fertility, couples are increasingly offered treatment with assisted reproductive techniques (ART). However, these techniques are expensive and do not cure the causes of subfertility, but rather overcome some of its barriers. Since integrity of sperm DNA is one of the major determinants of normal fertilisation and embryo growth in natural and assisted conception (Agarwal 2003; Aitken 2010; Evenson 2006), there is a clear rationale for antioxidant therapy.

One of the other reasons for this review, apart from finding out if antioxidant therapy can overcome some of the barriers of subfertility, is that the global vitamin and supplement market has grown exponentially over the last years. The market value is expected to reach 278 billion USD by 2024 (Grand View Research 2016). The low costs and low apparent risks of supplements are appealing to both, patients and healthcare providers. However, most antioxidants are uncontrolled by regulation and the evidence for their effectiveness is not based on randomised controlled trials (RCTs). Vitamins and supplements are dispensed through various retail outlets, including health food shops, online retailers, health centres, fitness clubs, supermarkets, and pharmacies (Showell 2017).

The purpose of this Cochrane Review is to assess the effectiveness and safety of different antioxidants and dosages used by men of subfertile couples, through evaluation of live birth rates, clinical pregnancy rates and adverse events. This is an update of a review first published in 2011 (Showell 2011), updated in 2014 (Showell 2014), and in 2019 (Smits 2019).

OBJECTIVES

To evaluate the effectiveness and safety of supplementary oral antioxidants compared with placebo, no treatment or another antioxidant in subfertile men.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Randomised controlled trials (RCTs).
- Cross-over trials are included: however, we only used 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

- Studies that included subfertile men (male factor subfertility),part of a couple 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) and intracytoplasmic sperm injection (ICSI), or intrauterine insemination (IUI).
- Male factor subfertility was defined as men who were part of a couple referred to a fertility clinic with abnormal semen parameters, including elevated sperm DNA fragmentation or other seminal biomarkers of oxidative stress. Men with subfertility and varicocele were also included

In situations where individuals were randomised again following failed cycles, the data would not be pooled in a meta-analysis unless individual data could be excluded.

Exclusion criteria

- Studies enrolling only men attending a fertility clinic exclusively as the result of female partner or idiopathic infertility.
- Studies enrolling men taking any other fertility-enhancing drugs.
- Studies enrolling men who had chemotherapy treatment in the past.

Types of interventions

Inclusion criteria

- Any type or dose of oral antioxidant supplementation (individual or combined) that can be obtained without prescription and is not regulated as a pharmaceutical drug, versus placebo or no treatment.
- Any type or dose of oral antioxidant supplementation (individual or combined) versus another type or dose of oral antioxidant (head-to-head).

Interventions were considered 'combined antioxidants' if they included three or more antioxidants in the intervention arm.

Exclusion criteria

- Interventions that included plant extracts (for example garlic) or herbal substances.

Studies that included antioxidants plus a plant extract (for example garlic) were included if the antioxidant agent was the main focus of the investigation.

Definition of antioxidant in male fertility: a substance that has the ability to protect spermatozoa against endogenous oxidative damage by directly neutralising hydroxyl, superoxide, and hydrogen peroxide radicals, chelation of redox metals or by functioning as a component of an antioxidant enzyme.

Types of outcome measures

Primary outcomes

- Live birth rate per couple randomised, defined as delivery of a live fetus after 20 completed weeks of gestation. Live births are counted as birth events, i.e. twin live birth is counted as one live birth event.

Secondary outcomes

- Clinical pregnancy rate per couple, defined as a viable intrauterine pregnancy, diagnosed by ultrasonographic examination of at least one fetus with a discernable heartbeat. A twin pregnancy is counted as one pregnancy event.
- Any adverse event (including miscarriage) reported by the study
- Level of sperm DNA fragmentation, defined as percentage (%) of sperm with abnormal DNA integrity estimated by either toluidine blue (TB) staining, sperm chromatin structure assay (SCSA) or terminal transferase dUTP nick end labelling (TUNEL) assay.
- Total sperm motility: any sperm movement in any direction (progressive plus forward plus non-progressive motility), provided as percentage (%).
- Progressive sperm motility: sperm with forward progression, defined as WHO category A + B, provided as percentage (%)
- Sperm concentration: number of sperm (10^6)/mL.

Search methods for identification of studies

We searched for all published and unpublished RCTs investigating oral antioxidant supplementation for subfertile men, without language restriction and in consultation with the Gynaecology and Fertility Group (CGF) Information Specialist *(*MGS).

Electronic searches

We searched the following electronic databases for relevant trials:

- The Cochrane Gynaecology and Fertility Group's (CGF) Specialised Register of Controlled Trials, ProCite platform (searched 15 February 2021) (Appendix 1);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2021, issue 2 on 15 February 2021) in the Cochrane Library (now containing records from CINAHL), (Appendix 2);

- MEDLINE, Ovid platform (searched from 1946 to 15 February 2021) (Appendix 3);
- Embase, Ovid platform (searched from 1980 to 15 February 2021) (Appendix 4);
- PsycINFO, Ovid platform (searched from 1806 to 15 February 2021) (Appendix 5);
- AMED, Ovid platform (searched from 1985 to 15 February 2021) (Appendix 6);
- Epistemonikos, Web platform (searched 18 February 2021) (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* (Version 5.1.0, Chapter 6, 6.4.11) (Higgins 2011). The Embase and PsychINFO searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (https://www.sign.ac.uk/what-we-do/methodology/search-filters/).

Searching other resources

The following other resources were searched (last search February 2021):

- International trial registers: the ClinicalTrials database, a service of the US National Institutes of Health (clinicaltrials.gov/ct2/home) and the and the World Health Organization International Trials Registry Platform search portal (ICTRP) (https://trialsearch.who.int/Default.aspx)) (Appendix 8; Appendix 9);
- Google scholar, using the keywords 'antioxidants male infertility' and 'antioxidants sperm random';
- 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 10);
- ProQuest Dissertations and Theses (http://search.proquest.com.ezproxy.auckland.ac.nz/pqdtft/advanced?accountid=8424) was also searched (Appendix 11);
- Web of Knowledge for conference proceedings and published trials (Appendix 12);
- Appropriate journals were handsearched for trial conference abstracts in consultation with the CGF Information Specialist.

We handsearched reference lists of relevant trials and systematic reviews retrieved by the search and contacted experts in the field to obtain additional trials.

Data collection and analysis

Selection of studies

Review authors WL and RS did an initial screen of titles and abstracts retrieved by the search. The search was conducted by MGS and WL. We retrieved the full texts of all potentially eligible studies. Two review authors (WL and RM-P) independently examined these full-text articles for compliance with the inclusion criteria and selected eligible studies. We corresponded with study investigators as required, to clarify study eligibility. Disagreements were resolved by discussion. If any reports required translation, we described the process used for data collection. We documented the selection process with a “PRISMA” flow chart (see Figure 1).

Figure 1.

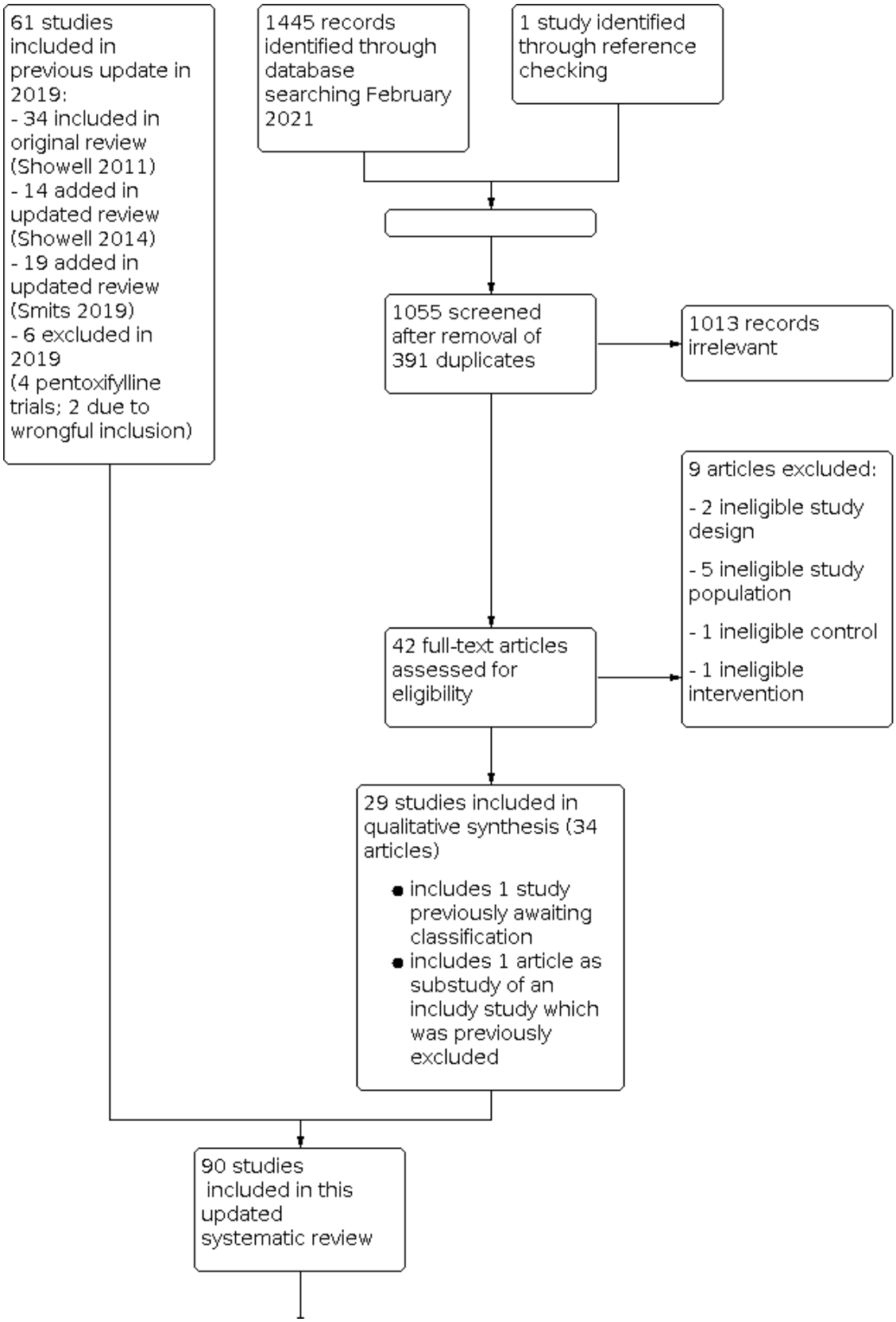
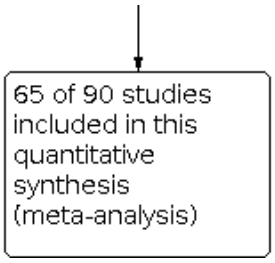


Figure 1. (Continued)



Data extraction and management

Three review authors (WL, KF and JB) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. Any disagreements were resolved by discussion. Data extracted included study characteristics and outcome data (see data extraction table for details, Characteristics of included studies and Characteristics of excluded studies). Where studies had multiple publications, the review authors collated the multiple reports under a single study ID with multiple references.

We corresponded with study investigators for further data on methods and/or results, as required.

Assessment of risk of bias in included studies

Three review authors (WL, KF and JB) independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool to assess: selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other potential sources of bias (Higgins 2011). Judgements were assigned as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 8.5 (Higgins 2011). Disagreements were resolved by discussion; when needed we consulted a third party to achieve agreement (MGS, VJ or RM-P). We described all judgements fully and present the conclusions in the risk of bias table (Characteristics of included studies), which is incorporated in the interpretation of review findings by means of sensitivity analyses (see below). 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.

We considered that the blinding status of participants could influence findings for the outcomes of live birth, pregnancy and adverse events, as antioxidants are easily available, and it would be possible for participants to self-medicate. Therefore, if the participants were not blinded or the study was not placebo-controlled, or both, we considered the study to be at high risk of bias.

Measures of treatment effect

We collected dichotomous data for live birth, pregnancy rate, miscarriage and adverse events and for the continuous data for sperm quality measurements we collected mean differences (MDs) and the associated standard deviations (SDs).

Sperm parameter outcomes, if reported, were analysed at the time points of three, six and nine months post-randomisation. All studies were analysed in this way regardless of whether the participants were treated for three, six or nine months.

Unit of analysis issues

The primary analysis of the outcomes of live birth, pregnancy and adverse events was per couple randomised, counting multiple births as one live birth event. The sperm outcome analyses were per man randomised. Only the first-phase data from cross-over trials were included.

Dealing with missing data

We analysed the data on an intention-to-treat (ITT) basis as far as possible (i.e. including all randomised participants in analyses, in the groups to which they were randomised). Attempts were made to obtain missing data from the original trialists and the results of author contact are reported in Characteristics of included studies. When data were unobtainable, we undertook imputation of individual values for live birth only; live birth was assumed not to have occurred in participants without a reported outcome. For other outcomes, we analysed only the available data. Any imputation undertaken was subjected to sensitivity analysis (see below).

If studies reported sufficient detail to calculate MDs but gave no information on an associated SD, we assumed the outcome to have a SD equal to the highest SD from other studies within the same analysis.

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 by the measure of the I^2. If an 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 may be due to differences between trials rather than to chance alone (Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were 10 or more studies in an analysis, we used a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We conducted statistical analysis of the data using Review Manager 5 (RevMan 2014). We expressed the dichotomous data for live birth, pregnancy rate, miscarriage and adverse events as Peto odds ratios (ORs) with 95% confidence intervals (CIs) and combined them in a meta-analysis with Review Manager 5 software using the Peto method and a fixed-effect model (Higgins 2011). Continuous outcomes, i.e. sperm parameters, provided as median and interquartile range (IQR) or median and range were adjusted to mean and SD (Wan 2014). A fixed-effect model was used on sperm outcomes. The Peto OR has mathematically sound properties that are consistent with benefit or harm and work well in small samples with rare events. This effect measure is appropriate when considering subfertility. For continuous data (for example sperm quality measurements) MDs between treatment groups were calculated with associated SDs and 95% CIs. The results were displayed on forest plots where possible.

We considered pregnancy outcomes to be positive, and higher pregnancy rates of benefit. We considered the outcomes of miscarriage and adverse events to be negative effects, and higher numbers harmful. We combined data for the following comparisons.

- Antioxidants versus placebo or no treatment
- Antioxidants versus antioxidants (head-to-head)

Adverse events as reported in the studies were included in the two comparisons above.

The total sperm motility, progressive sperm motility and concentration outcomes were divided into three groups: measurement after starting treatment, at three, six and nine months or more, as reported by the studies. Studies were analysed together if they reported these outcomes at the same point in time, for example a study that stopped treatment at three months but measured at six or nine months was measured in the same analysis as those that were treated for six or nine months.

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 studies 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.

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

Statistical analysis was performed using Review Manager 5.4.1 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

Where data were available, we conducted subgroup analyses to determine the separate evidence within the following subgroups.

- Studies that included different types of antioxidant
- Studies that included couples who were also receiving IVF/ICSI treatment (for the outcomes of live birth and clinical pregnancy)
- Over time analysis for sperm outcomes of motility and concentration, at three, six and nine months

If we detected substantial heterogeneity, we explored possible explanations in subgroup analyses (e.g. differing populations) and/or sensitivity analyses (e.g. differing risk of bias). We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We conducted sensitivity analyses (using the fixed-effect model in RevMan software) on the primary outcomes if we detected a high degree of heterogeneity (I^2 = 50% or more), excluding studies to assess if there is a change in effect:

- for studies with a high risk of bias, or
- for studies using no treatment as a control group instead of placebo (for outcomes of live birth and clinical pregnancy), or
- for studies enrolling men who are part of a couple undergoing IUI, or
- enrolling men with varicocele, or
- for studies that reported both live birth and clinical pregnancy rate in order to assess any overestimation of effect and reporting bias, or
- for studies where results had been imputed, or
- for studies that reported remarkably low SDs as the review authors considered that these data were potentially erroneous (a post hoc sensitivity analysis).

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings; table using GRADEpro (GRADEpro GDT 2015) and Cochrane methods (Higgins 2011). This table evaluates the overall certainty of the body of evidence for the main review outcomes (live birth, clinical pregnancy, and the adverse events) for the main review comparison (antioxidant compared with placebo or no treatment). We assessed the certainty of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias. Judgements about evidence certainty (high, moderate, low or very low) were made by three review authors (WL, KF and JB) working independently, with disagreements resolved by discussion. Judgements were justified, documented, and incorporated into reporting of results for each outcome.

We extracted study data, formatted our comparisons in data tables and prepared a summary of findings table before writing the results and conclusions of our review.

RESULTS

Description of studies

Results of the search

2011 version of review

We assessed 590 abstracts for inclusion from the title and abstract found in a search dated from inception to August 2010. The MEDLINE search produced 406 abstracts; there were six abstracts from CENTRAL, three from CINAHL, 62 from Embase, 107 from the Cochrane Gynaecology and Fertility Group' (CGF) database and three from PsycINFO. Two conference abstracts were found from handsearching the conference proceedings of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). One title was found from reference lists in reviews. After removal of inappropriate and duplicate studies, we retrieved the full texts of 53 studies. Five non-English studies were assessed for inclusion: two Chinese, one Bulgarian, one Japanese and one Iranian. The two Chinese studies (Li 2005; Li 2005a), the Japanese study (Akiyama 1999), and the Iranian study (Peivandi 2010) were included in the analysis. The Bulgarian study (Nikolova 2007) was excluded as it did not use random allocation (see Characteristics of excluded studies). We excluded 15 articles and found four ongoing studies in searches of the clinical trial registers.

A total of 34 studies were included in the 2011 version of the review (Showell 2011).

2014 update

We assessed 483 abstracts for inclusion from the title and abstract found in a search dated from 1 August 2010 to 30 January 2014. After duplicates were removed 338 remained. We assessed 34 of these papers in full text.

Eleven of the full-text reports assessed studies were in a language other than English and required translation, five of these were in Chinese, two in Persian and one each in Japanese, Russian, Italian, and Portuguese (see Acknowledgements for those who helped with translation). Five of the Chinese studies were excluded: three (Chen 2012; Tang 2011; Wang 2010a) due to an inappropriate intervention, one was not randomised (Wu 2012), and one had an inappropriate population (Lu 2010). The Portuguese study (Verzeletti 2012) was excluded as it used a herbal intervention. Five non-English studies were included: one in Persian (Eslamian 2013), one Japanese (Kumamoto 1988), one Italian (Morgante 2010), one Russian (Sivkov 2011), and one Chinese (Wang 2010).

We excluded 20 articles, and included 14 articles. An updated search was run in August 2014 where six studies (Anarte 2013; Gopinath 2013; Iacono 2014 Nadjarzadeh 2014; Nashivochnikova 2014; Nematollahi-Mahani 2014) were placed in 'Studies awaiting assessment'. There were six ongoing studies found in the new searches.

We included 14 new trials in the 2014 update: Attallah 2013; Azizollahi 2013; Dimitriadis 2010; Eslamian 2013; Kumamoto 1988; Martinez-Soto 2010; Morgante 2010; Nadjarzadeh 2011; Poveda 2013; Pryor 1978; Safarinejad 2011; Safarinejad 2012; Sivkov 2011; Wang 2010.

A total of 48 studies were included in the 2014 update (Showell 2014).

2018 update

We assessed 979 abstracts for inclusion from the title and abstract found in a search dated from January 2014 until February 2018. One extra study was found through the grey literature search. After duplicates were removed, 718 articles remained. We assessed 58 of these papers in full text. One of the full-text articles assessed studies was in Chinese (Deng 2014) and one in Russian (Gamidov 2017); both required translation. We excluded 22 studies (28 articles), and included 19 studies (29 articles). Twelve studies were classified as ongoing studies. One study was placed in 'Studies awaiting assessment' (Goswami 2015).

We removed and excluded four pentoxifylline studies that were previously included in the 2014 update and the original review (Merino 1997; Micic 1988; Safarinejad 2011; Wang 1983). Furthermore, we removed two previously included studies due to the discovery that the population did not meet the inclusion criteria: they included men with idiopathic infertility with normal sperm parameters, and no male factor infertility. (Ciftci 2009; Keskes-Ammar 2003).

We included 19 new trials in the 2018 update: Barekat 2016; Blomberg Jensen 2018; Boonyarangkul 2015; Busetto 2018; Cyrus 2015; Deng 2014; Ener 2016; Exposito 2016; Gamidov 2017; Gopinath 2013; Haghighian 2015; Haje 2015; Martinez 2015; Mehni 2014; Micic 2019; Pourmand 2014; Raigani 2014; Sharifzadeh 2016; Sofikitis 2016.

A total of 61 studies were included in the 2018 update (Smits 2019).

2021 update

We assessed 1445 abstracts for inclusion from the title and abstract found in a search dated from February 2018 until February 2021. After duplicates were removed, 1055 articles remained. We assessed 42 of these papers in full text.

Three of the full-text articles assessed studies were in Chinese (Cheng 2018; Sun 2018; Zhou 2016) and three were in Russian (Gamidov 2019; Popova 2019; Vinogradov 2019); all required translation. One study was found eligible through reference checking and was included (Safarinejad 2011b). In total, we excluded nine articles and included 29 studies (34 articles). One study was placed in "Studies awaiting classification", because of unclear study population (Kuzmenko 2018). See the PRISMA flow chart (Figure 1).

One previously excluded study was added as a sub-study to an included study (Raigani 2014).

In the current update, six of the 12 previously 'ongoing studies' were included (Amini 2020; Bahmyari 2021; Eslamian 2020; Joseph 2020; Kumalic 2020; Steiner 2020). One study remained as an ongoing study (NCT03337360). The manuscript of one trial was submitted, but not yet published and was therefore placed in "Studies awaiting classification" (NCT01407432). Three other former ongoing studies were placed in "Studies awaiting classification" with a status of "completed" and "recruitment

stopped" in the trial registry (DRKS00011616; NCT00975117; NCT01828710). One former ongoing study was excluded, because of withdrawal on the trial registry website (NCT03104998).

The authors from the one study placed in "Studies awaiting assessment" in the previous update (Goswami 2015) were contacted and confirmed that the study was a randomised clinical trial.

We added 11 new ongoing studies (CTRI/2019/03/018303; IRCT20120215009014N322; IRCT20140622018187N9; IRCT20190406043177N1; IRCT20190714044209N1; IRCT20200911048689N1; NCT03634644; NCT04193358; NCT04256278; NCT04509583; PACTR201802003076341).

We included 29 new studies (34 articles) in this update: Abbasi 2020; Alahmar 2019; Alahmar 2020; Amini 2020; Ardestani 2019; Bahmyari 2021; Cheng 2018; Eslamian 2020; Gamidov 2019; Gonzalez-Ravina 2018; Goswami 2015; Huang 2020; Joseph 2020; Kizilay 2019; Kopets 2020; Korshunov 2018; Kumalic 2020; Lu 2018; Nouri 2019; Popova 2019; Saeed Alkumait 2020; Safarinejad 2011b; Schisterman 2020; Steiner 2020; Stenqvist 2018; Sun 2018; Tsounapi 2018; Vinogradov 2019; Zhou 2016.

A total of 90 studies have been included in this update (Characteristics of included studies). A total of 67 studies were excluded (Characteristics of excluded studies).

Included studies

Study design and setting

The studies came from 31 different countries. Twenty-one studies were from Iran (Abbasi 2020; Amini 2020; Ardestani 2019; Azizollahi 2013; Bahmyari 2021; Barekat 2016; Cyrus 2015; Eslamian 2013; Eslamian 2020; Haghighian 2015; Mehni 2014; Nadjarzadeh 2011; Nouri 2019; Peivandi 2010; Pourmand 2014; Raigani 2014; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2011b; Safarinejad 2012; Sharifzadeh 2016). Ten studies were based in Italy (Balercia 2005; Balercia 2009; Biagiotti 2003; Busetto 2018; Cavallini 2004; Galatioto 2008; Lenzi 2003; Lenzi 2004; Lombardo 2002; Morgante 2010). Nine studies were from China (Cheng 2018; Deng 2014; Huang 2020; Li 2005; Li 2005a; Lu 2018; Sun 2018; Wang 2010; Zhou 2016). Six were from Russia (Gamidov 2017; Gamidov 2019; Korshunov 2018; Popova 2019; Sivkov 2011; Vinogradov 2019), four from Iraq (Alahmar 2019; Alahmar 2020; Haje 2015; Saeed Alkumait 2020), and four from the USA (Dawson 1990; Schisterman 2020; Sigman 2006; Steiner 2020). Three studies each were from India (Gopinath 2013; Goswami 2015; Joseph 2020), Japan (Akiyama 1999; Dimitriadis 2010; Kumamoto 1988), the UK (Kessopoulou 1995; Pryor 1978; Scott 1998) and Spain (Exposito 2016; Gonzalez-Ravina 2018; Martinez-Soto 2010). Two studies each were from Kuwait (Omu 1998; Omu 2008), Greece (Sofikitis 2016; Tsounapi 2018) and Turkey (Ener 2016; Kizilay 2019). A single study was set in each of the following countries: Australia (Tremellen 2007), Belgium (Zalata 1998), Canada (Conquer 2000), Denmark (Blomberg Jensen 2018), Egypt (Attallah 2013), France (Greco 2005), Germany (Rolf 1999), Hungary (Zavaczki 2003), Mexico (Martinez 2015), the Netherlands (Wong 2002), Panama (Poveda 2013), Saudi Arabia (Suleiman 1996), Serbia (Micic 2019), Slovenia (Kumalic 2020), Sweden (Stenqvist 2018), Thailand (Boonyarangkul 2015), Tunisia (Nozha 2001), and Ukraine (Kopets 2020).

All included studies were randomised. Five studies had a randomised cross-over design (Akiyama 1999; Kessopoulou 1995; Lenzi 2003; Peivandi 2010; Pryor 1978). In the meta-analysis only the first phase data were used as all studies reported first and second phase data separately. The remaining 85 studies used a randomised parallel group design. One study (Li 2005) had a large imbalance between the intervention and control groups at the randomisation stage; 150 men were randomised, 90 into the treatment group and 60 into the control group. This appeared to be a blocked 3:2 allocation ratio. This method of randomisation was not explained in the report. Attempts were made to contact the author, but there has been no reply. Fifteen studies (Biagiotti 2003; Cavallini 2004; Conquer 2000; Dawson 1990; Gamidov 2017; Gopinath 2013; Goswami 2015; Kumamoto 1988; Martinez 2015; Mehni 2014; Raigani 2014; Saeed Alkumait 2020; Scott 1998; Sofikitis 2016; Zalata 1998) were three-armed, 11 (Azizollahi 2013; Balercia 2005; Boonyarangkul 2015; Cheng 2018; Eslamian 2020; Gonzalez-Ravina 2018; Haje 2015; Omu 2008; Poveda 2013; Safarinejad 2009; Wong 2002) were four-armed and one study was five-armed (Tsounapi 2018).

The duration of the treatment period ranged from three weeks with a three-week follow up (Dawson 1990) to 12 months treatment (Ener 2016). The longest follow-up periods were in the studies by Blomberg Jensen and Safarinejad with respectively a five-month (Blomberg Jensen 2018) and six and a half-month (Safarinejad 2009a) treatment duration and both with 14 months of follow-up. Ten studies reporting on either live birth rate or clinical pregnancy rate, only mentioned follow-up consultations during their treatment, however they did not report the length of follow-up after treatment (Azizollahi 2013; Attallah 2013; Barekat 2016; Busetto 2018; Gamidov 2019; Kessopoulou 1995; Omu 1998; Suleiman 1996; Tsounapi 2018; Zhou 2016).

Funding sources were stated by 36 studies (Abbasi 2020; Amini 2020; Bahmyari 2021; Barekat 2016; Blomberg Jensen 2018; Busetto 2018; Cheng 2018; Conquer 2000; Deng 2014; Eslamian 2013; Eslamian 2020; Haghighian 2015; Joseph 2020; Kessopoulou 1995; Kopets 2020; Kumalic 2020; Lenzi 2003; Lombardo 2002; Martinez-Soto 2010; Mehni 2014; Micic 2019; Nadjarzadeh 2011; Nouri 2019; Omu 1998; Peivandi 2010; Poveda 2013; Raigani 2014; Rolf 1999; Saeed Alkumait 2020; Safarinejad 2012; Schisterman 2020; Sharifzadeh 2016; Steiner 2020; Stenqvist 2018; Wang 2010; Zavaczki 2003). Eight of these studies stated that funding was from a commercial source (Abbasi 2020; Busetto 2018; Conquer 2000; Kumalic 2020; Martinez-Soto 2010; Micic 2019; Safarinejad 2012; Stenqvist 2018), and the remaining 28 obtained funding through non-commercial avenues or university grants. Nine studies specifically reported no funding (Cyrus 2015; Gonzalez-Ravina 2018; Gopinath 2013; Haje 2015; Huang 2020; Lombardo 2002; Popova 2019; Pourmand 2014; Safarinejad 2011b). Forty-five studies did not mention any funding sources.

Participants

The 90 studies included 10,303 subfertile men, 6262 in the intervention groups and 4041 men in the control groups. The age range of the participants was 18 to 65 years. Studies included couples who had attended a fertility clinic, with a fertile partner and had been trying to conceive with regular intercourse for over one year. Most men in the included studies had a deficient level of spermatozoa in the seminal fluid (oligospermia) or a low motility of sperm in the seminal fluid (asthenospermia). Five studies included

men with an increased level of DNA fragmentation or oxidative stress (Akiyama 1999; Gamidov 2019; Goswami 2015; Greco 2005; Stenqvist 2018), and one study included men with low acrosin activity (Sun 2018). Three studies also included fertile (Wong 2002) or normospermic men (Exposito 2016, Schisterman 2020) with subgroup analysis. Studies excluded men with any inflammatory disease, antibody problems or chromosomal problems; and most studies stated that they did not enrol men who smoked, took any additional medication or drank alcohol.

Two studies enrolled men with varicocele (Busetto 2018; Cavallini 2004), 10 studies enrolled men post-varicocelectomy (Abbasi 2020; Ardestani 2019; Azizollahi 2013; Barekat 2016; Cyrus 2015; Ener 2016; Gamidov 2017; Kizilay 2019; Lu 2018; Pourmand 2014), and one study enrolled men with chronic prostatitis (Sivkov 2011). Eight studies (Exposito 2016; Joseph 2020; Kessopoulou 1995; Kumalic 2020; Popova 2019; Schisterman 2020; Sigman 2006; Tremellen 2007) enrolled men who, as part of a couple, were undergoing in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI). One study specifically enrolled men who were undergoing ICSI with sperm obtained with testicular extraction (TESE) (Korshunov 2018). Three studies enrolled men who were part of a couple undergoing intrauterine insemination (IUI) (Attallah 2013; Schisterman 2020; Steiner 2020).

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

Interventions

A wide variety of antioxidants were used in the included studies. Comparisons covered antioxidants versus placebo or no treatment and head-to-head comparisons (antioxidant versus antioxidant).

The comparison 'antioxidants versus placebo or no treatment' included the following antioxidants: arginine, carnitines (L-carnitine, L-acetyl carnitine, L-carnitine plus L-acetyl carnitine), carotenoids (β-carotene), coenzyme Q10 (CoQ10), cysteines (ethylcysteine and N-acetylcysteine (NAC)), folic acid, magnesium, melatonin, polyunsaturated fatty acids (PUFAs) (alpha-lipoic-acid and docosahexaenoic acid (DHA)), resveratrol, selenium, vitamin B, vitamin C, vitamin D with calcium, vitamin E and zinc.

Combined antioxidants were used in 23 studies. They were labelled as Proxeed Plus (Busetto 2018; Micic 2019), Menevit (Tremellen 2007), Selznic (Sivkov 2011), SpermActin-forte (Gamidov 2017; Gamidov 2019), Spermotrend (Poveda 2013), Androdos (Popova 2019), Androferti (Stenqvist 2018), Profertil (Tsounapi 2018), and Brudy Plus (Vinogradov 2019). Eleven of these 23 studies used combined antioxidants without any brand name or labelling; vitamin E combined with selenium and folic acid (Ardestani 2019, Bahmyari 2021), a combination of vitamin E, C and zinc (Joseph 2020), l-carnitine, acetyl-Lcarnitine, vitamin C, folic acid, selenium, coenzyme Q10 and vitamin B12 (Kizilay 2019), “Verum TDS”: l-carnitine, l-acetyl-carnitine, l-arginine, glutathione, coenzyme Q10, zinc, vitamin B9, vitamin B12 and selenium (Kopets 2020), an antioxidant supplement containing vitamin E, vitamin C, selenium and l-carnitine (Korshunov 2018), vitamin C/D/E, selenium, L-carnitine, zinc, folic acid and lycopene (Steiner 2020), "N-acetylcysteine (NAC) with vitamins and micronutrients" (Galatioto 2008), selenium plus vitamin A/C/E (Scott 1998), a fixed dose combination (FDC) of coenzyme Q10, L-carnitine, lycopene and zinc (Gopinath 2013), and "essential fatty acid (EFA) mixture combined with α-tocopherol (vitamin E) and β-carotene, acetylcysteine and other antioxidants" (Zalata 1998). Goswami 2015 did not specify the brand name or content of the "combined oral antioxidant".

The second comparison, head-to-head, included t26 studies. The head-to-head comparisons were included in an attempt to assess whether one antioxidant was more effective than another. They looked at effects of ethylcysteine versus vitamin E (Akiyama 1999), 200 mg versus 400 mg of coenzyme Q10 (Alahmar 2019), coenzyme Q10 versus selenium (Alahmar 2020), zinc versus folic acid versus zinc plus folic acid (Azizollahi 2013; Raigani 2014; Wong 2002), L-carnitine versus L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine (Balercia 2005), l-carnitine versus coenzyme Q10 versus l-carnitine plus coenzyme Q10 versus vitamin B1 (Cheng 2018), 400 mg versus 800 mg of DHA (Conquer 2000), 1000 mg versus 200 mg of vitamin C (Dawson 1990), vitamin D plus calcium versus vitamin C plus vitamin E (Deng 2014), DHA plus vitamin E versus DHA versus vitamin E (Eslamian 2020), SpermActin Forte versus SpermActin Forte plus "vitamin complex" (Gamidov 2017), 0.5 g versus 1 g versus 2 g of DHA (Gonzalez-Ravina 2018), L-carnitine plus acetyl-L-carnitine versus vitamin E plus vitamin C (Li 2005), L-carnitine versus vitamin E plus vitamin C (Li 2005a), vitamin E plus selenium versus vitamin B (Nozha 2001), zinc versus zinc plus vitamin E versus zinc plus vitamin E and vitamin C (Omu 2008), glutathione versus coenzyme Q10 (Saeed Alkumait 2020), N-acetylcysteine versus selenium versus selenium plus N-acetylcysteine (Safarinejad 2009), selenium versus combined antioxidants (Scott 1998), l-carnitine versus vitamin E (Sun 2018), Profertil (combined antioxidant) versus l-carnitine (Tsounapi 2018), L-carnitine plus vitamin E versus vitamin E (Wang 2010), acetyl-cysteine versus essential fatty acid (EFA) plus α-tocopherol (vitamin E) plus β-carotene versus acetylcysteine plus EFA plus antioxidants (Zalata 1998), and vitamin E versus vitamin E plus amino acids (Zhou 2016).

In summary:

- 42/90 studies compared antioxidants with placebo;
- 10/90 studies compared antioxidants with no treatment;
- 11/90 studies compared one antioxidant with another antioxidant (head-to-head);
- 27/90 multi-arm studies: 19 of these compared antioxidants versus placebo, six compared antioxidants versus no treatment, one study compared antioxidants versus a diet rich in antioxidants versus placebo, and one study compared different types of antioxidants without use of a placebo or no treatment group.

Outcomes

The primary outcome for this review was as follows.

- Live birth per couple. Fourteen studies reported data for live birth in the antioxidant versus placebo or no treatment comparison (Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Gamidov 2019; Huang 2020; Joseph 2020; Kessopoulou 1995; Korshunov 2018; Kumalic 2020; Omu 1998; Schisterman 2020; Steiner 2020; Suleiman 1996; Tremellen 2007). One of these studies could also be included in the head-to-head comparison of live birth rate (Balercia 2005). In one study, the unpublished data on live births following ICSI treatment were used (Kumalic 2020). The data from Schisterman

2020 and Huang 2020 could not be used in the meta-analysis, as the number of patients in whom the outcome was assessed was not reported.

Secondary outcomes for this review were as follows.

- Clinical pregnancy rate per couple, as reported by 22 studies in the antioxidant versus placebo or no treatment comparison (Attallah 2013; Azizollahi 2013; Balercia 2005; Balercia 2009; Barekat 2016; Busetto 2018; Gamidov 2019; Huang 2020; Joseph 2020; Kessopoulou 1995; Kizilay 2019; Kopets 2020; Korshunov 2018; Omu 1998; Popova 2019; Schisterman 2020; Steiner 2020; Stenqvist 2018; Suleiman 1996; Tremellen 2007; Tsounapi 2018; Zavaczki 2003). Two of these studies could also be included in the head-to-head comparison of clinical pregnancy rate (Balercia 2005; Tsounapi 2018); two more studies in the head-to-head comparison reported on clinical pregnancy rate (Cheng 2018; Deng 2014). From one study, the unpublished data on clinical pregnancy following ICSI treatment were used (Kumalic 2020). The data from Schisterman 2020 and Huang 2020 could not be used in the meta-analysis, as the number of patients with male subfertility in whom the outcome was assessed, was not reported. Data for biochemical and undefined pregnancy can be seen in Table 1.
- Adverse events (miscarriage, ectopic pregnancy, stillbirth, gastrointestinal discomfort, euphoria, headache, upper respiratory infection and nasopharyngitis) were reported by 23 studies (Busetto 2018; Cavallini 2004; Gamidov 2017; Gamidov 2019; Gopinath 2013; Joseph 2020; Kessopoulou 1995; Kizilay 2019; Kopets 2020; Korshunov 2018; Kumalic 2020; Omu 1998; Pourmand 2014; Safarinejad 2009a; Safarinejad 2011b; Schisterman 2020; Sharifzadeh 2016; Sigman 2006; Steiner 2020; Stenqvist 2018; Suleiman 1996; Tremellen 2007; Zavaczki 2003) in the antioxidant versus placebo or no treatment comparison. Safarinejad 2011b and Steiner 2020 reported different types of gastrointestinal discomfort separately, which made the data unuseable for meta-analysis. Adverse events were not reported as an outcome in any of the studies in the head-to-head comparisons, except that the study by Li (Li 2005) reported that no side effects were found in either the treatment or control groups.
- DNA fragmentation at three months or less was reported by 13 studies (Abbasi 2020; Barekat 2016; Boonyarangkul 2015; Gamidov 2017; Gamidov 2019; Gonzalez-Ravina 2018; Greco 2005; Huang 2020; Kumalic 2020; Martinez-Soto 2010; Raigani 2014; Steiner 2020; Stenqvist 2018), comparing antioxidants versus placebo or no treatment. One study in the head-to-head comparison reported on DNA fragmentation (Cheng 2018). Data from one study were not usable as the investigators used the Comet assay and reported DNA tail length, which is not a percentage and can therefore not be pooled with the other results (Boonyarangkul 2015)(Analysis 1.8).
- DNA fragmentation at six months was reported by four studies (Gamidov 2019; Micic 2019; Schisterman 2020; Stenqvist 2018), comparing antioxidants versus placebo or no treatment.
- Total sperm motility at three months or less was reported by 30 studies in the antioxidants versus placebo or no treatment comparison (Abbasi 2020; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Barekat 2016; Conquer 2000; Dimitriadis 2010; Ener 2016; Eslamian 2020; Gopinath 2013; Greco 2005; Kumalic 2020; Lenzi 2003; Lu 2018; Martinez-Soto 2010; Morgante 2010; Nadjarzadeh 2011; Nouri 2019; Omu 2008; Peivandi 2010; Raigani 2014; Scott 1998; Sigman 2006; Sivkov 2011; Steiner 2020; Stenqvist 2018; Tsounapi 2018; Vinogradov 2019; Zavaczki 2003; Zhou 2016) and by 14 studies in the head-to-head comparison (Akiyama 1999; Alahmar 2019; Alahmar 2020; Azizollahi 2013; Balercia 2005; Cheng 2018; Conquer 2000; Dawson 1990; Eslamian 2020; Li 2005; Omu 2008; Scott 1998; Tsounapi 2018; Zhou 2016).
- Total sperm motility at six months was reported by 19 studies in the antioxidants versus placebo or no treatment comparison (Ardestani 2019; Azizollahi 2013; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Busetto 2018; Ener 2016; Gopinath 2013; Kizilay 2019; Lenzi 2004; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2012; Schisterman 2020; Sigman 2006; Steiner 2020; Stenqvist 2018; Suleiman 1996; Wong 2002). Four studies reported this in the head-to-head comparison (Azizollahi 2013; Balercia 2005; Safarinejad 2009; Wong 2002).
- Total sperm motility at nine months or more was reported by five studies in the antioxidants versus placebo or no treatment comparison (Balercia 2005; Balercia 2009; Ener 2016; Safarinejad 2009a; Safarinejad 2012). One study reported this in the head-to-head comparison (Balercia 2005).
- Progressive sperm motility at three months or less was reported by 26 studies in the antioxidants versus placebo or no treatment comparison (Abbasi 2020; Amini 2020; Attallah 2013; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Boonyarangkul 2015; Cyrus 2015; Dawson 1990; Eslamian 2020; Gonzalez-Ravina 2018; Haghighian 2015; Huang 2020; Joseph 2020; Kumalic 2020; Martinez-Soto 2010; Mehni 2014; Morgante 2010; Nadjarzadeh 2011; Nouri 2019; Peivandi 2010; Popova 2019; Rolf 1999; Sharifzadeh 2016; Tsounapi 2018; Vinogradov 2019). Thirteen studies reported this in the head-to-head comparison (Alahmar 2019; Alahmar 2020; Balercia 2005; Cheng 2018; Deng 2014; Eslamian 2020; Gonzalez-Ravina 2018; Li 2005; Li 2005a; Sun 2018; Tsounapi 2018; Wang 2010; Zhou 2016).
- Progressive sperm motility at six months was reported by 13 studies in the antioxidants versus placebo or no treatment comparison (Ardestani 2019; Azizollahi 2013; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Boonyarangkul 2015; Cavallini 2004; Gamidov 2019; Kizilay 2019; Micic 2019; Saeed Alkumait 2020; Safarinejad 2011b; Stenqvist 2018). Two studies reported this in the head-to-head comparison (Balercia 2005; Saeed Alkumait 2020).
- Progressive sperm motility at nine months or more was reported by two studies in the antioxidants versus placebo or no treatment comparison (Balercia 2005; Balercia 2009). One study reported this in the head-to-head comparison (Balercia 2005).
- Sperm concentration at three months or less was reported by 34 studies in the antioxidants versus placebo or no treatment comparison (Abbasi 2020; Amini 2020; Attallah 2013; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Barekat 2016; Boonyarangkul 2015; Conquer 2000; Cyrus 2015; Dimitriadis 2010; Ener 2016; Eslamian 2020; Gonzalez-Ravina 2018; Gopinath 2013; Greco 2005; Haghighian 2015; Huang 2020; Joseph 2020; Kumalic 2020; Lu 2018; Martinez-Soto 2010; Mehni 2014; Morgante 2010; Nadjarzadeh 2011; Nouri 2019; Peivandi 2010; Rolf 1999; Scott 1998; Sharifzadeh 2016; Steiner 2020; Tsounapi 2018; Vinogradov 2019; Zavaczki 2003), and 14 in the head-to-head comparison (Alahmar 2019; Alahmar 2020; Akiyama 1999; Azizollahi 2013; Balercia 2005; Cheng 2018;

Conquer 2000; Eslamian 2020; Gonzalez-Ravina 2018; Li 2005a; Scott 1998; Sun 2018; Tsounapi 2018; Wang 2010).

- Sperm concentration at six months was reported as an outcome by 20 studies in the antioxidants versus placebo or no treatment comparison (Ardestani 2019; Azizollahi 2013; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Boonyarangkul 2015; Busetto 2018; Cavallini 2004; Ener 2016; Gamidov 2019; Gopinath 2013; Kizilay 2019; Lenzi 2004; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2011b; Safarinejad 2012; Schisterman 2020; Stenqvist 2018; Wong 2002), and four studies in the head-to-head comparison (Azizollahi 2013; Balercia 2005; Safarinejad 2009; Wong 2002).
- Sperm concentration at nine months or more was reported by five studies in the antioxidants versus placebo or no treatment comparison (Balercia 2005; Balercia 2009; Ener 2016; Safarinejad 2009a; Safarinejad 2012), and one study in the head-to-head comparison (Balercia 2005).

Data were extracted from 67 of the included studies. The 23 remaining studies either did not report any data or the number of patients in whom the outcome was assessed was not reported (Alahmar 2020; Biagiotti 2003; Eslamian 2013; Eslamian 2020; Exposito 2016; Galatioto 2008; Goswami 2015; Haje 2015; Huang 2020; Kumamoto 1988; Lenzi 2003; Lombardo 2002; Lu 2018; Martinez 2015; Micic 2019; Nozha 2001; Poveda 2013; Pryor 1978; Sivkov 2011; Sofikitis 2016; Vinogradov 2019; Wong 2002; Zalata 1998). In the current update, we calculated the mean and standard deviation from data presented as median and (interquartile) range from six studies included in previous versions of this review (Blomberg Jensen 2018; Cavallini 2004; Gamidov 2019; Micic 2019; Raigani 2014; Wong 2002). Another study reported data for a treatment duration of three to six months, but did not specify this any further and therefore data could not be used in the meta-analysis (Haje 2015).

See Characteristics of included studies and the analyses 'data not usable for meta-analysis'(Analysis 1.8; Analysis 1.10; Analysis 1.16; Analysis 1.20; Analysis 1.22). Table 2 also describes the outcomes and conclusions of all included studies. Attempts were made to contact all authors of the included studies for further details and clarification.

Excluded studies

We retrieved the full text of studies that were identified as potentially eligible (see Figure 1). In this update we excluded nine studies, in total we excluded 67 studies. Previously excluded study Raigani 2010, excluded based on ineligible outcome (MTHFR polymorphisms), was included as a sub-study of the primary included study Raigani 2014. The most common reasons for exclusions were ineligible due to use of a different intervention, study design or population. See details in Characteristics of excluded studies.

In summary:

- 22/67 ineligible based on different intervention such as an added sperm wash or herbal extract; also pentoxifylline studies were excluded;
- 15/67 ineligible based on different study design; they were not randomised;
- 20/67 ineligible based on different population, either women, normospermic men or used the exact same population as other already included studies; in the search of this update; two of the studies was already included in the 2018 update;
- 2/67 ineligible based on different outcome;
- 6/67 ineligible based on different control group, fertile men without treatment or control group was not treated with placebo, no treatment or another antioxidant;
- 2 previously 'ongoing studies' were placed in excluded studies because they were terminated due to insufficient recruiting (NCT01075334; NCT01520584).

Ongoing studies

Twelve studies were “ongoing studies” in the 2018 update. In the current update, six of the 12 previously ongoing studies were included (Amini 2020; Bahmyari 2021; Eslamian 2020; Joseph 2020; Kumalic 2020; Steiner 2020). NCT03337360 continued as an ongoing study with the status of still recruiting. The former ongoing study NCT03104998 was excluded based on withdrawal on the trial registry website. The former ongoing study NCT01407432 was placed in Studies awaiting classification after a message from the author that the manuscript had been submitted but not yet published. Former ongoing studies NCT00975117 and NCT01828710 were also placed in Studies awaiting classification with the status of “completed” on the trial registry website. The recruitment for former ongoing study DRKS00011616 had stopped and was therefore placed in Studies awaiting classification as well. Authors were contacted for (unpublished) results, with no reply.

We added 11 new ongoing studies (CTRI/2019/03/018303; IRCT20120215009014N322; IRCT20140622018187N9; IRCT20190406043177N1; IRCT20190714044209N1; IRCT20200911048689N1; NCT03634644; NCT04193358; NCT04256278; NCT04509583; PACTR201802003076341). In this 2021 update, a total of 12 studies are classified as 'ongoing studies'.

Awaiting classification

One study was “awaiting classification” in the 2018 update of this review (Goswami 2015). We included the study after confirmation by the authors that this was a randomised controlled trial.

Four formerly ongoing studies were placed in Studies awaiting classification (DRKS00011616; NCT00975117; NCT01407432; NCT01828710). The authors from NCT01407432 replied that the manuscript was under submission. The authors from the other three studies did not reply when contacted for further information.

One study from the updated 2021 search was placed in Studies awaiting classification (Kuzmenko 2018). It was not clear whether the study population was infertile men with abnormal semen parameters. The full report of this study was requested from the authors, with no reply.

Risk of bias in included studies

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

Allocation

Sequence generation

All 90 included studies were randomised, six of these were cross-over studies (Akiyama 1999; Kessopoulou 1995; Lenzi 2003; Lombardo 2002; Peivandi 2010; Pryor 1978), and the remaining studies were parallel design studies.

Only 47 studies described their methods of sequence generation and were rated as low risk in this domain (Abbasi 2020; Amini 2020; Ardestani 2019; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Barekat 2016; Biagiotti 2003; Blomberg Jensen 2018; Busetto 2018; Cavallini 2004; Cheng 2018; Cyrus 2015; Eslamian 2013; Eslamian 2020; Exposito 2016; Galatioto 2008; Gamidov 2017; Gamidov 2019; Gonzalez-Ravina 2018; Gopinath 2013; Haghighian 2015; Huang 2020; Joseph 2020; Kessopoulou 1995; Kizilay 2019; Kopets 2020; Kumalic 2020; Lu 2018; Martinez-Soto 2010; Micic 2019; Nadjarzadeh 2011; Popova 2019; Rolf 1999; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2011b; Safarinejad 2012; Schisterman 2020; Scott 1998; Sharifzadeh 2016; Sigman 2006; Steiner 2020; Stenqvist 2018; Tremellen 2007; Wong 2002; Zhou 2016) (see Figure 2 and Figure 3).

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

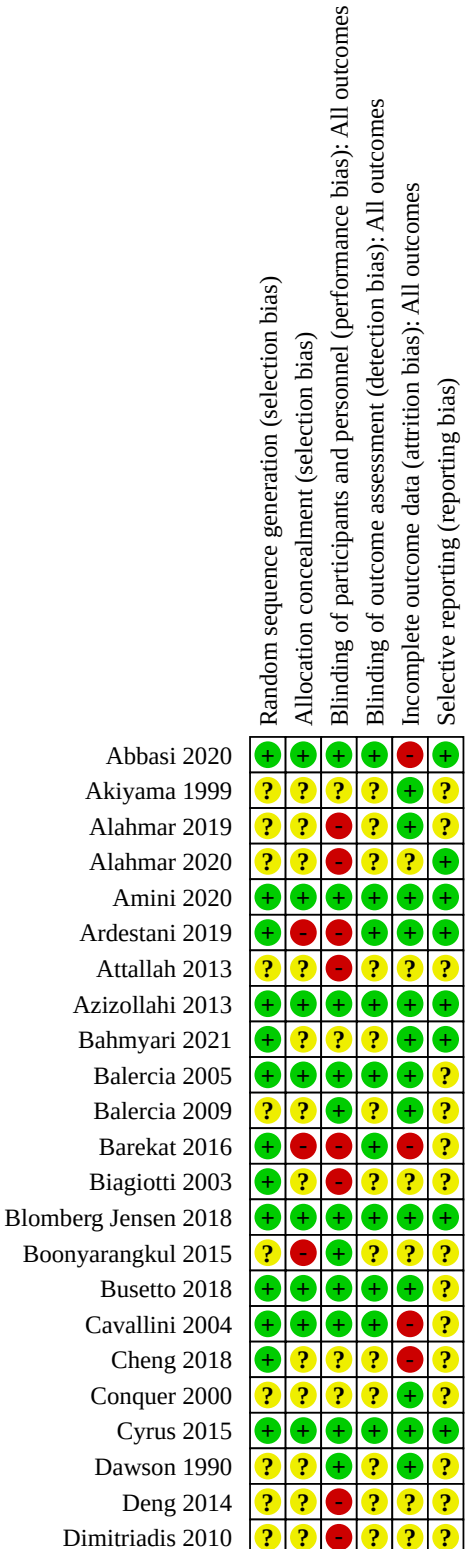


Figure 2. (Continued)

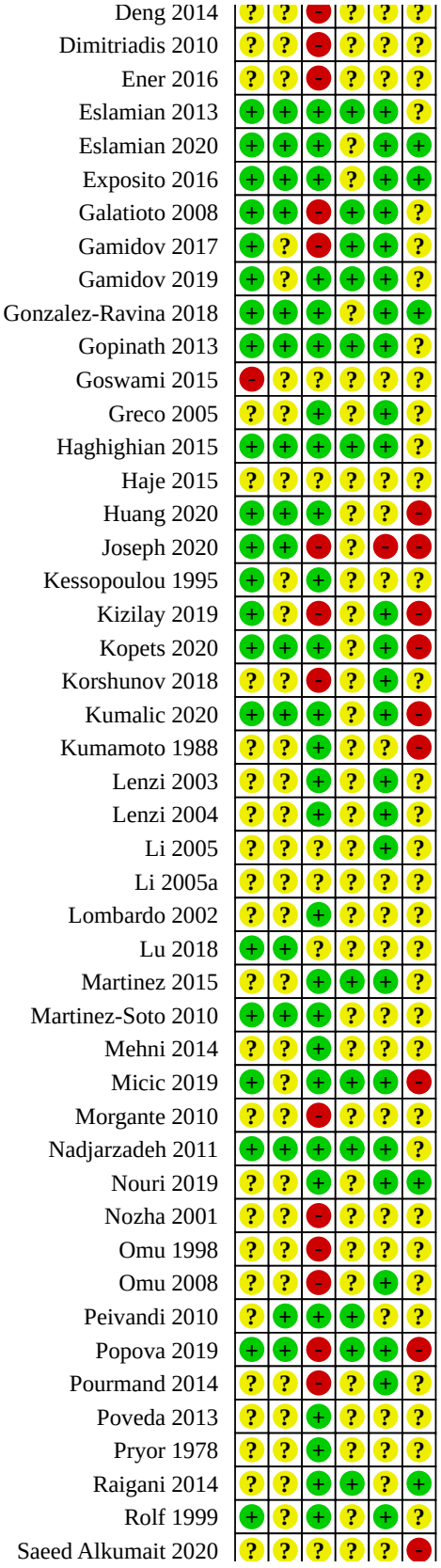


Figure 2. (Continued)

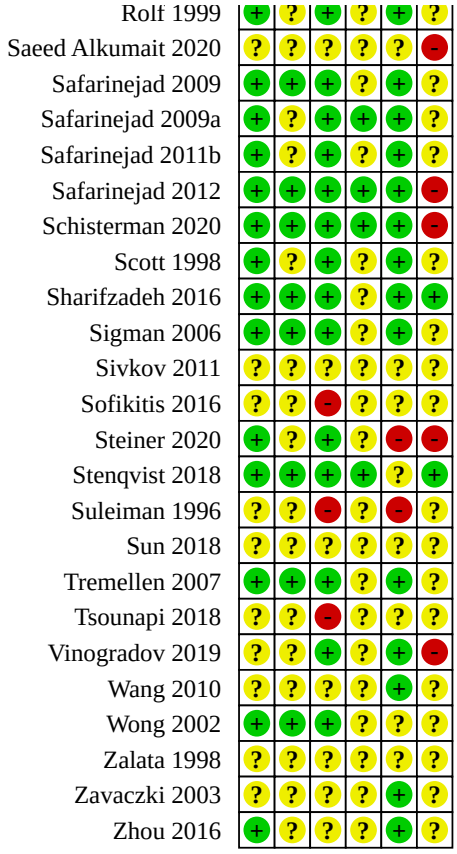
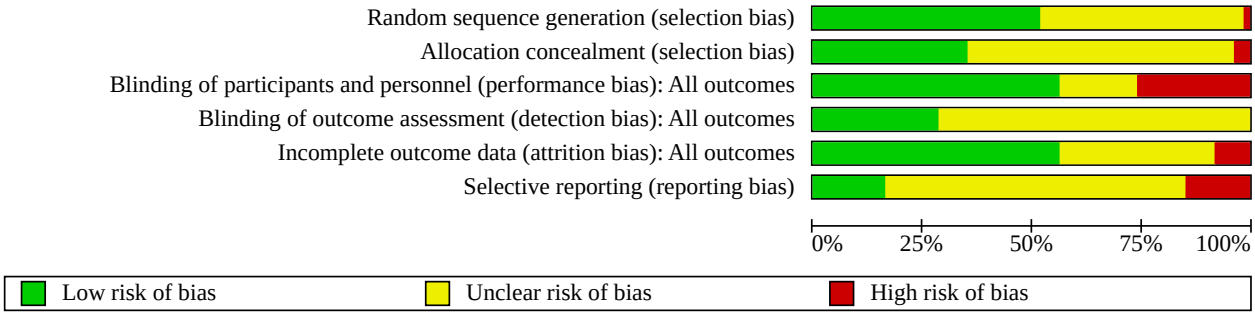


Figure 3. Methodological risk of bias graph: review authors' judgements about each methodological bias item presented as percentages across all included studies.



One study was rated as high risk in this domain, because the authors reported that "a placebo-controlled group was maintained in parallel" (Goswami 2015). The review team suspected that the placebo group in this study had not been randomised. Authors were contacted, with no reply to date.

The remaining 42 studies were rated as unclear risk (Alahmar 2019; Alahmar 2020; Akiyama 1999; Attallah 2013; Balercia 2009; Boonyarangkul 2015; Conquer 2000; Dawson 1990; Deng 2014; Dimitriadis 2010; Ener 2016; Greco 2005; Haje 2015; Korshunov 2018; Kumamoto 1988; Lenzi 2003; Lenzi 2004; Li 2005; Li 2005a; Lombardo 2002; Martinez 2015; Mehni 2014; Morgante 2010; Nouri 2019; Nozha 2001; Omu 1998; Omu 2008; Peivandi 2010; Pourmand 2014; Poveda 2013; Pryor 1978; Raigani 2014; Saeed Alkumait 2020; Sivkov 2011; Sofikitis 2016; Suleiman 1996; Sun 2018; Tsounapi 2018; Vinogradov 2019; Wang 2010; Zalata 1998; Zavaczki 2003).

The predominant method of randomisation was by computer-generated blocks. Tremellen 2007 reported a 2:1 ratio randomisation schedule, Cyrus 2015 reported a 3:2 randomisation

schedule, Li 2005 appeared to have a blocked 3:2 allocation, Kizilay 2019 appeared to have a 2:1 ratio, Gamidov 2019; Popova 2019; Sun 2018 appeared to have a 3:1 ratio, Micic 2019 appeared to have a 5:2 ratio and Zhou 2016 appeared to have a 7:5 ratio.

Allocation concealment

The methods of allocation concealment were generally quite poorly described in the included studies. Thirty-two studies described both their methods of randomisation and allocation concealment and were rated as low risk in this domain (Abbasi 2020; Amini 2020; Azizollahi 2013; Balercia 2005; Blomberg Jensen 2018; Busetto 2018; Cavallini 2004; Cyrus 2015; Eslamian 2013; Eslamian 2020; Exposito 2016; Galatioto 2008; Gonzalez-Ravina 2018; Gopinath 2013; Haghighian 2015; Huang 2020; Joseph 2020; Kopets 2020; Kumalic 2020; Lu 2018; Martinez-Soto 2010; Nadjarzadeh 2011; Peivandi 2010; Popova 2019; Safarinejad 2009; Safarinejad 2012; Schisterman 2020; Sharifzadeh 2016; Sigman 2006; Stenqvist 2018; Tremellen 2007; Wong 2002).

There were three studies with a high risk of allocation concealment: one due to the use of a randomisation table by the doctor (Barekat 2016); one due to great baseline imbalance for sperm parameters between the intervention and control group (Boonyarangkul 2015); and one due to the use of an open randomisation list, showing what the next randomisation would be (Ardestani 2019).

The remaining 55 studies were rated as unclear risk (Akiyama 1999; Alahmar 2019; Alahmar 2020; Attallah 2013; Bahmyari 2021; Balercia 2009; Biagiotti 2003; Cheng 2018; Conquer 2000; Dawson 1990; Deng 2014; Dimitriadis 2010; Ener 2016; Gamidov 2017; Gamidov 2019; Goswami 2015; Greco 2005; Haje 2015; Kessopoulou 1995; Kizilay 2019; Korshunov 2018; Kumamoto 1988; Lenzi 2003; Lenzi 2004; Li 2005; Li 2005a; Lombardo 2002; Martinez 2015; Mehni 2014; Micic 2019; Morgante 2010; Nozha 2001; Nouri 2019; Omu 1998; Omu 2008; Pourmand 2014; Poveda 2013; Pryor 1978; Raigani 2014; Rolf 1999; Saeed Alkumait 2020; Safarinejad 2009a; Safarinejad 2011b; Scott 1998; Sivkov 2011; Sofikitis 2016; Steiner 2020; Suleiman 1996; Sun 2018; Tsounapi 2018; Vinogradov 2019; Wang 2010; Zalata 1998; Zavaczki 2003; Zhou 2016). The methods of allocation concealment included anonymous coloured boxes, sealed opaque envelopes, and numbered bottles.

Blinding

Performance bias

Forty-three studies were described as randomised, double-blind controlled trials in which clinicians and participants were blinded (Azizollahi 2013; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Boonyarangkul 2015; Busetto 2018; Cavallini 2004; Cyrus 2015; Dawson 1990; Eslamian 2020; Exposito 2016; Gonzalez-Ravina 2018; Gopinath 2013; Greco 2005; Huang 2020; Kessopoulou 1995; Kopets 2020; Kumalic 2020; Kumamoto 1988; Lenzi 2003; Lenzi 2004; Lombardo 2002; Martinez 2015; Martinez-Soto 2010; Mehni 2014; Micic 2019; Nadjarzadeh 2011; Nouri 2019; Poveda 2013; Pryor 1978; Raigani 2014; Rolf 1999; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2011b; Safarinejad 2012; Scott 1998; Sharifzadeh 2016; Sigman 2006; Steiner 2020; Tremellen 2007; Vinogradov 2019; Wong 2002). In seven studies investigators, clinicians and participants were blinded (Abbasi 2020; Amini 2020; Eslamian 2013; Gamidov 2019; Haghighian 2015; Schisterman 2020; Stenqvist 2018). A total of fifty studies were rated as low risk (see Figure 3 and Figure 2). In one of the low risk studies (Dawson 1990), it was stated that a placebo was used as the control but only the participants were blinded.

Twenty-three other studies were rated high risk (Alahmar 2019; Alahmar 2020; Ardestani 2019; Attallah 2013; Barekat 2016; Biagiotti 2003; Deng 2014; Dimitriadis 2010; Ener 2016; Galatioto 2008; Gamidov 2017; Joseph 2020; Kizilay 2019; Korshunov 2018; Morgante 2010; Nozha 2001; Omu 1998; Omu 2008; Popova 2019; Pourmand 2014; Sofikitis 2016; Suleiman 1996; Tsounapi 2018). Of these high-risk studies, 18 studies used 'no treatment' as their comparator. Two studies were head-to-head trials and open-labelled (Alahmar 2019; Alahmar 2020; Deng 2014; Nozha 2001). The double-blinded trial Suleiman 1996 used a placebo, however they reported that if a couple became pregnant then "the treatment was stopped; otherwise it was continued for 6 months. The placebo was given for 6 months." This does appear that they did not stop the placebo. This could suggest that the investigators had knowledge of whether the participants were in the placebo or antioxidant group, therefore this study was rated as high risk.

Sixteen studies did not give a statement regarding blinding and were rated as unclear risk of bias (Akiyama 1999; Bahmyari 2021; Cheng 2018; Conquer 2000; Goswami 2015; Haje 2015; Li 2005; Li 2005a; Lu 2018; Saeed Alkumait 2020; Sivkov 2011; Sun 2018; Wang 2010; Zalata 1998; Zavaczki 2003; Zhou 2016). Seven of these studies used a placebo as the control but did not discuss blinding (Bahmyari 2021; Conquer 2000; Goswami 2015; Lu 2018; Saeed Alkumait 2020; Sivkov 2011; Zavaczki 2003).

As nutritional supplements with antioxidant properties are freely available, this could have introduced bias in the included studies. None of the included studies monitored or reported use of additional supplements other than the intervention during the study. However, most included studies reported the use of other nutritional supplement as an exclusion criterion and instructed participants to withhold from such supplement use during the study.

Detection bias

The methods of blinding outcome assessment were generally poorly described in the included studies. Only 26 studies reported this aspect of blinding and were therefore classified as low risk (Abbasi 2020; Amini 2020; Ardestani 2019; Azizollahi 2013; Balercia 2005; Barekat 2016; Blomberg Jensen 2018; Busetto 2018; Cavallini 2004; Cyrus 2015; Eslamian 2013; Galatioto 2008; Gamidov 2017; Gamidov 2019; Gopinath 2013; Haghighian 2015; Martinez 2015; Micic 2019; Nadjarzadeh 2011; Peivandi 2010; Popova 2019; Raigani 2014; Safarinejad 2009a; Safarinejad 2012; Schisterman 2020; Stenqvist 2018).

The other 64 studies were rated as unclear risk due to the lack of information (Akiyama 1999; Alahmar 2019; Alahmar 2020; Attallah 2013; Bahmyari 2021; Balercia 2009; Biagiotti 2003; Boonyarangkul 2015; Cheng 2018; Conquer 2000; Dawson 1990; Deng 2014; Dimitriadis 2010; Ener 2016; Eslamian 2020; Exposito 2016; Gonzalez-Ravina 2018; Greco 2005; Goswami 2015; Haje 2015; Huang 2020; Joseph 2020; Kessopoulou 1995; Kizilay 2019; Kopets 2020; Korshunov 2018; Kumalic 2020; Kumamoto 1988; Lenzi 2003; Lenzi 2004; Li 2005; Li 2005a; Lombardo 2002; Lu 2018; Martinez-Soto 2010; Mehni 2014; Morgante 2010; Nouri 2019; Nozha 2001; Omu 1998; Omu 2008; Pourmand 2014; Poveda 2013; Pryor 1978; Rolf 1999; Saeed Alkumait 2020; Safarinejad 2009; Safarinejad

2011b; Scott 1998; Sharifzadeh 2016; Sigman 2006; Sivkov 2011; Sofikitis 2016; Steiner 2020; Suleiman 1996; Sun 2018; Tremellen 2007; Tsounapi 2018; Vinogradov 2019; Wang 2010; Wong 2002; Zalata 1998; Zavaczki 2003; Zhou 2016).

Incomplete outcome data

Fifty-one studies were rated as low risk for incomplete outcome data (Akiyama 1999; Alahmar 2019; Amini 2020; Ardestani 2019; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Busetto 2018; Conquer 2000; Cyrus 2015; Dawson 1990; Eslamian 2013; Eslamian 2020; Exposito 2016; Gopinath 2013; Galatioto 2008; Gamidov 2017; Gamidov 2019; Gonzalez-Ravina 2018; Greco 2005; Haghighian 2015; Kizilay 2019; Kopets 2020; Korshunov 2018; Kumalic 2020; Lenzi 2003; Lenzi 2004; Li 2005; Martinez 2015; Micic 2019; Nadjarzadeh 2011; Nouri 2019; Omu 2008; Popova 2019; Pourmand 2014; Rolf 1999; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2011b; Safarinejad 2012; Schisterman 2020; Scott 1998; Sharifzadeh 2016; Sigman 2006; Tremellen 2007; Vinogradov 2019; Wang 2010; Zavaczki 2003; Zhou 2016).

Thirty-two studies were rated as unclear, most of them did report the number of dropouts, but did not provide the reasons (Alahmar 2020; Attallah 2013; Biagiotti 2003; Boonyarangkul 2015; Deng 2014; Dimitriadis 2010; Ener 2016; Goswami 2015; Haje 2015; Huang 2020; Kessopoulou 1995; Kumamoto 1988; Li 2005a; Lombardo 2002; Lu 2018; Martinez-Soto 2010; Mehni 2014; Morgante 2010; Nozha 2001; Omu 1998; Peivandi 2010; Poveda 2013; Pryor 1978; Raigani 2014;Saeed Alkumait 2020; Sivkov 2011; Sofikitis 2016; Stenqvist 2018; Sun 2018; Tsounapi 2018; Wong 2002; Zalata 1998).

Six studies were rated as high risk of attrition bias due to lack of compliance directly related to treatment and high dropout rates (16% to 42%) (Abbasi 2020; Barekat 2016; Cavallini 2004; Cheng 2018; Joseph 2020; Suleiman 1996). One study was rated as high risk of attrition bias despite the fact that high dropout rates were accounted for, because the results tables appeared to have additional missing data without clarification (Steiner 2020).

None of the included studies reported on "missing not at random", which could be introduced by participants not returning for a subsequent semen analysis if a pregnancy occurred before that date.

Only 10 studies (Balercia 2009; Blomberg Jensen 2018; Busetto 2018; Eslamian 2020; Galatioto 2008; Joseph 2020; Pryor 1978; Safarinejad 2011b; Schisterman 2020; Steiner 2020) actually stated that they used intention-to-treat (ITT) in their analysis. However, Pryor 1978 stated they had used ITT, but the data were not presented. Most of the other included studies accounted for the participants that withdrew from their studies and then analysed the groups using a per protocol approach.

Five studies (Azizollahi 2013; Barekat 2016; Cheng 2018; Kizilay 2019; Wang 2010) did not use ITT, however the numbers of dropouts were given for each intervention and control group, and therefore we were able to use ITT in the data analysis by making the assumption of no event for the binary outcomes. No imputation was carried out on the continuous outcome data; these were analysed as they were reported in the studies.

Nine studies had over 20% withdrawal from their studies. Cavallini 2004 had a 30% dropout rate and reasons were provided for only 53 out of the 55 dropouts; these reasons included refusal due to the chance of taking a placebo and preference for assisted reproduction techniques (ARTs). There also remained some confusion in this study on the total numbers randomised and analysed. Abbasi 2020 and Joseph 2020 both had a dropout rate of around 32%; Azizollahi 2013 had a 30% dropout rate; Li 2005a; Steiner 2020; Suleiman 1996, Nadjarzadeh 2011, and Barekat 2016 had slightly over 20% withdrawal from their studies.

One study (Suleiman 1996) had a large imbalance in numbers. There were found to be 52 in the treatment group and 35 in the placebo group once the code had been broken at the end of the study. There was no indication of how the randomisation was performed. The reasons given for dropout were only accounted for broadly: many couples had left the region and some simply failed to continue; no numbers were given for individual dropout reasons (see Figure 3 and Figure 2). The numbers of participants that were initially randomised to each group were not available, so ITT for the dichotomous outcomes was not possible.

Selective reporting

Study protocols were only available for 18 out of the 90 included studies (Amini 2020; Ardestani 2019; Azizollahi 2013; Bahmyari 2021; Blomberg Jensen 2018; Cyrus 2015; Eslamian 2020; Exposito 2016; Gonzalez-Ravina 2018; Joseph 2020; Kopets 2020; Kumalic 2020; Nouri 2019; Raigani 2014; Schisterman 2020; Sharifzadeh 2016; Steiner 2020; Stenqvist 2018). The study protocol of Alahmar 2019 was published after completion of the study and was therefore rated as unclear risk.

Thirteen studies were rated at high risk of reporting bias. Kumamoto 1988 performed subgroup analysis post-treatment and Safarinejad 2012 did not pre-specify outcomes. Two of these 13 studies were rated at high risk of reporting bias because outcomes defined in the study protocol were not reported in the full text of the study (Kopets 2020; Kumalic 2020). Nine of these 13 studies were rated at high risk of reporting bias because outcomes defined in the methods section of the articles were not reported in the outcomes section, or the results of certain subgroups of the study population were omitted (Huang 2020; Joseph 2020; Kizilay 2019; Micic 2019; Popova 2019; Saeed Alkumait 2020; Schisterman 2020; Steiner 2020; Vinogradov 2019).

Seven studies were rated as unclear risk as they were conference abstracts (Attallah 2013; Biagiotti 2003; Goswami 2015; Korshunov 2018; Lombardo 2002; Sofikitis 2016; Zalata 1998), and two studies were rated as unclear as it was possible that these were two publications of the same study that were reporting on different intervention arms (Li 2005; Li 2005a). Obtaining help with Chinese translation did not clarify this and attempts to contact the authors were unsuccessful. The remaining 52 studies were rated as unclear risk in this domain because there were no published study protocols available.

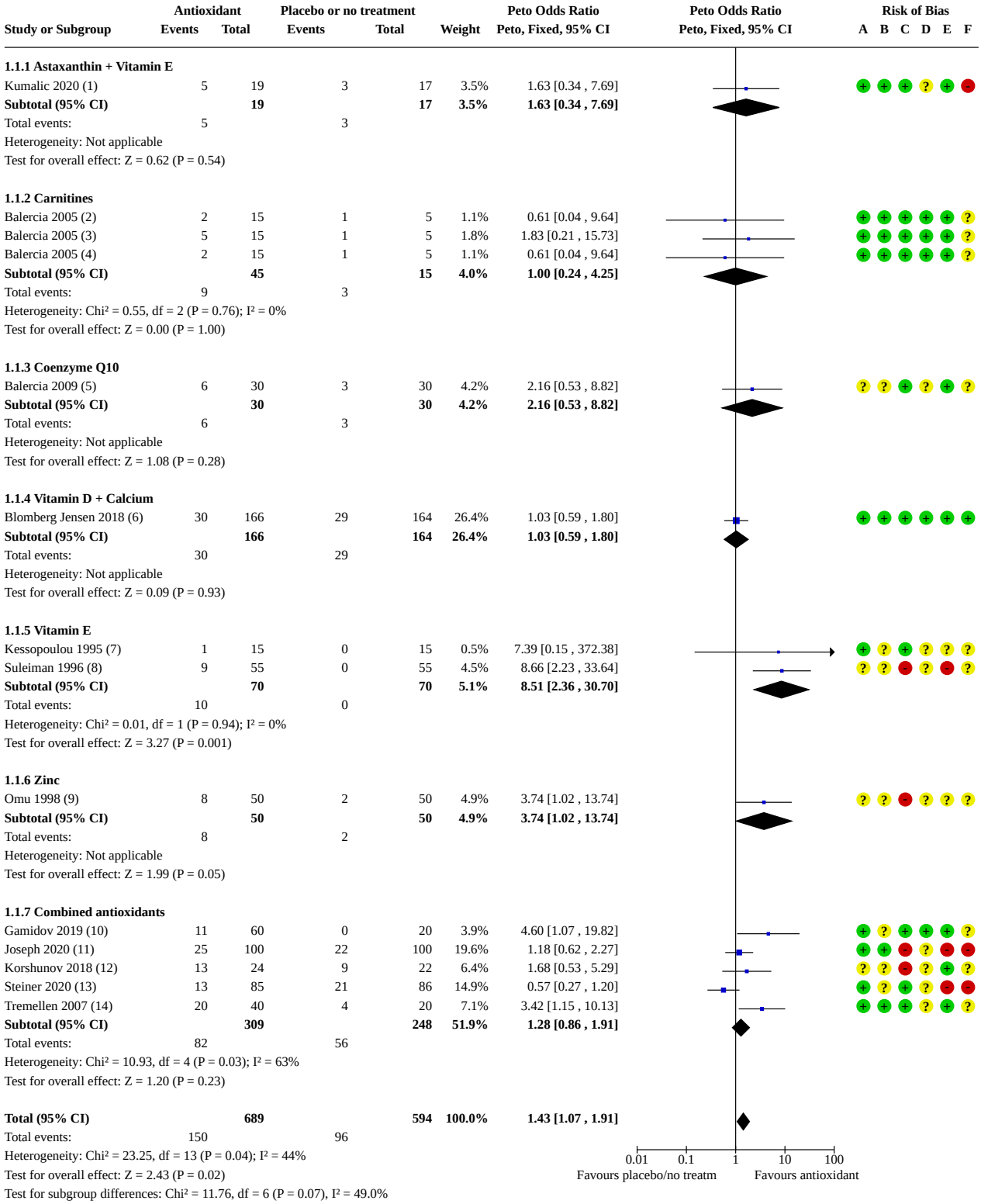
Other potential sources of bias

There were no other sources of bias in the included studies.

In summary, none of the included studies was rated as low risk of bias in all domains. More than half of the included studies (52 of the 90 included studies) was rated as unclear risk of bias in at least one domain. Thirty-eight included studies were rated as high risk of bias in at least one domain (Figure 2).

In the comparison of antioxidant versus placebo or no treatment with the outcome of live birth, half of the studies was rated as unclear risk of bias in at least one domain. The other half of the studies in this comparison was rated as high risk of bias in at least one domain (Figure 4).

Figure 4. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.1 Live birth; type of antioxidant.



Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.

(2) L-acetyl carnitine 3000 mg. Natural conception. Additional data from author received.

Figure 4. (Continued)

(1) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.
(2) L-acetyl carnitine 3000 mg. Natural conception. Additional data from author received.
(3) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Natural conception. Additional data from author received.
(4) L-carnitine 3000 mg. Natural conception. Additional data from author received.
(5) Coenzyme Q10 200 mg. Natural conception. Additional data from author received.
(6) Vitamin D 1400IU + Calcium 500 mg. Natural conception for 11/ 59 pregnancies, no significant difference between groups.
(7) Vitamin E 600 mg. IVF.
(8) Vitamin E 300 mg. Natural conception. Unable to use ITT as it was unknown from which group the 23 were lost from.
(9) Zinc 500 mg. Natural conception.
(10) SpermActin Forte. From e-mail: natural conception.
(11) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(12) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(13) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D. Natural conception and IUI with ovulation induction with Clomid.
(14) Menevit. IVF: 3 sets of twin pregnancies in the combined antioxidants group and nil in the control group. Each twin pregnancy was counted as one pregnancy event.

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

Effects of interventions

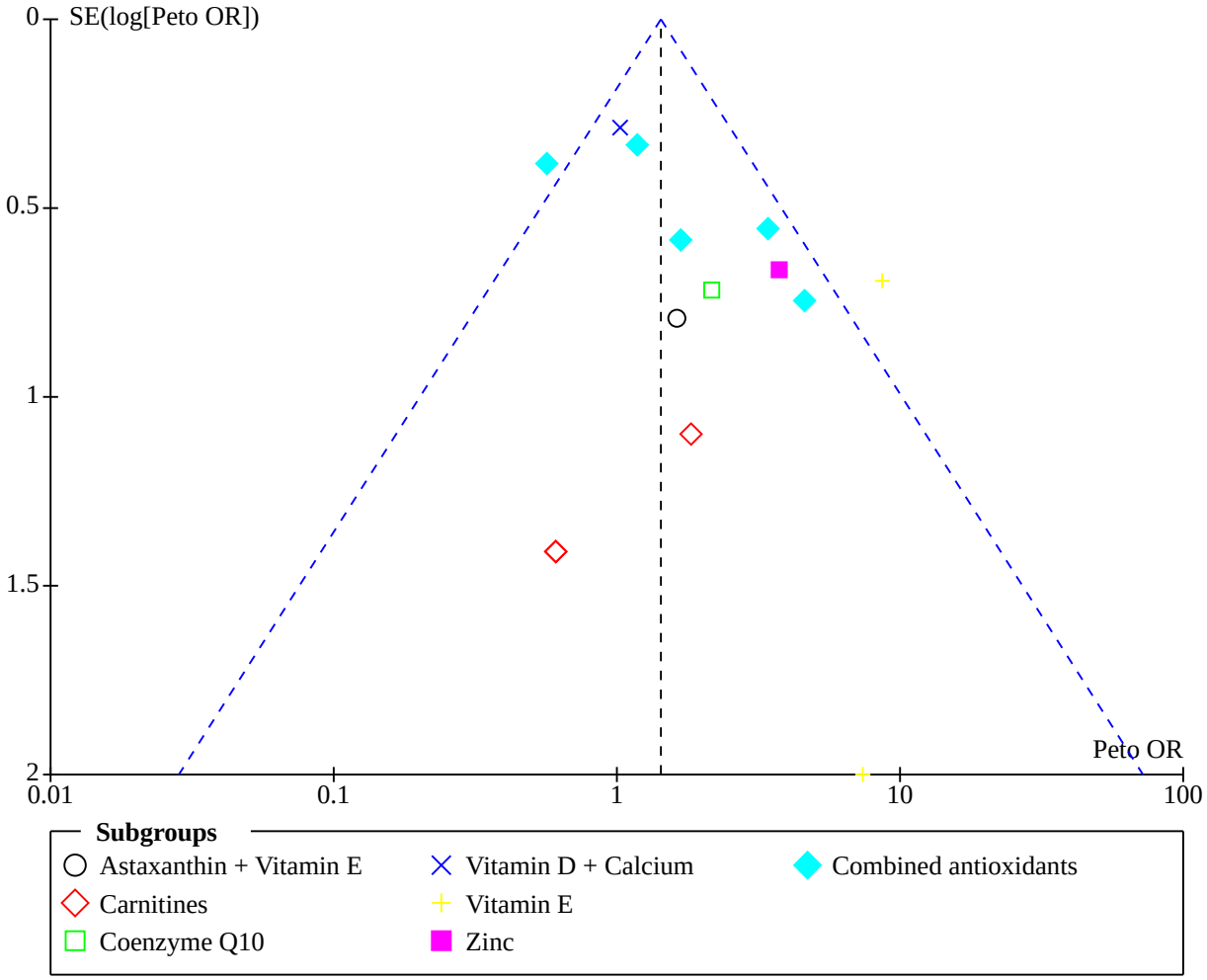
See: **Summary of findings 1** Antioxidants compared to placebo or no treatment for patients with male subfertility

1 Antioxidants versus placebo or no treatment (natural conception and undergoing fertility treatment)

1.1 Live birth; type of antioxidant

See Analysis 1.1 and Figure 4, Figure 5.

Figure 5. Funnel plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.1 Live birth; type of antioxidant.



Only 12 studies reported on live birth; seven of these had methodological inadequacies as they did not describe their methods of randomisation or allocation concealment. Three studies reported that all clinical pregnancies led to a live birth (Balercia 2005; Balercia 2009; Kessopoulou 1995). The meta-analysis of the 12 studies showed that antioxidants were associated with increased live birth rate compared with placebo or no treatment (Peto odds ratio (OR) 1.43, 95% confidence interval (CI) 1.07 to 1.91, 1283 men, 12 RCTs, P = 0.02, I^2 = 44%, very low-certainty evidence). This means that, for subfertile men with a baseline expected live birth rate of 16%, use of an antioxidant could increase this rate to between 17% and 27% (Summary of findings 1).

1.1.1 One study reported on this outcome comparing astaxanthin plus vitamin E versus placebo (Kumalic 2020). There was no evidence of increased live birth rate (Peto OR 1.63, 95% CI 0.34 to 7.69, 36 men, P = 0.54, I^2 = not applicable).

1.1.2 One study reported on this outcome comparing carnitines versus placebo (Balercia 2005). There was no evidence of increased live birth rate (Peto OR 1.00, 95% CI 0.24 to 4.25; 60 men, P = 1.00, I^2 = not applicable).

1.1.3 One study reported on this outcome comparing coenzyme Q10 versus placebo (Balercia 2009). There was no evidence of increased live birth rate (Peto OR 2.16, 95% CI 0.53 to 8.82; 60 men, P = 0.28, I^2 = not applicable).

1.1.4 One study reported on this outcome comparing vitamin D plus calcium versus placebo (Blomberg Jensen 2018). There was no evidence of increased live birth rate (Peto OR 1.03, 95% CI 0.59 to 1.80, 330 men, P = 0.93, I^2 = not applicable).

1.1.5 Two studies reported on this outcome comparing vitamin E versus placebo (Kessopoulou 1995; Suleiman 1996). There appeared to be evidence of increased live birth rate (Peto OR 8.51, 95% CI 2.36 to 30.70, 140 men, 2 RCTs, P = 0.001, I^2 = 0%).

1.1.6 One study reported on this outcome comparing zinc versus no treatment (Omu 1998). There was no evidence of increased live birth rate (Peto OR 3.74, 95% CI 1.02 to 13.74, 100 men, P = 0.05, I^2 = not applicable).

1.1.7 Five studies reported on this outcome comparing combined antioxidants versus placebo or no treatment (Gamidov 2019;

Joseph 2020; Korshunov 2018; Steiner 2020; Tremellen 2007). There was no evidence of increased live birth rate (Peto OR 1.28, 95% CI 0.86 to 1.91, 557 men, P = 0.23, I^2 = 63%). The results from Tremellen 2007 also included three sets of twins in the combined antioxidant group and nil in the placebo group. Each twin birth was counted as one event as stated in the methods section in the review protocol.

There was no evidence that different antioxidants had differing effects (test for subgroup differences Chi^2 = 11.76, P = 0.07).

A sensitivity analysis was carried out using as-treated data, which did not show a different result compared with the intention-to-treat data (Peto OR 1.49, 95% CI 1.10 to 2.00, 1090 men, 12 RCTs, P = 0.009, I^2 = 28%).

Sensitivity analysis for studies with no treatment as control

Three studies (Joseph 2020; Korshunov 2018; Omu 1998) used 'no treatment' as the control group instead of placebo. When these studies were removed from the analysis, no evidence of increased live birth remained when compared with placebo only (Peto OR 1.39, 95% CI 0.98 to 1.97, 937 men, 9 RCTs, P = 0.06, I^2 = 52%).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 9.50, P = 0.09).

Sensitivity analysis for studies reporting live birth and clinical pregnancy

The 12 studies that reported live birth had an OR for live birth of 1.43, and in these same studies the OR for clinical pregnancy was 1.62. When we pooled all 20 studies reporting the clinical pregnancy rate there was a higher OR 1.89. This suggests that there is no overestimation of live birth. However, the true effect is unknown unless all studies reporting on clinical pregnancy rate also reported on live birth rate.

Sensitivity analysis for studies rated as high risk of bias

When the four studies (Joseph 2020; Korshunov 2018; Omu 1998; Suleiman 1996) rated with a high risk of bias were removed from the analysis, there was no evidence of association between antioxidants and an increased live birth rate when compared with placebo (Peto OR 1.22, 95% CI 0.85 to 1.75, 827 men, 8 RCTs, P = 0.27, I^2 = 32%).

1.2 Live birth; in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI)

See Analysis 1.2.

There were only five studies in women undergoing IVF/ICSI which reported on live birth (Joseph 2020; Kessopoulou 1995; Korshunov 2018; Kumalic 2020; Tremellen 2007). There appeared to be evidence of increased live birth rate, in those couples undergoing IVF/ICSI, with antioxidant use when compared with placebo (Peto OR 1.63, 95% CI 1.01 to 2.16, 5 RCTs, 372 men, P = 0.04, I^2 = 0%).

1.3 Clinical pregnancy; type of antioxidant

See Analysis 1.3 and Figure 6 and Figure 7.

Figure 6. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.3 Clinical pregnancy; type of antioxidant.

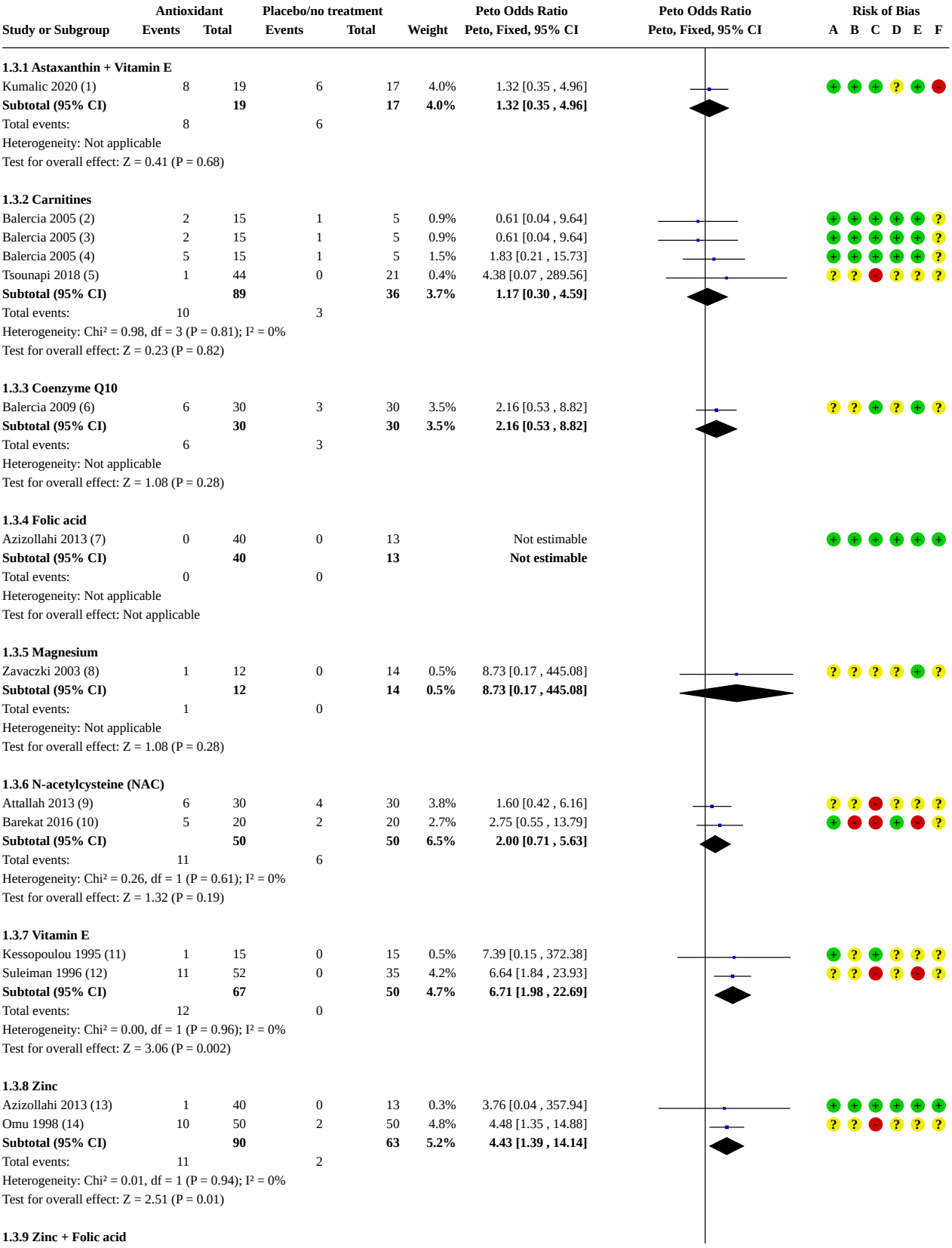
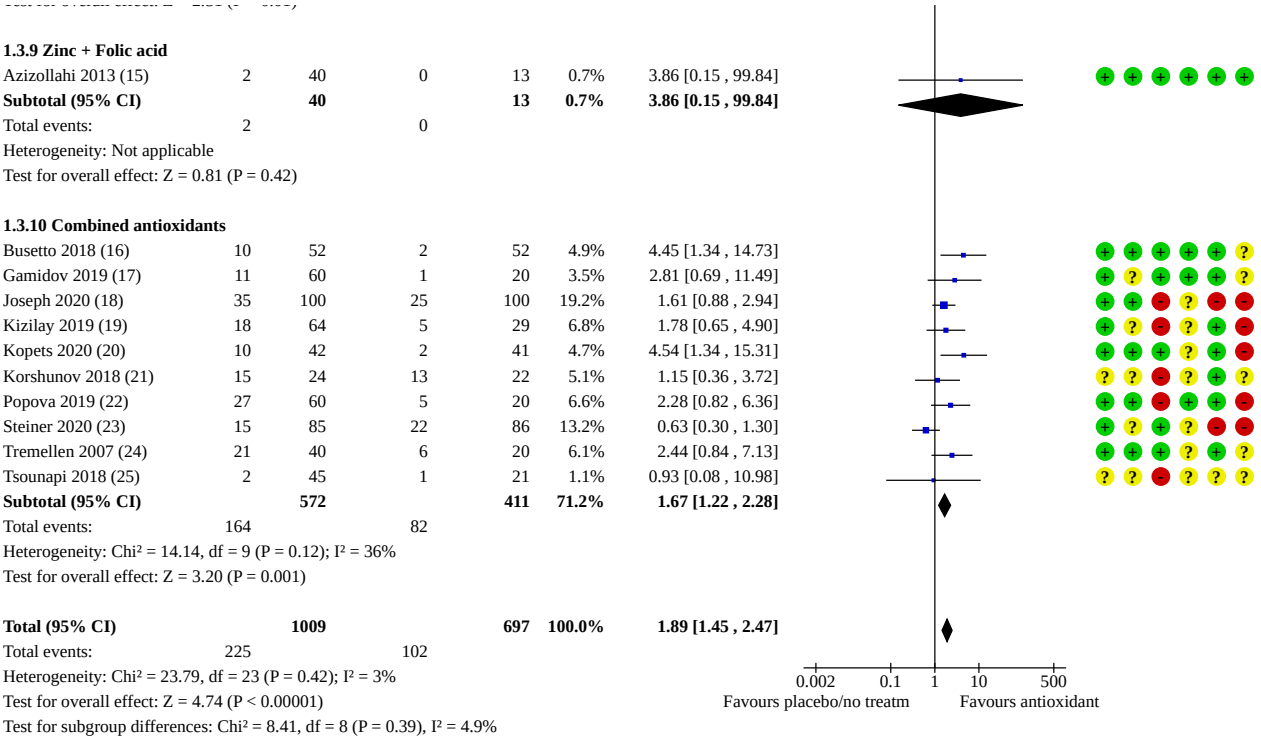


Figure 6. (Continued)



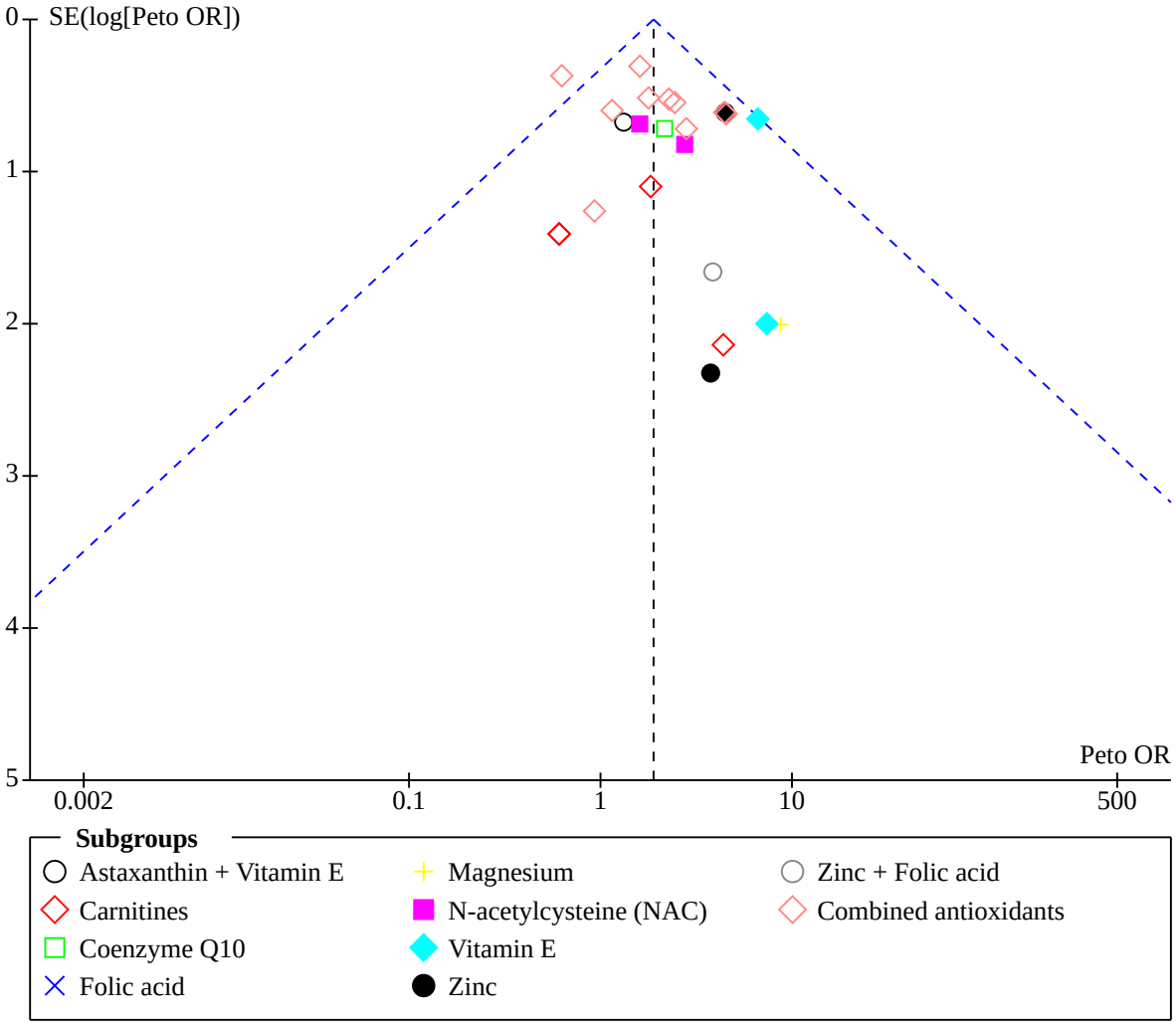
Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.
(2) L-acetyl carnitine 3000 mg. Natural conception.
(3) L-carnitine 3000 mg. Natural conception.
(4) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Natural conception.
(5) L-carnitine 1000 mg. Appear to be spontaneous. Trial with 5 arms, 1 event in control group used in "Combined antioxidants" subgroup.
(6) Coenzyme Q10 200 mg. Natural conception.
(7) Folic acid 5 mg. Natural conception. After varicocelectomy. Additional data from authors received on pregnancy and dropouts.
(8) Magnesium 3000 mg. Natural conception.
(9) N-acetylcysteine (NAC) 600 mg. IUI.
(10) N-acetylcysteine (NAC) 200 mg. Natural conception. After varicocelectomy
(11) Vitamin E 600 mg. IVF.
(12) Vitamin E 300 mg. Natural conception.
(13) Zinc 66 mg. Natural conception. After varicocelectomy. Additional data from authors received on pregnancy and dropouts.
(14) Zinc 500 mg. Natural conception.
(15) Zinc 66 mg + Folic acid 5 mg. Natural conception. After varicocelectomy. Additional data from authors received on pregnancy and dropouts.
(16) Proxeed plus. Spontaneous. Also 1 spontaneous abortion. Varicocele patients
(17) SpermActin Forte. Spontaneous. Clarification in e-mail, see included studies table.
(18) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(19) L-carnitine 1 g + acetyl-L-carnitine 0,5 g + fructose 1 g + citric acid 50 mg + vitamin C 90 mg + zinc 10 mg + folic acid 200 mcg + selenium 50 mcg + coenzyme Q10 20 mg +
(20) Verum TDS (l-carnitine/ l-acetyl-carnitine 1990 mg + l-arginine 250 mg + glutathione 100 mg + coenzyme Q10 40 mg + zinc 7.5 mg + vitamin B9 234 mg + vitamin B12 2 mcg
(21) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(22) Androdoz. IVF/ICSI.
(23) Vitamin C 500 mg + vitamin E 400 mg + selenium 0.20 mg + l-carnitine 1000 mg + zinc 20 mg + folic acid 1000 mg + lycopene 10 mg + vitamin D 2,000 IU. Natural conceptic
(24) Menevit. Additional data from author received: IVF: 3 sets of twin pregnancies in the combined antioxidants group, each twin was counted as one pregnancy event.
(25) Profertil. Appear to be spontaneous.

Risk of bias legend

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

Figure 7. Funnel plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.5 Clinical pregnancy; type of antioxidant.



Only 20 studies (with 25 intervention arms) reported on clinical pregnancy rate; six of these had methodological inadequacies with high risk of bias for methods of randomisation, allocation concealment or blinding. The meta-analysis of these studies showed that antioxidants were associated with an increased clinical pregnancy rate when compared with placebo or no treatment (Peto OR 1.89, 95% CI 1.45 to 2.47, 1706 men, 20 RCTs, 25 intervention arms, P < 0.00001, I^2 = 3%, low-certainty evidence). This means that, for subfertile men with a baseline expected clinical pregnancy rate of 15%, use of an antioxidant could increase this rate to between 20% and 30% (Summary of findings 1).

1.3.1 One study reported on this outcome comparing astaxanthin plus vitamin E versus placebo (Kumalic 2020). There was no evidence of increased clinical pregnancy rate (Peto OR 1.32, 95% CI 0.35 to 4.96, 36 men, P = 0.68, I^2 = not applicable).

1.3.2 Two studies reported on this outcome comparing carnitines versus placebo (Balercia 2005; Tsounapi 2018). There was no evidence of increased clinical pregnancy rate (Peto OR 1.17, 95% CI 0.30 to 4.59, 125 men, 2 RCTs, P = 0.82, I^2 = 0%). In Tsounapi 2018, the one and only event in the control group was used in the "Combined antioxidants" subgroup (1.5.11), as all results for clinical pregnancies were pooled.

1.3.3 One study reported on this outcome comparing coenzyme Q10 versus placebo (Balercia 2009). There was no evidence of increased clinical pregnancy rate (Peto OR 2.16, 95% CI 0.53 to 8.82, 60 men, 1 RCT, P = 0.28, I^2 = not applicable).

1.3.4 One study reported on this outcome comparing folic acid versus placebo (Azizollahi 2013). There was no OR estimable due to the occurrence of zero pregnancies in both groups.

1.3.5 One study reported on this outcome comparing magnesium versus placebo (Zavaczki 2003). There was no evidence of increased clinical pregnancy rate (Peto OR 8.73, 95% CI 0.17 to 445.08, 1 RCT, 26 men, P = 0.28, I^2 = not applicable).

1.3.6 Two studies reported on this outcome comparing N-acetylcysteine versus placebo or no treatment (Attallah 2013;

Barekat 2016). There was no evidence of increased clinical pregnancy rate (Peto OR 2.00, 95% CI 0.71 to 5.63, 100 men, 2 RCTs, P = 0.19, I^2 = 0%).

1.3.7 Two studies reported on this outcome comparing vitamin E versus placebo (Kessopoulou 1995; Suleiman 1996). There appeared to be an increased clinical pregnancy rate (Peto OR 6.71, 95% CI 1.98 to 22.69, 2 RCTs, 117 men, P = 0.002, I^2 = 0%).

1.3.8 Two studies reported on this outcome comparing zinc versus placebo or no treatment (Azizollahi 2013; Omu 1998). There appeared to be an increased clinical pregnancy rate (Peto OR 4.43, 95% CI 1.39 to 14.14, 2 RCTs, 153 men, P = 0.01, I^2 = 0%).

1.3.9 One study reported on this outcome comparing zinc with folic acid versus placebo (Azizollahi 2013). There was no evidence of increased clinical pregnancy rate (Peto OR 3.86, 95% CI 0.15 to 99.84, 53 men, 1 RCT, P = 0.42, I^2 = not applicable).

1.3.10 Ten studies reported on this outcome comparing combined antioxidants versus placebo or no treatment (Busetto 2018; Gamidov 2019; Joseph 2020; Kizilay 2019; Kopets 2020; Korshunov 2018; Popova 2019; Steiner 2020; Tremellen 2007; Tsounapi 2018). There appeared to be an increased clinical pregnancy rate (Peto OR 1.67, 95% CI 1.22 to 2.28, 983 men, 10 RCTs, P = 0.001, I^2 = 36%).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 8.41, P = 0.39).

Sensitivity analysis for studies with no treatment as control

Seven studies used 'no treatment' as control group instead of placebo (Attallah 2013; Joseph 2020; Kizilay 2019; Korshunov 2018; Omu 1998; Popova 2019; Tsounapi 2018). When these studies were removed from the analysis, the association between antioxidant use and increased clinical pregnancy rate remained (Peto OR 1.96, 95% CI 1.36 to 2.83, 996 men, 13 RCTs, 17 intervention arms, P = 0.0003, I^2 = 25%).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 6.43, P = 0.60).

Sensitivity analysis for studies rated as high risk of bias

When the seven studies rated with a high risk of bias were removed from the analysis, there remained an association between antioxidants and an increased clinical pregnancy rate (Peto OR 1.78, 95% CI 1.26 to 2.51, 1042 men, 13 RCTs, P = 0.001, I^2 = 8%) (Attallah 2013; Barekat 2016; Joseph 2020; Korshunov 2018; Omu 1998; Suleiman 1996; Tsounapi 2018).

Sensitivity analysis for studies enrolling men with varicocele

When the four studies that enrolled men with varicocele or after varicocelectomy were removed from the analysis, the use of antioxidants remained associated with increased clinical pregnancy rate when compared with placebo or no treatment (Peto OR 1.78, 95% CI 1.34 to 2.38, 1179 men, 15 RCTs, P < 0.0001, I^2 = 23%) (Azizollahi 2013; Barekat 2016; Busetto 2018; Kizilay 2019).

Sensitivity analysis for studies enrolling men in couples undergoing intrauterine insemination (IUI)

Two studies reported on men in couples undergoing IUI (Attallah 2013; Steiner 2020). When these studies were removed from the analysis there remained an association between the use of antioxidants and increased clinical pregnancy rate when compared with placebo or no treatment (Peto OR 2.25, 95% CI 1.69 to 3.00, 1245 men, 17 RCTs, P < 0.0001, I^2 = 0%).

1.4 Clinical pregnancy; IVF/ICSI

See Analysis 1.4.

There were six studies in women undergoing IVF/ICSI which reported on clinical pregnancy rate (Joseph 2020; Kessopoulou 1995; Korshunov 2018; Kumalic 2020; Popova 2019; Tremellen 2007). The meta-analysis of these studies showed an increase in clinical pregnancy in those couples undergoing IVF/ICSI, when antioxidant use was compared with placebo or no treatment (Peto OR 1.73, 95% CI 1.15 to 2.61, 452 men, 6 RCTs, P = 0.009, I^2 = 0%).

1.5 Adverse events

See Analysis 1.5 and Figure 8.

Figure 8. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.5 Adverse events.

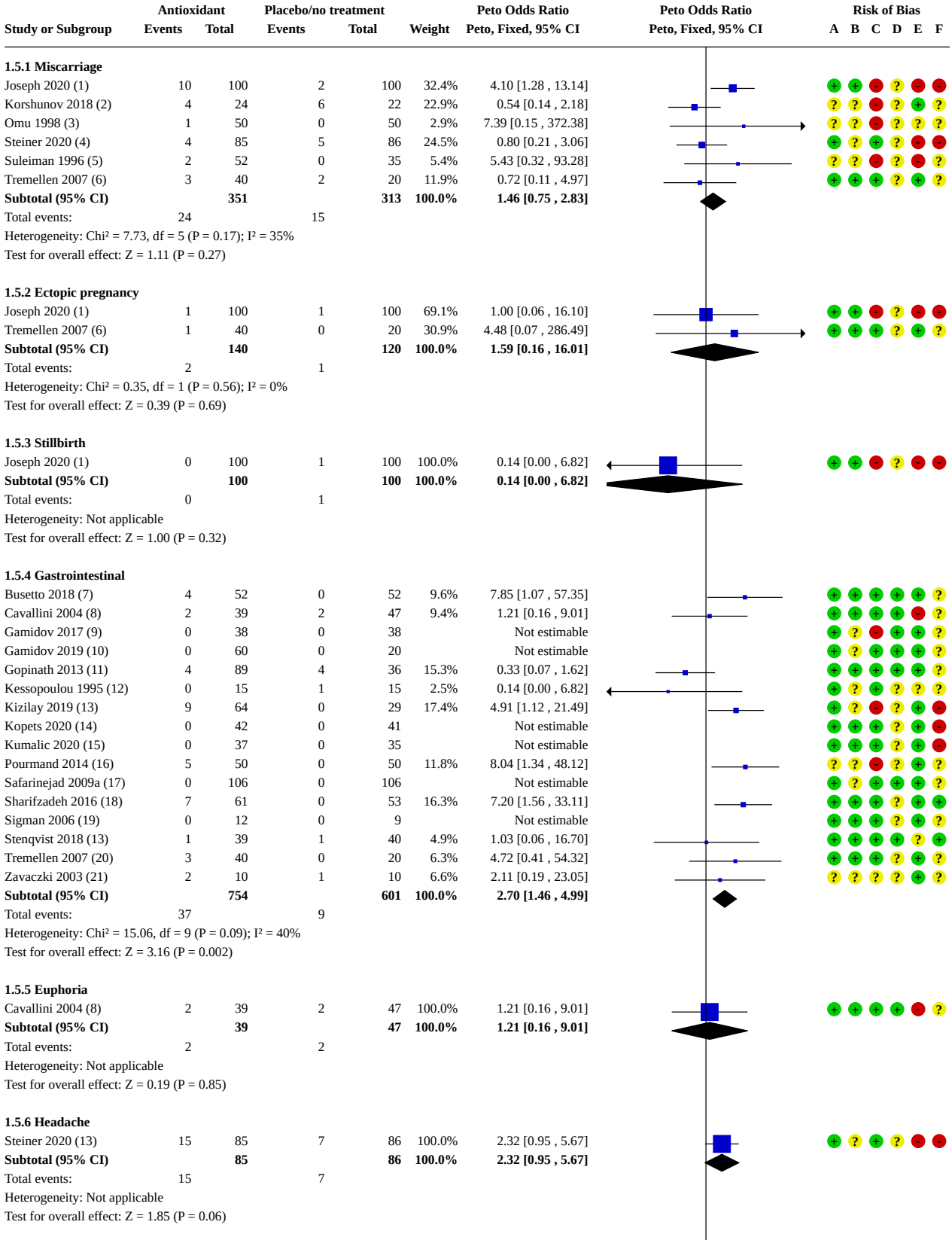


Figure 8. (Continued)

Test for overall effect: Z = 1.85 (P = 0.06)

1.5.7 Upper respiratory infection

Steiner 2020 (22)	4	85	4	86	100.0%	1.01 [0.25 , 4.17]
Subtotal (95% CI)		**85**		**86**	**100.0%**	**1.01 [0.25 , 4.17]**
Total events:	4		4			

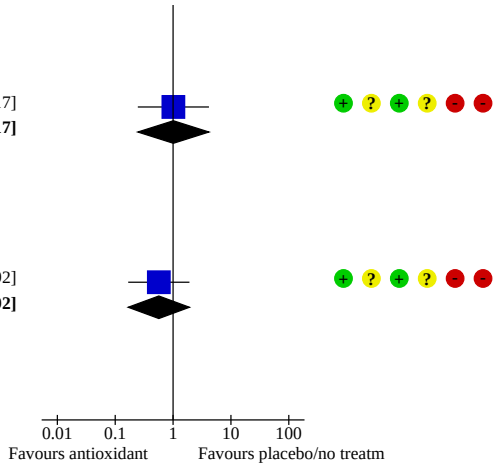
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)

1.5.8 Nasofaryngitis

Steiner 2020 (13)	4	85	7	86	100.0%	0.57 [0.17 , 1.92]
Subtotal (95% CI)		**85**		**86**	**100.0%**	**0.57 [0.17 , 1.92]**
Total events:	4		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Chi² = 8.19, df = 7 (P = 0.32), I² = 14.5%



Footnotes

(1) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(2) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(3) Zinc 500 mg versus no treatment. Natural conception.
(4) Combined antioxidants versus placebo. Natural conception and IUI.
(5) Vitamin E 300 mg versus placebo. Natural conception.
(6) Combined antioxidants (Menevit) versus placebo. IVF.
(7) Combined antioxidants (Proxeed Plus) versus placebo.
(8) L-carnitine 1 x 2000 mg/day + acetyl-L-carnitine 500 x 2 mg/day + glycerine suppository versus placebo. After varicocelectomy.
(9) Combined antioxidant (SpermActin-forte) versus no treatment.
(10) Combined antioxidants (SpermActin Forte) versus placebo.
(11) 1 or 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg) versus placebo.
(12) Vitamin E 600 mg versus placebo.
(13) Combined antioxidants versus placebo.
(14) Combined antioxidant (Verum TDS) versus placebo TDS
(15) Astaxanthin 16 mg + Vitamin E 40 mg versus placebo.
(16) L-carnitine 750 mg versus no treatment.
(17) Coenzyme Q10 300 mg versus placebo.
(18) Zinc solution 0.5% 10 ml versus placebo solution 10 ml.
(19) L-carnitine 2000 mg + L-acetylcarnitine 1000 mg versus placebo.
(20) Combined antioxidants (Menevit) versus placebo.
(21) Magnesium 3000 mg versus placebo.
(22) Combined antioxidants versus placebo. Upper respiratory infections.

Risk of bias legend

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

The adverse events reported in the studies were miscarriage, ectopic pregnancy, stillbirth, gastrointestinal disorders, euphoria, headache, upper respiratory infection, and nasopharyngitis.

1.5.1 Miscarriage. Only six studies reported on miscarriage and the event rate was very low (28 miscarriages from 618 couples) (Joseph 2020; Korshunov 2018; Omu 1998; Steiner 2020; Suleiman 1996; Tremellen 2007). The analysis of these six studies showed no evidence of increased miscarriage between the use of antioxidants when compared with placebo or no treatment (Peto OR 1.46, 95% CI0.75 to 2.83, 6 RCTs, 664 men, P = 0.27, I^2 = 3%, very low-certainty evidence). This means that, for subfertile men with a baseline expected miscarriage rate of 5%, the chances of having a miscarriage could lie between 4% and 13% with the use of an antioxidant (Summary of findings 1).

1.5.2 Ectopic pregnancy. Only two studies (Joseph 2020; Tremellen 2007) reported on this adverse event and there was no evidence of increase of ectopic pregnancy when antioxidants were compared with placebo or no treatment (Peto OR 1.59, 95% CI 0.16 to 16.01, 2 RCTs, 260 men, P = 0.69, I^2 = 0%).

1.5.3 Stillbirth. Only one study (Joseph 2020) reported on this adverse event and there was no evidence of increase of stillbirth when antioxidants were compared with no treatment (Peto OR 0.14, 95% CI 0.00 to 6.82, 1 RCT, 200 men, P = 0.32, I^2 = not applicable).

1.5.4 Gastrointestinal. The analysis of 16 studies showed an association between the use of antioxidants and an increase in gastrointestinal discomfort when compared with placebo or no treatment (Peto OR 2.70, 95% CI 1.46 to 4.99, 1355 men, 16 RCTs, P

= 0.002, I^2 = 40%, low-certainty evidence) (Busetto 2018; Cavallini 2004; Gamidov 2017; Gamidov 2019; Gopinath 2013; Kessopoulou 1995; Kizilay 2019; Kopets 2020; Kumalic 2020; Pourmand 2014; Safarinejad 2009a; Sharifzadeh 2016; Sigman 2006; Stenqvist 2018; Tremellen 2007; Zavaczki 2003). However, the event rate was very low, so we could not be sure of these results. Six of these 16 studies reported no events, therefore a funnel plot was not created.

1.5.5 Euphoria. Only one study (Cavallini 2004) reported on this adverse event and there was no evidence of increased occurrence of euphoria when antioxidants were compared with placebo (Peto OR 1.21, 95% CI 0.16 to 9.01, 1 RCT, 86 men, P = 0.85, I^2 = not applicable).

1.5.6 Headache. Only one study (Steiner 2020) reported on this adverse event and there was no evidence of increased occurrence of headache when antioxidants were compared with placebo (Peto OR 2.32, 95% CI 0.95 to 5.67, 1 RCT, 171 men, P = 0.06, I^2 = not applicable).

1.5.7 Upper respiratory infection. Only one study (Steiner 2020) reported on this adverse event and there was no evidence of increased occurrence of upper respiratory infection when antioxidants were compared with placebo (Peto OR 1.01, 95% CI 0.25 to 4.17, 1 RCT, 171 men, P = 0.99, I^2 = not applicable).

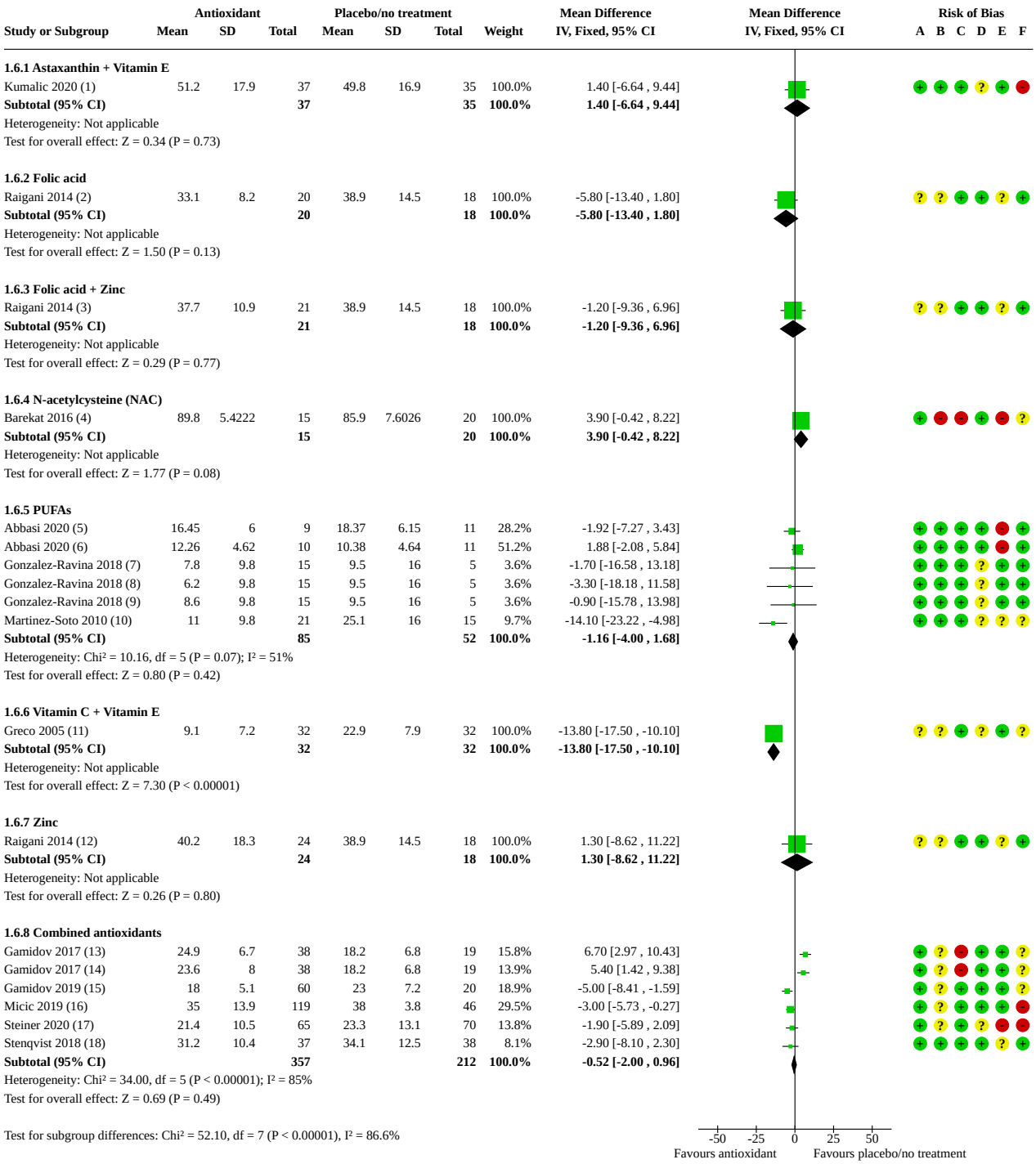
1.5.8 Nasopharyngitis. Only one study (Steiner 2020) reported on this adverse event and there was no evidence of increased occurrence of nasopharyngitis when antioxidants were compared with placebo (Peto OR 0.57, 95% CI 0.17 to 1.92, 1 RCT, 171 men, P = 0.36, I^2 = not applicable).

It was unlikely that the adverse events ectopic pregnancy, stillbirth, euphoria, headache, upper respiratory infection, and nasopharyngitis were related to intake of antioxidants especially with the reported extreme low event rate. Therefore, these outcomes were not included in the 'Summary of findings' table.

1.6 Sperm DNA fragmentation at three months or less; type of antioxidant

See Analysis 1.6, Figure 9.

Figure 9. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.6 Sperm DNA fragmentation; type of antioxidant.



Footnotes

(1) TUNEL assay. Astaxanthin 16 mg + Vitamin E 40 mg.
(2) Toluidine blue (TB) staining. Folic acid 5 mg.
(3) Toluidine blue (TB) staining. Folic acid 5 mg + Zinc 220 mg.
(4) TUNEL assay. N-acetylcysteine (NAC) 200 mg. Post varicocelectomy.
(5) SCSA assay. Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(6) TUNEL assay. Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(7) TUNEL assay. Docosahexaenoic acid (DHA) 1 g.
(8) TUNEL assay. Docosahexaenoic acid (DHA) 2 g.
(9) TUNEL assay. Docosahexaenoic acid (DHA) 0.5 g.

Figure 9. (Continued)

(8) TUNEL assay. Docosahexaenoic acid (DHA) 2 g.
(9) TUNEL assay. Docosahexaenoic acid (DHA) 0.5 g.
(10) TUNEL assay. Brudy Plus (DHA 1000 mg + eicosapentaenoic acid (EPA) 135 mg). At 10 weeks.
(11) TUNEL assay. Vitamin C 1000 mg + Vitamin E 1000 mg. At 2 months.
(12) Toluidine blue (TB) staining. Zinc 220 mg.
(13) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(14) SpermActin Forte. After varicocelectomy.
(15) TUNEL assay. SpermActin Forte.
(16) Sperm chromatin dispersion test (Halosperm). Proxeed plus.
(17) Sperm chromatin structure analysis (SCSA) test. Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(18) Sperm chromatin structure analysis (SCSA) test. Androferti.

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

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.6.1 Astaxanthin plus vitamin E did not show evidence of decreased sperm DNA fragmentation when compared with placebo (Kumalic 2020) mean difference(MD) 1.40, 95% CI -6.64 to 9.44, 72 men, 1 RCT, P = 0.73, I^2 = not applicable).

1.6.2 Folic acid did not show evidence of decreased sperm DNA fragmentation when compared with placebo (Raigani 2014) (MD -5.80, 95% CI -13.40 to 1.80, 38 men, 1 RCT, P = 0.13, I^2 = not applicable).

1.6.3 Folic acid plus zinc did not show evidence of decreased sperm DNA fragmentation when compared with placebo (Raigani 2014) (MD -1.20, 95% CI -9.36 to 6.96, 39 men, 1 RCT, P = 0.77, I^2 = not applicable).

1.6.4 N-acetylcysteine (NAC) did not show evidence of decreased sperm DNA fragmentation when compared with no treatment (Barekat 2016) (MD 3.90, 95% CI -0.42 to 8.22, 35 men, 1 RCT, P = 0.08, I^2 = not applicable).

1.6.5 Three studies (six intervention arms) compared polyunsaturated fatty acids (PUFAs) with placebo. Gonzalez-Ravina 2018 did not report SDs, we assumed the outcome to have an SD equal to the highest SD from other studies within this analysis. As heterogeneity was high (51%), we have not reported the pooled analysis; individually their results were:

- Abbasi 2020 (two intervention arms) did not show evidence of decreased sperm DNA fragmentation when alpha-lipoic acid (ALA) was compared with placebo (MD 0.53, 95% CI -2.65 to 3.72, 41 men, P = 0.74, I^2 = 20%);
- Gonzalez-Ravina 2018 (three intervention arms) did not show evidence of decreased sperm DNA fragmentation when docosahexaenoic acid (DHA) was compared with placebo (MD -1.97, 95% CI -10.55 to 6.62, 60 men, P = 0.65, I^2 = 0%);
- Martinez-Soto 2010 did show evidence of decreased sperm DNA fragmentation when Brudy Plus (DHA plus eicosapentaenoic acid (EPA)) was compared with placebo (MD -14.10, 95% CI -23.22 to -4.98, 36 men, P = 0.002, I^2= not applicable).

1.6.6 Vitamin C plus vitamin E appeared to be associated with decreased sperm DNA fragmentation when compared with placebo (Greco 2005) (MD -13.80, 95% CI -17.50 to -10.10, 64 men, 1 RCT, P < 0.00001, I^2 = not applicable).

1.6.7 Zinc did not show evidence of decreased sperm DNA fragmentation when compared with placebo (Raigani 2014) (MD 1.30, 95% -8.62 to 11.22, 42 men, 1 RCT, P = 0.80, I^2 = not applicable).

1.6.8 Five studies (six intervention arms) compared combined antioxidants with placebo or no treatment. As heterogeneity was high (85%), we have not reported the pooled analysis; individually their results were:

- Gamidov 2017 (two intervention arms) did show evidence of increased sperm DNA fragmentation when combined antioxidants were compared with no treatment (MD 6.09, 95% CI 3.37 to 8.81, 114 men, P < 0.0001, I^2= 0%);
- Gamidov 2019 did show evidence of decreased sperm DNA fragmentation when combined antioxidants were compared with placebo (MD -5.00, 95% CI -8.41 to -1.59, 80 men, P = 0.004, I^2= not applicable);
- Micic 2019 did show evidence of decreased sperm DNA fragmentation when combined antioxidants were compared with placebo (MD -3.00, 95% CI -5.73 to -0.27, 165 men, P = 0.03, I^2= not applicable);
- Steiner 2020 did not show evidence of decreased sperm DNA fragmentation when combined antioxidants were compared with placebo (MD -1.90, 95% CI -5.89 to 2.09, 135 men, P = 0.35, I^2= not applicable);
- Stenqvist 2018 did not show evidence of decreased sperm DNA fragmentation when combined antioxidants were compared with placebo (MD -2.90, 95% CI -8.10 to 2.30, 75 men, P = 0.27, I^2= not applicable).

We performed a post-hoc sensitivity analysis of the combined antioxidants subgroup for studies enrolling men with varicocele. In the literature it is reported that men with varicocele have higher levels of sperm DNA fragmentation. One study in this subgroup reported on men with varicocele (Gamidov 2017). When this study was removed from the analysis, heterogeneity was low and there appeared to be an association between the use of combined

antioxidants and decreased sperm DNA fragmentation (MD -3.31, 95% CI -5.08 to -1.54, 455 men, 4 RCTs, P = 0.0002, I^2 = 0%).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 52.10, P < 0.00001).

1.7 Sperm DNA fragmentation at six months; type of antioxidant

See Analysis 1.7.

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.7.1 Three studies compared combined antioxidants with placebo. As heterogeneity was high (74%), we have not reported the pooled analysis; individually their results were:

- Gamidov 2019 did show evidence of decreased sperm DNA fragmentation (MD -7.10, 95% CI -10.79 to -3.41, 80 men, P = 0.0002, I^2 = not applicable);
- Micic 2019 did show evidence of decreased sperm DNA fragmentation (MD -4.70, 95% CI -7.12 to -2.28, 165 men, P = 0.0001, I^2 = not applicable);
- Stenqvist 2018 did not show evidence of decreased sperm DNA fragmentation (MD 2.90, 95% CI -3.11 to 8.91, 75 men, P = 0.34, I^2 = not applicable).

1.7.2 Zinc plus folic acid did not show evidence of decreased sperm DNA fragmentation when compared with placebo (Schisterman 2020) (MD 3.00, 95% CI 0.02 to 5.98, 853 men, P = 0.05, I^2 = not applicable).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 17.51, P < 0.0001).

1.8 Data not usable for meta-analysis

See Analysis 1.8.

One study reported on DNA fragmentation, but could not be included in the forest plots of the meta-analysis. Boonyarangkul 2015 reported the tail length in micrometer measured with the Comet assay instead of a percentage. They reported no statistically significant difference in tail length when folic acid was compared with placebo after 3 months and 6 months.

1.9 Total sperm motility at three months or less; type of antioxidant

See Analysis 1.9 and Figure 10

Figure 10. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.9 Total sperm motility at 3 months or less; type of antioxidant.

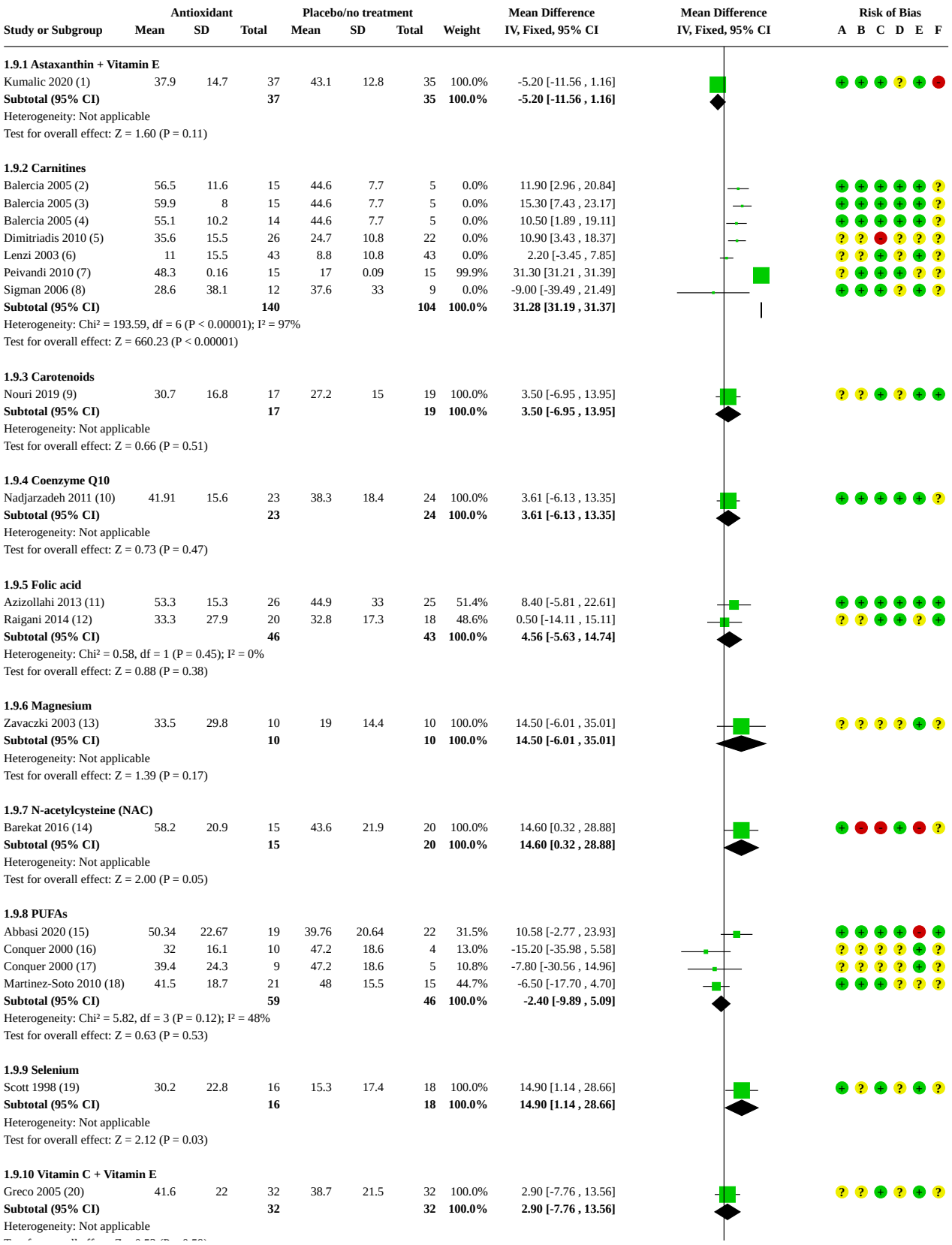
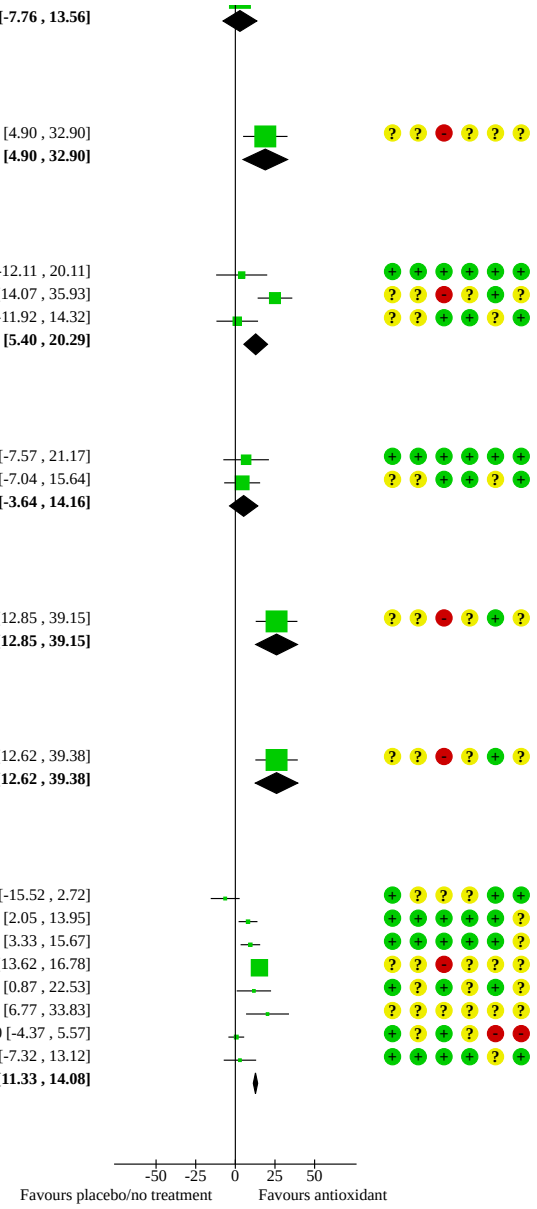


Figure 10. (Continued)

Subtotal (95% CI)			**32**			**32**	**100.0%**	**2.90 [-7.76 , 13.56]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.53 (P = 0.59)									
1.9.11 Vitamin E									
Ener 2016 (21)	61.4	18.3	22	42.5	28.7	23	100.0%	18.90 [4.90 , 32.90]	
Subtotal (95% CI)			**22**			**23**	**100.0%**	**18.90 [4.90 , 32.90]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.65 (P = 0.008)									
1.9.12 Zinc									
Azizollahi 2013 (22)	48.9	27.7	32	44.9	33	25	21.4%	4.00 [-12.11 , 20.11]	
Omu 2008 (23)	49	12	11	24	12	8	46.4%	25.00 [14.07 , 35.93]	
Raigani 2014 (24)	34	26	24	32.8	17.3	18	32.2%	1.20 [-11.92 , 14.32]	
Subtotal (95% CI)			**67**			**51**	**100.0%**	**12.85 [5.40 , 20.29]**	
Heterogeneity: Chi² = 8.94, df = 2 (P = 0.01); I² = 78%									
Test for overall effect: Z = 3.38 (P = 0.0007)									
1.9.13 Zinc + Folic acid									
Azizollahi 2013 (25)	51.7	17.2	29	44.9	33	25	38.4%	6.80 [-7.57 , 21.17]	
Raigani 2014 (26)	37.1	18.8	21	32.8	17.3	18	61.6%	4.30 [-7.04 , 15.64]	
Subtotal (95% CI)			**50**			**43**	**100.0%**	**5.26 [-3.64 , 14.16]**	
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%									
Test for overall effect: Z = 1.16 (P = 0.25)									
1.9.14 Zinc + Vitamin E									
Omu 2008 (27)	50	18	12	24	12	8	100.0%	26.00 [12.85 , 39.15]	
Subtotal (95% CI)			**12**			**8**	**100.0%**	**26.00 [12.85 , 39.15]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.88 (P = 0.0001)									
1.9.15 Zinc + Vitamin E + Vitamin C									
Omu 2008 (28)	50	20	14	24	12	8	100.0%	26.00 [12.62 , 39.38]	
Subtotal (95% CI)			**14**			**8**	**100.0%**	**26.00 [12.62 , 39.38]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.81 (P = 0.0001)									
1.9.16 Combined antioxidants									
Bahmyari 2021 (29)	30.3	19.3	30	36.7	17.2	32	2.3%	-6.40 [-15.52 , 2.72]	
Gopinath 2013 (30)	50.1	11.3	43	42.1	10.6	18	5.3%	8.00 [2.05 , 13.95]	
Gopinath 2013 (31)	51.6	13	46	42.1	10.6	18	5.0%	9.50 [3.33 , 15.67]	
Morgante 2010 (32)	40.3	6.4	90	25.1	4.2	90	75.4%	15.20 [13.62 , 16.78]	
Scott 1998 (33)	27	20.3	30	15.3	17.4	18	1.6%	11.70 [0.87 , 22.53]	
Sivkov 2011 (34)	38.3	20.3	15	18	17.4	15	1.0%	20.30 [6.77 , 33.83]	
Steiner 2020 (35)	42.8	16.4	82	42.2	16.1	82	7.6%	0.60 [-4.37 , 5.57]	
Stenqvist 2018 (36)	62.8	18.1	37	59.9	26.4	38	1.8%	2.90 [-7.32 , 13.12]	
Subtotal (95% CI)			**373**			**311**	**100.0%**	**12.71 [11.33 , 14.08]**	
Heterogeneity: Chi² = 57.38, df = 7 (P < 0.00001); I² = 88%									
Test for overall effect: Z = 18.14 (P < 0.00001)									
Test for subgroup differences: Chi² = 1086.87, df = 15 (P < 0.00001), I² = 98.6%									



Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg.
(2) L-acetyl carnitine 3000 mg.
(3) L-carnitine 3000 mg.
(4) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(5) L-carnitine 1000 mg.
(6) L-carnitine 2000 mg. Only mean, no SD given.
(7) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(8) L-carnitine 2000 mg + L-acetylcarnitine 1000 mg.
(9) Lycopene 25 mg.
(10) Coenzyme Q10 200 mg.
(11) Folic acid 5 mg. After varicocelectomy.
(12) Folic acid 5 mg. At 16 weeks.
(13) Magnesium 3000 mg.
(14) N-acetylcysteine (NAC) 200 mg. After varicocelectomy.
(15) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(16) Docosahexaenoic acid (DHA) 800 mg.
(17) Docosahexaenoic acid (DHA) 400 mg.
(18) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(19) Selenium 100 ug

Figure 10. (Continued)

(17) Docosahexaenoic acid (DHA) 400 mg.
(18) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(19) Selenium 100 µg.
(20) Vitamin C 1000 mg + Vitamin E 1000 mg. At 2 months.
(21) Vitamin E 600 mg. Varicocele patients.
(22) Zinc 66 mg. After varicocelectomy.
(23) Zinc 500 mg.
(24) Zinc 220 mg. At 16 weeks.
(25) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(26) Zinc 220 mg + Folic acid 5 mg. At 16 weeks.
(27) Zinc 400 mg + Vitamin E 20 mg.
(28) Zinc 400 mg + Vitamin E 20 mg + Vitamin C 10 mg.
(29) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(30) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(31) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(32) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(33) Selenium 100 µg + Vitamin A 1 mg + Vitamin C 10 mg + Vitamin E 15 mg.
(34) Selznic (selenium + zinc + vitamins).
(35) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(36) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
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(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

We analysed this outcome using a fixed-effect-model and used subtotals as pooling was not possible.

1.9.1 Astaxanthin plus vitamin E did not show evidence of an increase in total sperm motility compared with placebo (Kumalic 2020) (MD -5.20, 95% CI -11.56 to 1.16, 72 men, 1 RCT, P = 0.11, I^2 = not applicable).

1.9.2 Five studies (seven intervention arms) comparing carnitines with placebo or no treatment did show an increase in total sperm motility (Balercia 2005; Dimitriadis 2010; Lenzi 2003; Peivandi 2010; Sigman 2006) (MD 31.28, 95% CI 31.19 to 31.37, 244 men, 5 RCTs, 7 intervention arms, P < 0.00001, I^2 = 97%). One study (Lenzi 2003) did not report standard deviations (SDs); we assumed the outcome to have an SD equal to the highest SD from other studies within this analysis. The heterogeneity was extremely high due to the fact that one study (Peivandi 2010) had very small SDs when compared with data in the other studies. However, the authors confirmed, when contacted, that they are indeed SDs and not standard errors (SEs). When these two studies were removed from the analysis, carnitines appeared to be associated with an increase in total sperm motility when compared with placebo or no treatment, with low heterogeneity (MD 11.83, 95% CI 7.78 to 15.87, 128 men, 3 RCTs, 5 intervention arms, P < 0.00001, I^2 = 0%).

1.9.3 Carotenoids did not show evidence of an increase in total sperm motility compared with placebo (Nouri 2019) (MD 3.50, 95% CI -6.95 to 13.95, 36 men, 1 RCT, P = 0.51, I^2 = not applicable).

1.9.4 Coenzyme Q10 did not show evidence of an increase in total sperm motility compared with placebo (Nadjarzadeh 2011) (MD 3.61, 95% CI -6.13 to 13.35, 47 men, 1 RCT, P = 0.47, I^2 = not applicable).

1.9.5 Two studies compared folic acid with placebo and did not show evidence of an increase in total sperm motility (Azizollahi 2013; Raigani 2014) (MD 4.56, 95% CI -5.63 to 14.74, 89 men, 2 RCTs, P = 0.38, I^2 = 0%).

1.9.6 Magnesium did not show evidence of an increase in total sperm motility compared with placebo (Zavaczki 2003) (MD 14.50, 95% CI -6.01 to 35.01, 20 men, 1 RCT, P = 0.17, I^2 = not applicable).

1.9.7 N-acetylcysteine (NAC) did not show evidence of an increase in total sperm motility compared with placebo (Barekat 2016) (MD 14.60, 95% CI 0.32 to 28.88, 35 men, P = 0.05, I^2 = not applicable).

1.9.8 Three studies (four intervention arms) compared polyunsaturated fatty acids (PUFAs) with placebo and did not show evidence of an increase in total sperm motility (Abbasi 2020; Conquer 2000; Martinez-Soto 2010) (MD -2.40, 95% CI -9.89 to 5.09, 105 men, 3 RCTs, 4 intervention arms, P = 0.53, I^2 = 48%).

1.9.9 Selenium appeared to be associated with an increase in total sperm motility compared with placebo (Scott 1998) (MD 14.90, 95% CI 1.14 to 28.66, 34 men, 1 RCT, P = 0.03, I^2 = not applicable).

1.9.10 Vitamin C plus vitamin E did not show evidence of an increase in total sperm motility compared with placebo (Greco 2005) (MD 2.90, 95% CI -7.76 to 13.56, 64 men, 1 RCT, P = 0.59, I^2 = not applicable).

1.9.11 Vitamin E appeared to be associated with an increase in total sperm motility compared with no treatment (Ener 2016) (MD 18.90, 95% CI 4.90 to 32.90, 45 men, 1 RCT, P = 0.008, I^2 = not applicable).

1.9.12 Three studies compared zinc with placebo or no treatment (Azizollahi 2013; Omu 2008; Raigani 2014). As the heterogeneity was high (78%), we have not reported the pooled analysis; individually their results were:

- Azizollahi 2013 did not show evidence of an increase in total sperm motility at three months when compared with placebo (MD 4.00, 95% CI -12.11 to 20.11, 57 men, P = 0.63);
- Omu 2008 did show an increase in total sperm motility at three months when compared with no treatment (MD 25.00, 95% CI 14.07 to 35.93, 19 men, P < 0.00001);
- Raigani 2014 did not show evidence of an increase in total sperm motility at 16 weeks when compared with placebo (MD 1.20, 95% CI -11.92 to 14.32, 42 men, P = 0.86).

1.9.13 Two studies compared zinc plus folic acid with placebo and did not show evidence of an increase in total sperm motility (Azizollahi 2013; Raigani 2014) (MD 5.26, 95% CI -3.64 to 14.16, 93 men, 2 RCTs, P = 0.25, I^2 = 0%).

1.9.14 Zinc plus vitamin E appeared to be associated with an increase in total sperm motility compared with no treatment (Omu 2008) (MD 26.00, 95% CI 12.85 to 39.15, 20 men, 1 RCT, P = 0.0001, I^2 = not applicable)

1.9.15 Zinc plus vitamin E plus vitamin C appeared to be associated with an increase in total sperm motility compared with no treatment (Omu 2008) (MD 26.00, 95% CI 12.62 to 39.38, 22 men, 1 RCT, P = 0.0001, I^2 = not applicable).

1.9.16 Seven studies (eight intervention arms) compared combined antioxidants with placebo or no treatment (Bahmyari 2021; Gopinath 2013; Morgante 2010; Scott 1998; Sivkov 2011; Steiner 2020; Stenqvist 2018). As heterogeneity was high (88%), we have not reported the pooled analysis; individually their results were:

- Bahmyari 2021 did not show evidence of increased total sperm motility when compared with placebo (MD -6.40, 95% CI -15.52 to 2.72, 62 men, P = 0.17);
- Gopinath 2013 did show an increase in total sperm motility when compared with placebo (MD 8.72, 95% CI 4.44 to 13.01, 125 men, P < 0.0001);
- Morgante 2010 did show an increase in total sperm motility when compared with no treatment (MD 15.20, 95% CI 13.62 to 16.78, 180 men, P < 0.00001);
- Scott 1998 did show an increase in total sperm motility when compared with placebo (MD 11.70, 95% CI 0.87 to 22.53, 48 men, P = 0.003);
- Sivkov 2011 did show an increase in total sperm motility when compared with placebo (MD 20.30, 95% CI 6.77 to 33.83, 30 men, P = 0.003);
- Steiner 2020 did not show evidence of increased total sperm motility when compared with placebo (MD 0.60, 95% CI -4.37 to 5.57, 164 men, P = 0.81);
- Stenqvist 2018 did not show evidence of increased total sperm motility when compared with placebo (MD 2.90, 95% CI -7.31 to 13.12, 75 men, P = 0.58).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 1086.87, P < 0.00001).

1.10 Data not usable for meta-analysis

Analysis 1.10

Data from two studies could not be used in the forest plot. Galatioto 2008 reported percentage of WHO class A motile sperm instead of class A plus B, and Kessopoulou 1995 reported median differences. Both studies found no difference between intervention and placebo or no treatment for this outcome.

1.11 Total sperm motility at six months or less; type of antioxidant

See Analysis 1.11.

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.11.1 Three studies (five intervention arms) compared carnitines with placebo (Balercia 2005; Lenzi 2004; Sigman 2006). As the heterogeneity was high (78%), we have not reported the pooled analysis for these studies; individually their results were:

- Balercia 2005 (three arms) did show an increased total sperm motility at six months when compared with placebo (MD 18.63, 95% CI 12.92 to 24.35, 59 men, P < 0.00001);
- Lenzi 2004 did not show evidence of increased total sperm motility at six months when compared with placebo (MD 1.50, 95% CI-4.56 to 7.56, 56 men, P = 0.63);
- Sigman 2006 did not show evidence of increased total sperm motility at six months when compared with placebo (MD -7.70, 95% CI -33.24 to 17.84, 21 men, P = 0.55).

1.11.2 Three studies compared coenzyme Q10 with placebo (Balercia 2009; Safarinejad 2009a; Safarinejad 2012). As the heterogeneity was extremely high (99%), we have not reported the pooled analysis; individually their results were:

- Balercia 2009 did show an increased total sperm motility when compared with placebo (MD 4.50, 95% 0.74 to 8.26, 60 men, P = 0.02);
- Safarinejad 2009a did show an increased total sperm motility when compared with placebo (MD 4.50, 95% CI 3.89 to 5.11, 194 men, P < 0.000001);
- Safarinejad 2012 did show an increased total sperm motility when compared with placebo (MD 10.40, 95% CI 9.77 to 11.03, 225 men, P < 0.000001).

1.11.3 Two studies compared folic acid with placebo (Azizollahi 2013; Wong 2002) and did not show evidence of increased total sperm motility (MD 0.16, 95% CI -6.96 to 7.29, 98 men, 2 RCTs, P = 0.96, I^2 = 0).

1.11.4 N-acetylcysteine (NAC) appeared to be associated with an increased total sperm motility when compared with placebo (MD 1.90, 95% CI 1.20 to 2.60, 211 men, P < 0.00001, I^2 = not applicable) (Safarinejad 2009).

1.11.5 Selenium appeared to be associated with an increased total sperm motility when compared with placebo (MD 3.20, 95% CI 2.50 to 3.90, 211 men, P < 0.00001, I^2 = not applicable) (Safarinejad 2009).

1.11.6 Selenium plus N-acetylcysteine appeared to be associated with increased total sperm motility when compared with placebo (Safarinejad 2009) (MD 6.30, 95% CI 5.60 to 7.00, 210 men, P < 0.00001, I^2 = not applicable).

1.11.7 Vitamin D plus calcium did not show evidence of increased total sperm motility when compared with placebo (Blomberg

Jensen 2018) (MD -4.00, 95% CI -9.57 to 1.57, 260 men, P = 0.16, I^2 = not applicable).

1.11.8 Two studies compared vitamin E with placebo or no treatment (Ener 2016; Suleiman 1996). There appeared to be an association between vitamin E and an increased total sperm motility (MD 11.60, 95% CI 6.18 to 17.02, 132 men, 2 RCTs, P < 0.0001, I^2 = 16%).

1.11.9 Two studies compared zinc with placebo (Azizollahi 2013; Wong 2002) and did not show evidence of increased total sperm motility (MD 0.00, 95% CI -6.95 to 6.95, 105 men, P = 1.00, I^2 = 0%).

1.11.10 Three studies compared zinc plus folic acid to placebo (Azizollahi 2013; Schisterman 2020; Wong 2002) and did not show evidence of increased total sperm motility (MD 0.24, 95% CI -2.54 to 3.02, 956 men, P = 0.87, I^2 = 0%).

1.11.11 Four studies compared combined antioxidants with placebo or no treatment (Busetto 2018; Gopinath 2013; Kizilay 2019; Stenqvist 2018) and did not show evidence of increased total sperm motility. As the heterogeneity was high (69%), we have not reported the pooled analysis; individually their results were:

- Busetto 2018 did show increased total sperm motility when compared with placebo (MD 4.40, 95% CI 1.49 to 7.31, 104 men, P = 0.003);
- Gopinath 2013 (three arms), did show increased total sperm motility when compared with placebo (MD 12.44, 95% CI 8.29 to 16.59, 125 men, P < 0.00001);
- Kizilay 2019 did show increased total sperm motility compared with no treatment (MD 7.60, 95% CI 3.58 to 11.62, 90 men, P = 0.0002);
- Stenqvist 2018 did not show evidence of increased total sperm motility compared with placebo (MD -0.80, 95% CI -9.36 to 7.76, 75 men, P = 0.85).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 254.81, P < 0.00001).

1.12 Total sperm motility at nine months or more; type of antioxidant

See Analysis 1.12.

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.12.1 One study reported on different types of carnitines. Carnitines appeared to be associated with an increased total sperm motility when compared with placebo (Balercia 2005) (MD 8.54, 95% CI 3.01 to 14.07, 59 men, P = 0.002, I^2 = 0%).

1.12.2 Three studies reported on coenzyme Q10 (Balercia 2009; Safarinejad 2009a; Safarinejad 2012). As the heterogeneity was extremely high (98%), we have not reported the pooled analysis; individually their results were:

- Balercia 2009 did not show evidence of increased total sperm motility when compared with placebo (MD -2.30, 95% CI -5.94 to 1.34, 60 men, P = 0.22);
- Safarinejad 2009a did show increased total sperm motility when compared with placebo (MD 1.40, 95% CI 0.79 to 2.01, 194 men, P < 0.00001);
- Safarinejad 2012 did show increased total sperm motility when compared with placebo (MD 5.40, 95% CI 4.80 to 6.00, 225 men, P < 0.00001).

1.12.3 Vitamin E did not show evidence of increased total sperm motility when compared with no treatment (Ener 2016) (MD 2.20, 95% CI -8.48 to 12.88, 45 men, 1 RCT, P = 0.69, I^2 = not applicable).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 3.42, P = 0.18).

1.13 Total sperm motility over time

See Analysis 1.13

This analysis was only useful in directly comparing the same studies reporting at the three time points and not in comparing results of meta-analyses that included different subsets of studies.

1.13.1 Total sperm motility at three months or less. We analysed this outcome using a fixed-effect model (MD 31.17, 95% CI 31.07 to 31.26, 1638 men, 25 RCTs, 36 intervention arms, P < 0.00001, I^2 = 97%) and used subtotals (Abbasi 2020; Attallah 2013; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Barekat 2016; Conquer 2000; Dimitriadis 2010; Ener 2016; Gopinath 2013; Greco 2005; Kumalic 2020; Lenzi 2003; Martinez-Soto 2010; Morgante 2010; Nadjarzadeh 2011; Nouri 2019; Omu 2008; Peivandi 2010; Raigani 2014; Scott 1998; Sigman 2006; Steiner 2020; Stenqvist 2018; Zavaczki 2003).

1.13.2 Total sperm motility at six months. We analysed this outcome using a fixed-effect model (MD 5.77, 95% CI 5.45 to 6.10, 2880 men,17 RCTs, 26 intervention arms, P < 0.00001, I^2 = 94%) and used subtotals (Azizollahi 2013; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Busetto 2018; Ener 2016; Gopinath 2013; Kizilay 2019; Lenzi 2004; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2012; Schisterman 2020; Sigman 2006; Stenqvist 2018; Suleiman 1996; Wong 2002).

1.13.3 Total sperm motility at nine months or more. We analysed this outcome using a fixed-effect model (MD 3.36, 95% CI 2.94 to 3.78, 583 men, 5 RCTs, 7 intervention arms, P < 0.00001, I^2 = 94%) and used subtotals (Balercia 2005; Balercia 2009; Ener 2016; Safarinejad 2009a; Safarinejad 2012).

Two of the studies included in the analysis of the semen parameter outcomes (Safarinejad 2009; Safarinejad 2009a) had consistently reported SDs very much smaller than those reported by most of the other included studies. The review authors considered that these were potentially erroneous, but an attempt to check with the study authors was unsuccessful. One other study (Peivandi 2010), also had very small SDs when compared with data in the other studies, but the authors confirmed, when contacted, that they are indeed SDs and not SEs. We tried to manage these analyses in two different ways: firstly we assumed the outcome to have a SD equal to the highest SD from other studies within the same analysis and secondly by treating the data as SEs and converting back to SDs, however heterogeneity remained high in both situations so for the final analyses we reverted to the SDs as reported in the studies. The low SDs may have been due to the strict inclusion and exclusion criteria indicating that the study was homogenous

in nature, however we were unable to carry out a sensitivity analysis on these studies as pooling was not possible due to high heterogeneity.

1.14 Progressive sperm motility at three months or less; type of antioxidant

See Analysis 1.14 and Figure 11.

Figure 11. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.14 Progressive sperm motility at 3 months or less; type of antioxidant.

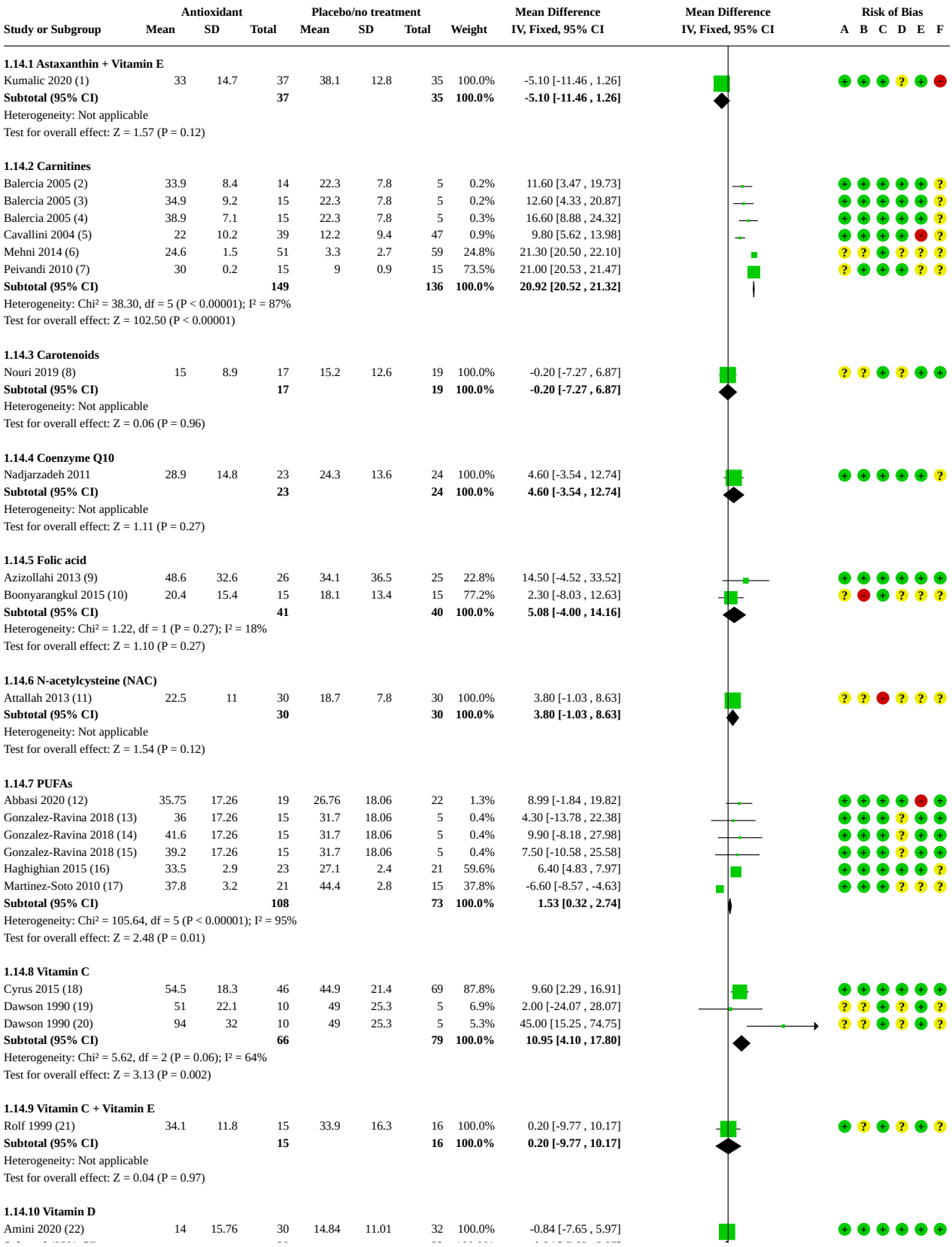
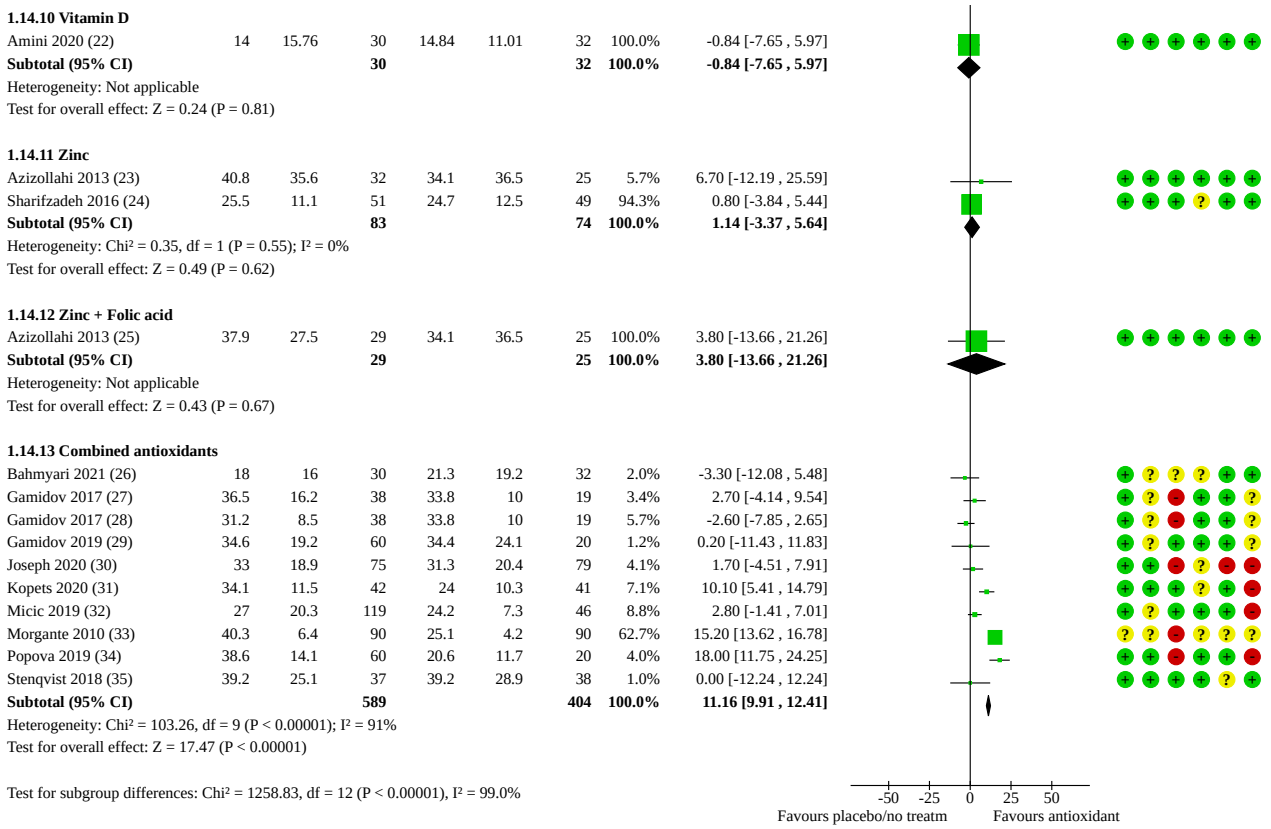


Figure 11. (Continued)



1.14.10 Vitamin D								
Amini 2020 (22)	14	15.76	30	14.84	11.01	32	100.0%	-0.84 [-7.65 , 5.97]
Subtotal (95% CI)			**30**			**32**	**100.0%**	**-0.84 [-7.65 , 5.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
1.14.11 Zinc								
Azizollahi 2013 (23)	40.8	35.6	32	34.1	36.5	25	5.7%	6.70 [-12.19 , 25.59]
Sharifzadeh 2016 (24)	25.5	11.1	51	24.7	12.5	49	94.3%	0.80 [-3.84 , 5.44]
Subtotal (95% CI)			**83**			**74**	**100.0%**	**1.14 [-3.37 , 5.64]**
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.49 (P = 0.62)								
1.14.12 Zinc + Folic acid								
Azizollahi 2013 (25)	37.9	27.5	29	34.1	36.5	25	100.0%	3.80 [-13.66 , 21.26]
Subtotal (95% CI)			**29**			**25**	**100.0%**	**3.80 [-13.66 , 21.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.14.13 Combined antioxidants								
Bahmyari 2021 (26)	18	16	30	21.3	19.2	32	2.0%	-3.30 [-12.08 , 5.48]
Gamidov 2017 (27)	36.5	16.2	38	33.8	10	19	3.4%	2.70 [-4.14 , 9.54]
Gamidov 2017 (28)	31.2	8.5	38	33.8	10	19	5.7%	-2.60 [-7.85 , 2.65]
Gamidov 2019 (29)	34.6	19.2	60	34.4	24.1	20	1.2%	0.20 [-11.43 , 11.83]
Joseph 2020 (30)	33	18.9	75	31.3	20.4	79	4.1%	1.70 [-4.51 , 7.91]
Kopets 2020 (31)	34.1	11.5	42	24	10.3	41	7.1%	10.10 [5.41 , 14.79]
Micic 2019 (32)	27	20.3	119	24.2	7.3	46	8.8%	2.80 [-1.41 , 7.01]
Morgante 2010 (33)	40.3	6.4	90	25.1	4.2	90	62.7%	15.20 [13.62 , 16.78]
Popova 2019 (34)	38.6	14.1	60	20.6	11.7	20	4.0%	18.00 [11.75 , 24.25]
Stenqvist 2018 (35)	39.2	25.1	37	39.2	28.9	38	1.0%	0.00 [-12.24 , 12.24]
Subtotal (95% CI)			**589**			**404**	**100.0%**	**11.16 [9.91 , 12.41]**
Heterogeneity: Chi² = 103.26, df = 9 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 17.47 (P < 0.00001)								

Test for subgroup differences: Chi² = 1258.83, df = 12 (P < 0.00001), I² = 99.0%

Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg.
(2) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(3) L-acetyl carnitine 3000 mg.
(4) L-carnitine 3000 mg.
(5) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Only WHO class A motile sperm.
(6) L-carnitine 1000 mg.
(7) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(8) Lycopene 25 mg.
(9) Folic acid 5 mg. After varicocelectomy.
(10) Folic acid 5 mg.
(11) N-acetylcysteine (NAC) 600 mg.
(12) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(13) Docosahexaenoic acid (DHA) 1 g.
(14) Docosahexaenoic acid (DHA) 2 g.
(15) Docosahexaenoic acid (DHA) 0.5 g.
(16) Alpha-lipoic acid (ALA) 600 mg.
(17) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(18) Vitamin C 500 mg. After varicocelectomy.
(19) Vitamin C 200 mg.
(20) Vitamin C 1000 mg.
(21) Vitamin C 1000 mg + Vitamin E 800 mg. At 2 months.
(22) Vitamin D3 50,000IU/week for 8 weeks, followed by 50,000IU/month for 1 month
(23) Zinc 66 mg. After varicocelectomy.
(24) Zinc 10 ml solution of 0.5%.
(25) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(26) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(27) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(28) SpermActin Forte (acetyl-L-carnitine + L-carnitine + alpha-lipoic acid). After varicocelectomy.
(29) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(30) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.
(31) 1 dose TDS (l-carnitine/ l-acetyl-carnitine + l-arginine + glutathione + coenzyme Q10 + zinc + vitamin B9 + vitamin B12 + selenium).
(32) Proxeed plus (l-carnitine + acetyl-l-carinitine + fumarate + fructose + critic acid + zinc + coenzyme Q10 + selenium + vitamin C + folic acid + vitamin B12).
(33) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(34) Androdoz (l-arginine + l-carnitine + l-carnosine + coenzyme Q10 + glycyrrhizic acid).
(35) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

Figure 11. (Continued)

(34) Androdoz (l-arginine + l-carnitine + l-carnosine + coenzyme Q10 + glycyrrhizic acid).
(35) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

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

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.14.1 Astaxanthin plus vitamin E did not show evidence of increased progressive sperm motility when compared with placebo (Kumalic 2020) (MD -5.10, 95% CI -11.46 to 1.26, 72 men, 1 RCT, P = 0.12, I^2 = not applicable).

1.14.2 Four studies with carnitines reported an increase in progressive sperm motility when compared with placebo (Balercia 2005; Cavallini 2004; Mehni 2014; Peivandi 2010). As the heterogeneity was high (87%), we have not reported the pooled analysis; individually their results were:

- Balercia 2005 (three arms) did show an increase in progressive sperm motility when compared with placebo (MD 13.72, 95% CI 9.08 to 18.35, 59 men, P < 0.00001);
- Cavallini 2004 did show an increase in progressive sperm motility when compared with placebo (MD 9.80, 95% CI 5.62 to 13.98, 86 men, P < 0.00001);
- Mehni 2014 did show an increase in progressive sperm motility when compared with placebo (MD 21.30, 95% CI 20.50 to 22.10, 110 men, P < 0.00001);
- Peivandi 2010 did show an increase in progressive sperm motility when compared with placebo (MD 21.00, 95% CI 20.53 to 21.47, 30 men, P < 0.00001).

1.14.3 Carotenoids did not show evidence of increased progressive sperm motility when compared with placebo (Nouri 2019) (MD -0.20, 95% CI -7.27 to 6.87, 36 men, 1 RCT, P = 0.96, I^2 = not applicable).

1.14.4 Coenzyme Q10 did not show evidence of increased progressive sperm motility when compared with placebo (Nadjarzadeh 2011) (MD 4.60, 95% CI -3.54 to 12.74, 47 men, 1 RCT, P = 0.27, I^2 = not applicable).

1.14.5 Two studies compared folic acid to placebo and did not show evidence of increased progressive sperm motility (Azizollahi 2013; Boonyarangkul 2015) (MD 5.08, 95% CI -4.00 to 14.16, 81 men, 2 RCTs, P = 0.27, I^2 = 18%).

1.14.6 N-acetylcysteine (NAC) did not show evidence of increased progressive sperm motility when compared with no treatment (Attallah 2013) (MD 3.80, 95% CI -1.03 to 8.63, 60 men, 1 RCT, P = 0.12, I^2 = not applicable).

1.14.7 Four studies (six intervention arms) compared PUFAs with placebo (Abbasi 2020; Gonzalez-Ravina 2018; Haghighian 2015; Martinez-Soto 2010). Gonzalez-Ravina 2018 did not report SDs; we assumed the outcome to have an SD equal to the highest SD from other studies within this analysis. The heterogeneity was extremely high (95%), which may be due to the relatively small SDs reported in Haghighian 2015 and Martinez-Soto 2010. We tried to manage these small SDs by imputing SDs from studies of a similar size and by considering the SDs to be SEs and converting them to SDs. Despite these efforts, heterogeneity remained high, and we reverted the SDs as reported in the studies. We have not reported the pooled analysis; individually their results were:

- Abbasi 2020 did not show evidence of increased progressive sperm motility when compared with placebo (MD 8.99, 95% CI -1.84 to 19.82, 41 men, P = 0.10);
- Gonzalez-Ravina 2018 (three intervention arms) did not show evidence of increased progressive sperm motility when compared with placebo (MD 7.23, 95% CI -3.21 to 17.67, 60 men, P = 0.17);
- Haghighian 2015 did show an increase in progressive sperm motility when compared with placebo (MD 6.40, 95% CI 4.83 to 7.97, 44 men, P < 0.00001);
- Martinez-Soto 2010 did show a decrease in progressive sperm motility when compared with placebo (MD -6.60, 95% CI -8.57 to -4.63, 36 men, P < 0.00001).

1.14.8 Two studies (three intervention arms) compared vitamin C with placebo and did show an increase in progressive sperm motility (Cyrus 2015; Dawson 1990). As the heterogeneity was high (64%), we have not reported the pooled analysis; individually their results were:

- Cyrus 2015 did show an increase in progressive sperm motility when compared with placebo (MD 9.60, 95% CI 2.29 to 16.91, 115 men, P = 0.01);
- Dawson 1990 did not show evidence of increased progressive sperm motility when vitamin C 200 mg was compared with placebo (MD 2.00, 95% CI -24.07 to 28.07, 15 men, P = 0.88);
- Dawson 1990 did show an increase in progressive sperm motility when vitamin C 1000 mg was compared with placebo (MD 45.00, 95% CI 15.25 to 74.75, 15 men, P = 0.03).

1.14.9 Vitamin C plus vitamin E did not show evidence of increased progressive sperm motility when compared with placebo (Rolf 1999) (MD 0.20, 95% CI -9.77 to 10.17, 31 men, 1 RCT, P = 0.97, I^2 = not applicable).

1.14.10 Vitamin D did not show evidence of increased progressive sperm motility when compared with placebo (Amini 2020) (MD -0.84, 95% CI -7.65 to 5.97, 62 men, 1 RCT, P = 0.81, I^2 = not applicable).

1.14.11 Two studies with zinc did not show evidence of increased progressive sperm motility when compared with placebo (Azizollahi 2013; Sharifzadeh 2016) (MD 1.14, 95% CI -3.37 to 5.64, 157 men, 2 RCTs, P = 0.62, I^2 = 0%).

1.14.12 Zinc plus folic acid did not show evidence of increased progressive sperm motility when compared with placebo (Azizollahi 2013) (MD 3.80, 95% CI -13.66 to 21.26, 54 men, 1 RCT, P = 0.67, I^2 = not applicable).

1.14.13 Nine studies (10 intervention arms) compared antioxidants with placebo or no treatment (Bahmyari 2021; Gamidov 2017; Gamidov 2019; Joseph 2020; Kopets 2020; Micic 2019; Morgante 2010; Popova 2019; Stenqvist 2018). As the heterogeneity was very high (91%), we have not reported the pooled analysis; individually their results were:

- Bahmyari 2021 did not show evidence of increased progressive sperm motility when compared with placebo (MD -3.30, 95% CI -12.08 to 5.48, 62 men, P = 0.46);
- Gamidov 2017 (two arms) did not show evidence of increased progressive sperm motility when compared with placebo (MD -0.42, 95% CI -5.53 to 4.69, 57 men, P = 0.87);
- Gamidov 2019 did not show evidence of increased progressive sperm motility when compared with placebo (MD 0.20, 95% CI -11.43 to 11.83, 80 men, P = 0.97);
- Joseph 2020 did not show evidence of increased progressive sperm motility when compared with placebo (MD 1.70, 95% CI -4.51 to 7.91, 154 men, P = 0.59);
- Kopets 2020 did show an in increase in progressive sperm motility when compared with placebo (MD 10.10, 95% CI 5.41 to 14.79, 83 men, P < 0.0001);
- Micic 2019 did not show evidence of increased progressive sperm motility when compared with placebo (MD2.80, 95% CI -1.41 to 7.01, 165 men, P = 0.19);
- Morgante 2010 did show an increase in progressive sperm motility when compared with placebo (MD 15.20, 95% CI 13.62 to 16.78, 180 men, 1 RCT, P < 0.00001, I^2 = not applicable).
- Popova 2019 did show an increase in progressive sperm motility when compared with placebo (MD 18.00, 95% CI 11.75 to 24.25, 80 men, P < 0.00001);
- Stenqvist 2018 did not show evidence of increased progressive sperm motility when compared with placebo (MD 0.00, 95% CI -12.24 to 12.24, 75 men, P = 1.00).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 1258.83, P < 0.00001).

1.15 Progressive sperm motility at six months; type of antioxidant

See Analysis 1.15.

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.15.1 Two studies (four intervention arms) compared carnitines with placebo (Balercia 2005; Cavallini 2004) and did show increased progressive sperm motility (MD 11.66, 95% CI 8.68 to 14.64, 145 men, 2 RCTs, 4 intervention arms, P < 0.00001, I^2 = 49%).

1.15.2 Coenzyme Q10 appeared to be associated with increased progressive sperm motility when compared with placebo (Balercia 2009) (MD 5.00, 95% CI 2.13 to 7.87, 60 men, 1 RCT, P = 0.0006, I^2 = not applicable).

1.15.3 Two studies with folic acid did not show evidence of increased progressive sperm motility when compared with placebo (Azizollahi 2013; Boonyarangkul 2015) (MD -1.77, 95% CI -10.21 to 6.67, 81 men, 2 RCTs, P = 0.68, I^2 = 0%).

1.15.4 PUFAs appeared to be associated with increased progressive sperm motility when compared with placebo (Safarinejad 2011b) (MD 8.80, 95% CI 8.11 to 9.49, 227 men, 1 RCT, P < 0.00001, I^2 = not applicable).

1.15.5 Vitamin D plus calcium did not show evidence of increased progressive sperm motility when compared with placebo (Blomberg Jensen 2018) (MD -4.00, 95% CI -9.59 to 1.59, 260 men, P = 0.16, I^2 = not applicable).

1.15.6 Zinc did not show evidence of increased progressive sperm motility when compared with placebo (Azizollahi 2013) (MD 2.00, 95% CI -13.56 to 17.56, 57 men, 1 RCT, P = 0.80, I^2 = not applicable).

1.15.7 Zinc plus folic acid did not show evidence of increased progressive sperm motility when compared with placebo (Azizollahi 2013) (MD 2.70, 95% CI -14.58 to 19.98, 54 men, 1 RCT, P = 0.76, I^2 = not applicable).

1.15.8 Five studies compared antioxidants with placebo or no treatment (Ardestani 2019; Gamidov 2019; Kizilay 2019; Micic 2019; Stenqvist 2018). As heterogeneity was high (65%), we have not reported the pooled analysis; individually their results were:

- Ardestani 2019 did not show evidence of increased progressive sperm motility when compared with no treatment (MD 3.90, 95% CI -4.10 to 11.90, 60 men, P < 0.34);
- Gamidov 2019 did show an increase in progressive sperm motility when compared with placebo (MD 13.20, 95% CI 4.46 to 21.94, 80 men, P =0.003);
- Kizilay 2019 did not show evidence of increased progressive sperm motility when compared with placebo (MD 1.90, 95% CI -0.85 to 4.65, 90 men, P = 0.18);
- Micic 2019 did show an increase in progressive sperm motility when compared with placebo (MD 6.70, 95% CI 3.36 to 10.04, 180 men, P < 0.0001);
- Stenqvist 2018 did not show evidence of increased progressive sperm motility when compared with placebo (MD -3.40, 95% CI -12.89 to 6.09, 75 men, P = 0.48).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 54.94, P < 0.00001).

1.16 Data not suitable for meta analysis

See Analysis 1.16.

One study provided data as percentage improvement and therefore could not be used in the forest plot (Saeed Alkumait 2020). The percentage improvement in the intervention groups was higher compared with placebo (P = 0.01).

1.17 Progressive sperm motility at nine months or more; type of antioxidant

See Analysis 1.17.

We analysed this outcome using a fixed-effect model and used subtotals as pooling was not possible.

1.17.1 Carnitines appeared to be associated with an increase in progressive sperm motility when compared with placebo (Balercia 2005, three intervention arms) (MD 7.77, 95% CI 2.68 to 12.87, 59 men, 1 RCT, 3 intervention arms, P = 0.003, I^2 = 0%).

1.17.2 Coenzyme Q10 did not show evidence of increased progressive sperm motility when compared with placebo (Balercia 2009) (MD -0.90, 95% CI -2.68 to 0.88, 60 men, 1 RCT, P = 0.32, I^2 = not applicable).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 9.93, P = 0.002).

1.18 Progressive sperm motility over time

See Analysis 1.18.

This analysis was only useful in directly comparing the same studies reporting at the three time points and not in comparing results of meta-analyses that included different subsets of studies.

1.18.1 Progressive sperm motility at three months or less. We analysed this outcome using a fixed-effect model (MD 17.98, 95% CI 17.62 to 18.34, 2054 men, 27 RCTs, 35 intervention arms, P < 0.00001, I^2 = 98%) and used subtotals (Abbasi 2020; Amini 2020; Attallah 2013; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Boonyarangkul 2015; Cavallini 2004; Cyrus 2015; Dawson 1990; Gamidov 2017; Gamidov 2019; Gonzalez-Ravina 2018; Haghighian 2015; Joseph 2020; Kopets 2020; Kumalic 2020; Martinez-Soto 2010; Mehni 2014; Micic 2019; Morgante 2010; Nadjarzadeh 2011; Nouri 2019; Peivandi 2010; Popova 2019; Rolf 1999; Stenqvist 2018).

1.18.2 Progressive sperm motility at six months. We analysed this outcome using a fixed-effect model (MD 8.05, 95% CI 7.43 to 8.66, 1304 men, 12 RCTs, 16 intervention arms, P < 0.00001, I^2 = 79%) and used subtotals (Ardestani 2019; Azizollahi 2013; Balercia 2005; Balercia 2009; Blomberg Jensen 2018; Boonyarangkul 2015; Cavallini 2004; Gamidov 2019; Kizilay 2019; Micic 2019; Safarinejad 2011b; Stenqvist 2018).

1.18.3 Progressive sperm motility at nine months or more. We analysed this outcome using a fixed-effect model (MD 0.04, 95% CI -1.64 to 1.72, 119 men, 2 RCTs, 4 intervention arms, P = 0.96, I^2 = 72%) and used subtotals (Balercia 2005; Balercia 2009).

1.19 Sperm concentration at three months or less; type of antioxidant

See Analysis 1.19 and Figure 12.

Figure 12. Forest plot of comparison: 1 Antioxidant(s) versus placebo or no treatment, outcome: 1.19 Sperm concentration at 3 months or less; type of antioxidant.

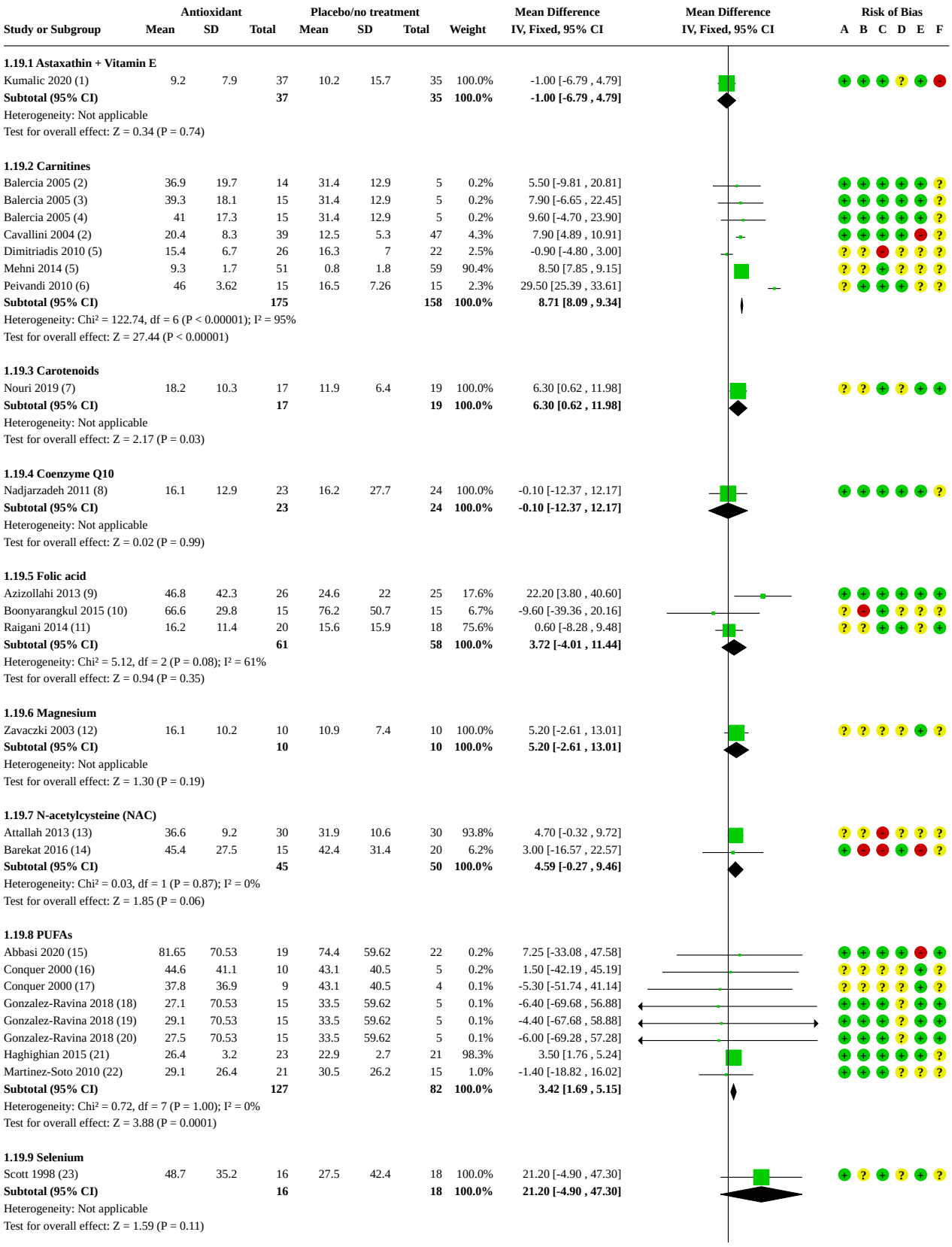
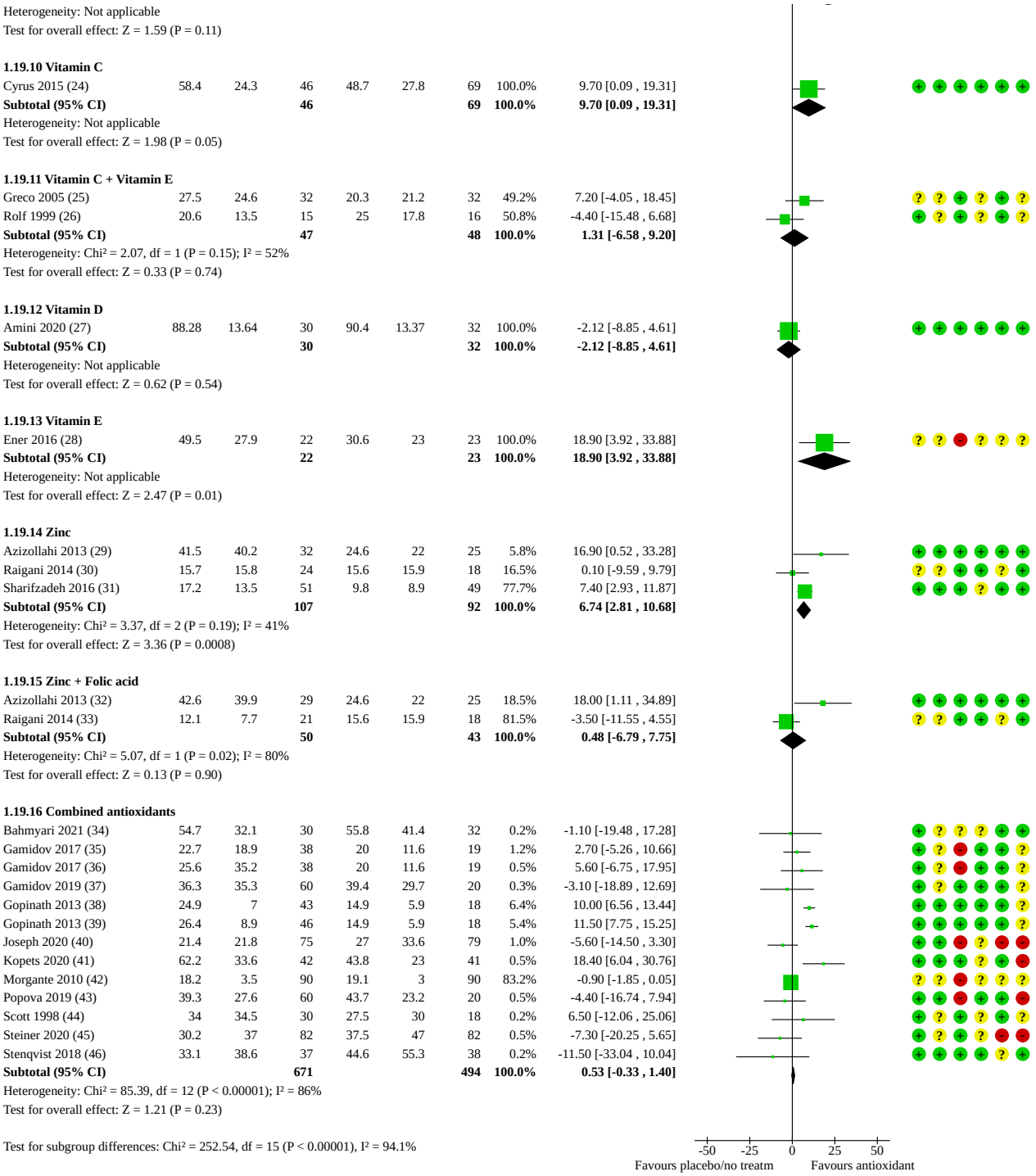


Figure 12. (Continued)



Heterogeneity: Not applicable								
Test for overall effect: Z = 1.59 (P = 0.11)								
1.19.10 Vitamin C								
Cyrus 2015 (24)	58.4	24.3	46	48.7	27.8	69	100.0%	9.70 [0.09 , 19.31]
Subtotal (95% CI)			**46**			**69**	**100.0%**	**9.70 [0.09 , 19.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.98 (P = 0.05)								
1.19.11 Vitamin C + Vitamin E								
Greco 2005 (25)	27.5	24.6	32	20.3	21.2	32	49.2%	7.20 [-4.05 , 18.45]
Rolf 1999 (26)	20.6	13.5	15	25	17.8	16	50.8%	-4.40 [-15.48 , 6.68]
Subtotal (95% CI)			**47**			**48**	**100.0%**	**1.31 [-6.58 , 9.20]**
Heterogeneity: Chi² = 2.07, df = 1 (P = 0.15); I² = 52%								
Test for overall effect: Z = 0.33 (P = 0.74)								
1.19.12 Vitamin D								
Amini 2020 (27)	88.28	13.64	30	90.4	13.37	32	100.0%	-2.12 [-8.85 , 4.61]
Subtotal (95% CI)			**30**			**32**	**100.0%**	**-2.12 [-8.85 , 4.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.54)								
1.19.13 Vitamin E								
Ener 2016 (28)	49.5	27.9	22	30.6	23	23	100.0%	18.90 [3.92 , 33.88]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**18.90 [3.92 , 33.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.47 (P = 0.01)								
1.19.14 Zinc								
Azizollahi 2013 (29)	41.5	40.2	32	24.6	22	25	5.8%	16.90 [0.52 , 33.28]
Raigani 2014 (30)	15.7	15.8	24	15.6	15.9	18	16.5%	0.10 [-9.59 , 9.79]
Sharifzadeh 2016 (31)	17.2	13.5	51	9.8	8.9	49	77.7%	7.40 [2.93 , 11.87]
Subtotal (95% CI)			**107**			**92**	**100.0%**	**6.74 [2.81 , 10.68]**
Heterogeneity: Chi² = 3.37, df = 2 (P = 0.19); I² = 41%								
Test for overall effect: Z = 3.36 (P = 0.0008)								
1.19.15 Zinc + Folic acid								
Azizollahi 2013 (32)	42.6	39.9	29	24.6	22	25	18.5%	18.00 [1.11 , 34.89]
Raigani 2014 (33)	12.1	7.7	21	15.6	15.9	18	81.5%	-3.50 [-11.55 , 4.55]
Subtotal (95% CI)			**50**			**43**	**100.0%**	**0.48 [-6.79 , 7.75]**
Heterogeneity: Chi² = 5.07, df = 1 (P = 0.02); I² = 80%								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.19.16 Combined antioxidants								
Bahmyari 2021 (34)	54.7	32.1	30	55.8	41.4	32	0.2%	-1.10 [-19.48 , 17.28]
Gamidov 2017 (35)	22.7	18.9	38	20	11.6	19	1.2%	2.70 [-5.26 , 10.66]
Gamidov 2017 (36)	25.6	35.2	38	20	11.6	19	0.5%	5.60 [-6.75 , 17.95]
Gamidov 2019 (37)	36.3	35.3	60	39.4	29.7	20	0.3%	-3.10 [-18.89 , 12.69]
Gopinath 2013 (38)	24.9	7	43	14.9	5.9	18	6.4%	10.00 [6.56 , 13.44]
Gopinath 2013 (39)	26.4	8.9	46	14.9	5.9	18	5.4%	11.50 [7.75 , 15.25]
Joseph 2020 (40)	21.4	21.8	75	27	33.6	79	1.0%	-5.60 [-14.50 , 3.30]
Kopets 2020 (41)	62.2	33.6	42	43.8	23	41	0.5%	18.40 [6.04 , 30.76]
Morgante 2010 (42)	18.2	3.5	90	19.1	3	90	83.2%	-0.90 [-1.85 , 0.05]
Popova 2019 (43)	39.3	27.6	60	43.7	23.2	20	0.5%	-4.40 [-16.74 , 7.94]
Scott 1998 (44)	34	34.5	30	27.5	30	18	0.2%	6.50 [-12.06 , 25.06]
Steiner 2020 (45)	30.2	37	82	37.5	47	82	0.5%	-7.30 [-20.25 , 5.65]
Stenqvist 2018 (46)	33.1	38.6	37	44.6	55.3	38	0.2%	-11.50 [-33.04 , 10.04]
Subtotal (95% CI)			**671**			**494**	**100.0%**	**0.53 [-0.33 , 1.40]**
Heterogeneity: Chi² = 85.39, df = 12 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 1.21 (P = 0.23)								
Test for subgroup differences: Chi² = 252.54, df = 15 (P < 0.00001), I² = 94.1%								

Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg.
(2) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(3) L-acetyl carnitine 3000 mg.
(4) L-carnitine 3000 mg.
(5) L-carnitine 1000 mg.
(6) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(7) Lycopene 25 mg.
(8) Coenzyme Q10 200 mg.
(9) Folic acid 5 mg. After varicocelectomy.

Figure 12. (Continued)

(7) Lycopene 25 mg.
(8) Coenzyme Q10 200 mg.
(9) Folic acid 5 mg. After varicocelectomy.
(10) Folic acid 5 mg.
(11) Folic acid 5 mg. At 16 weeks.
(12) Magnesium 3000 mg.
(13) N-acetylcysteine (NAC) 600 mg
(14) N-acetylcysteine (NAC) 200 mg. After varicocelectomy.
(15) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(16) Docosahexaenoic acid (DHA) 800 mg.
(17) Docosahexaenoic acid (DHA) 400 mg.
(18) Docosahexaenoic acid (DHA) 1 g.
(19) Docosahexaenoic acid (DHA) 2 g.
(20) Docosahexaenoic acid (DHA) 0.5 g.
(21) Alpha-lipoic acid (ALA) 600 mg.
(22) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(23) Selenium 100 µg.
(24) Vitamin C 500 mg. After varicocelectomy.
(25) Vitamin C 1000 mg + Vitamin E 1000 mg. 2 months.
(26) Vitamin C 1000 mg + Vitamin E 800 mg. 2 months.
(27) Vitamin D3 50,000IU/week for 8 weeks, followed by 50,000IU/month for 1 month
(28) Vitamin E 600 mg. After varicocelectomy.
(29) Zinc 66 mg. After varicocelectomy.
(30) Zinc 220 mg. At 16 weeks.
(31) Zinc 10 ml solution of 0.5%.
(32) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(33) Zinc 220 mg + Folic acid 5 mg. At 16 weeks.
(34) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(35) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(36) SpermActin Forte (acetyl-L-carnitine + L-carnitine fumarate + alpha-lipoic acid). After varicocelectomy.
(37) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(38) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(39) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(40) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.
(41) 1 dose TDS (l-carnitine/ l-acetyl-carnitine + l-arginine + glutathione + coenzyme Q10 + zinc + vitamin B9 + vitamin B12 + selenium)
(42) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(43) Androdoz (l-arginine 720 mg + l-carnitine 240 mg + l-carnosine 92 mg + coenzyme Q10 10 mg + glycyrrhizic acid 6 mg)
(44) Selenium 100 µg + Vitamin A 1 mg + Vitamin C 10 mg + Vitamin E 15 mg.
(45) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(46) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

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

We analysed this outcome using a fixed-effect model. We used only subtotals in this analysis.

1.19.1 Astaxanthin plus vitamin E did not show evidence of increased sperm concentration when compared with placebo (Kumalic 2020) (MD -1.00, 95% CI -6.79 to 4.79, 72 men, 1 RCT, P = 0.74, I^2 = not applicable).

1.19.2 Five studies (7 intervention arms) compared carnitines with placebo or no treatment and showed an increase in sperm concentration (Balercia 2005; Cavallini 2004; Dimitriadis 2010; Mehni 2014; Peivandi 2010). As the heterogeneity was extremely high (95%) we have not reported the pooled analysis; individually their results were:

- Balercia 2005 did not show evidence of increased sperm concentration when compared with placebo (MD 7.76, 95% CI -0.73 to 16.25, 59 men, P = 0.07, I^2 = 0%);
- Cavallini 2004 did show an increase in sperm concentration when compared with placebo (MD 7.90, 95% CI 4.89 to 10.91, 86 men, P < 0.00001, I^2 = not applicable);
- Dimitriadis 2010 did not show evidence of increased sperm concentration when compared with no treatment (MD -0.90, 95% CI -4.80 to 3.00, 48 men, P = 0.65, I^2 = not applicable);
- Mehni 2014 did show an increase in sperm concentration when compared with placebo (MD 8.50, 95% CI 7.85 to 9.15, 110 men, P < 0.00001, I^2 = not applicable);
- Peivandi 2010 did show an increase in sperm concentration when compared with placebo (MD 29.50, 95% CI 25.39 to 33.61, 30 men, P < 0.00001, I^2 = not applicable).

1.19.3 Carotenoids appeared to be associated with an increase in sperm concentration when compared with placebo (Nouri 2019) (MD 6.30, 95% CI 0.62 to 11.98, 36 men, 1 RCT, P = 0.03, I^2 = not applicable).

1.19.4 Coenzyme Q10 did not show evidence of increased sperm concentration when compared with placebo (Nadjarzadeh 2011) (MD -0.10, 95% CI -12.37 to 12.17, 47 men, 1 RCT, P = 0.99, I^2 = not applicable).

1.19.5 Three studies compared folic acid with placebo and did not show evidence of increased sperm concentration (Azizollahi 2013; Boonyarangkul 2015; Raigani 2014). As the heterogeneity was high (61%) we have not reported the pooled analysis; individually their results were:

- Azizollahi 2013 did show an increase in sperm concentration when compared with placebo (MD 22.20, 95% CI 3.80 to 40.60, 51 men, P = 0.02);
- Boonyarangkul 2015 did not show evidence of increased sperm concentration when compared with placebo (MD -9.60, 95% CI -39.36 to 20.16, 30 men, P = 0.53). However, in this study there was great baseline imbalance for sperm parameters between the intervention and control group;
- Raigani 2014 did not show evidence of increased sperm concentration when compared with placebo at 16 weeks (MD 0.60, 95% CI -8.28 to 9.48, 38 men, P =0.89).

1.19.6 Magnesium did not show evidence of increased sperm concentration when compared with placebo (Zavaczki 2003) (MD 5.20, 95% CI -2.61 to 13.01, 20 men, 1 RCT, P = 0.19, I^2 = not applicable).

1.19.7 Two studies compared N-acetylcysteine (NAC) with placebo or no treatment (Attallah 2013; Barekat 2016) and did not show evidence of increased sperm concentration (MD 4.59, 95% CI -0.27 to 9.46, 95 men, 2 RCTs, P = 0.06, I^2 = 0%).

1.19.8 Five studies (eight intervention arms) compared PUFAs with placebo or no treatment (Abbasi 2020; Conquer 2000; Gonzalez-Ravina 2018; Haghighian 2015; Martinez-Soto 2010) and did show an increase in sperm concentration (MD 3.42, 95% CI 1.69 to 5.15, 209 men, 5 RCTs, 8 intervention arms, P = 0.0001, I^2 = 0%). Haghighian 2015 reported remarkably small SDs compared with the other included studies. A sensitivity analysis was performed, showing no evidence of increased sperm concentration (MD -1.07, 95% CI -14.37 to 12.24, 165 men, 4 RCTs, 7 intervention arms, P = 0.88, I^2 = 0%).

1.19.9 Selenium did not show evidence of increased sperm concentration when compared with placebo (Scott 1998) (MD 21.20, 95% CI -4.90 to 47.30, 34 men, 1 RCT, P = 0.11, I^2 = not applicable).

1.19.10 Vitamin C did not show evidence of increased sperm concentration when compared with placebo (Cyrus 2015) (MD 9.70, 95% CI 0.09 to 19.31, 115 men, 1 RCT, P = 0.05, I^2 = not applicable).

1.19.11 Two studies compared vitamin C plus vitamin E with placebo (Greco 2005; Rolf 1999). As the heterogeneity was high (52%), we have not reported the pooled analysis; individually their results were:

- Greco 2005 did not show evidence of increased sperm concentration when compared with placebo (MD 7.20, 95% CI -4.05 to 18.45, 64 men, P = 0.21);
- Rolf 1999 did not show evidence of increased sperm concentration when compared with placebo (MD -4.40, 95% CI -15.48 to 6.68, 31 men, P = 0.44).

1.19.12 Vitamin D did not show evidence of increased sperm concentration compared with placebo (Amini 2020) (MD -2.12, 95% CI -8.85 to 4.61, 62 men, P = 0.54, I^2 = not applicable).

1.19.13 Vitamin E appeared to be associated with an increase in sperm concentration when compared with no treatment (Ener 2016) (MD 18.90, 95% CI 3.92 to 33.88, 45 men, 1 RCT, P = 0.01, I^2 = not applicable).

1.19.14 Three studies compared zinc with placebo (Azizollahi 2013; Raigani 2014; Sharifzadeh 2016). There appeared to be an association between zinc and increased sperm concentration (MD 6.74 95% CI 2.81 to 10.68, 199 men, 3 RCTs, P = 0.0008, I^2 = 41%).

1.19.15 Two studies compared folic acid plus zinc with placebo (Azizollahi 2013; Raigani 2014). As heterogeneity was high (80%), we have not reported the pooled analysis; individually their results were:

- Azizollahi 2013 did show an increase in sperm concentration when compared with placebo (MD 18.00, 95% CI 1.11 to 34.89, 54 men, P = 0.04);
- Raigani 2014 did not show evidence of increased sperm concentration when compared with placebo (MD -3.50, 95% CI -11.55 to 4.55, 39 men, P = 0.39).

1.19.16 Eleven studies (13 intervention arms) compared combined antioxidants with placebo or no treatment (Bahmyari 2021; Gamidov 2017; Gamidov 2019; Gopinath 2013; Joseph 2020; Kopets 2020; Morgante 2010; Popova 2019; Scott 1998; Steiner 2020; Stenqvist 2018). As the heterogeneity was very high (86%), we have not reported the pooled analysis; individually their results were:

- Bahmyari 2021 did not show evidence of increased sperm concentration when compared with placebo (MD -1.10, 95% CI -19.48 to 17.28, 62men, P = 0.91);
- Gamidov 2017 (two arms) did not show evidence of increased sperm concentration when compared with placebo (MD 3.55, 95% CI -3.14 to 10.24, 114 men, P = 0.30);
- Gamidov 2019 did not show evidence of increased sperm concentration when compared with placebo (MD -3.10, 95% CI -18.89 to 12.69, 80 men, P = 0.70);
- Gopinath 2013 did show an increase in sperm concentration when compared with placebo (MD 10.69, 95% CI 8.15 to 13.22, 125 men, P < 0.00001);
- Joseph 2020 did not show evidence of increased sperm concentration when compared with placebo (MD -5.60, 95% CI -14.50 to 3.30, 154 men, P = 0.22);
- Kopets 2020 did show an increase in sperm concentration when compared with placebo (MD 18.40, 95% CI 6.04 to 30.76, 83 men, P < 0.004);
- Morgante 2010 did not show evidence of an increased sperm concentration when compared with no treatment (MD -0.90, 95% CI -1.85 to 0.05, 180 men, P = 0.06);
- Popova 2019 did not show evidence of an increased sperm concentration when compared with placebo (MD -4.40, 95% CI -16.74 to 7.94, 80 men, P = 0.48);

- Scott 1998 did not show evidence of increased sperm concentration when compared with placebo (MD 6.50, 95% CI -16.66 to 29.66, 39 men, P = 0.58);
- Steiner 2020 did not show evidence of increased sperm concentration when compared with placebo (MD -7.30, 95% CI -20.25 to 5.65, 164 men, P = 0.27);
- Stenqvist 2018 did not show evidence of increased sperm concentration when compared with placebo (MD -11.50, 95% CI -33.04 to 10.04, 75 men, P = 0.30).

There was evidence that different antioxidants did not have differing effects (test for subgroup differences: Chi^2 = 252.54, P < 0.00001).

1.20 Data not usable for meta-analysis

See Analysis 1.20.

One study (Kessopoulou 1995) provided data as median differences and range and therefore could not be used in the forest plot. This study might indicate some improvement in sperm concentration in the intervention group when measured at three months, however these data were not rigorous and no conclusions could be made. One study (Lenzi 2003) provided data as the mean with no SD and did not report the number of patients in whom the outcome was assessed. The P value in Lenzi 2003 was 0.03, indicating that there may have been an association between L-carnitine and improved sperm concentration at three months.

1.21 Sperm concentration at six months; type of antioxidant

See Analysis 1.21.

We analysed this outcome using a fixed-effect model. We used only subtotals in this analysis.

1.21.1 Three studies (five intervention arms) compared carnitines with placebo (Balercia 2005; Cavallini 2004; Lenzi 2004). There appeared to be an association between carnitines and increased sperm concentration (MD 7.42, 95% CI 4.97 to 9.87, 201 men, 3 RCTs, 5 intervention arms, P < 0.00001, I^2 = 23%).

1.21.2 Three studies compared coenzyme Q10 with placebo (Balercia 2009; Safarinejad 2009a; Safarinejad 2012). As the heterogeneity was extremely high (96%) we have not reported the pooled analysis; individually their results were:

- Balercia 2009 did not show evidence of increased sperm concentration when compared with placebo (MD -1.50, 95% CI -11.39 to 8.39, 60 men, P = 0.77);
- Safarinejad 2009a did show an increase in sperm concentration when compared with placebo (MD 5.60, 95% CI 4.38 to 6.82, 194 men, P < 0.00001);
- Safarinejad 2012 did show an increase in sperm concentration when compared with placebo (MD 11.90, 95% CI 10.72 to 13.08, 225 men, P < 0.00001).

1.21.3 Three studies compared folic acid with placebo (Azizollahi 2013; Boonyarangkul 2015; Wong 2002). As the heterogeneity was high (58%) we have not reported the pooled analysis; individually their results were:

- Azizollahi 2013 did show an increase in sperm concentration when compared with placebo (MD 19.20, 95% CI 12.24 to 26.16, 51 men, P < 0.00001);
- Boonyarangkul 2015 did not show evidence of increased sperm concentration when compared with placebo (MD -22.80, 95% CI -60.44 to 14.84, 30 men, P = 0.24). However, in this study there was great baseline imbalance for sperm parameters between the intervention and control group;
- Wong 2002 did not show evidence of increased sperm concentration when compared with placebo (MD 15.00, 95% CI -1.19 to 31.19, 47 men, P = 0.07).

1.21.4 N-acetylcysteine (NAC) appeared to be associated with an increase in sperm concentration when compared with placebo (Safarinejad 2009) (MD 3.30, 95% CI 1.80 to 4.80, 211 men, 1 RCT, P < 0.0001, I^2 = not applicable).

1.21.5 PUFAs appeared to be associated with an increase in sperm concentration when compared with placebo (Safarinejad 2011b) (MD 12.50, 95% CI 11.39 to 13.61, 227 men, 1 RCT, P < 0.00001, I^2 = not applicable).

1.21.6 Selenium appeared to be associated with an increase in sperm concentration when compared with placebo (Safarinejad 2009) (MD 4.10, 95% CI 2.45 to 5.75, 211 men, 1 RCT, P < 0.00001, I^2 = not applicable).

1.21.7 Selenium plus N-acetylcysteine (NAC) appeared to be associated with an increase in sperm concentration when compared with placebo (Safarinejad 2009) (MD 8.60, 95% CI 6.89 to 10.31, 210 men, 1 RCT, P < 0.00001 I^2 = not applicable).

1.21.8 Vitamin D plus calcium did not show evidence of increased sperm concentration when compared with placebo (Blomberg Jensen 2018) (MD -2.50, 95% CI -8.18 to 3.18, 269 men, 1 RCT, P = 0.39, I^2 = not applicable).

1.21.9 Vitamin E did not show evidence of increased sperm concentration when compared with no treatment (Ener 2016) (MD 5.90, 95% CI -10.83 to 22.63, 45 men, 1 RCT, P = 0.49, I^2 = not applicable).

1.21.10 Two studies compared zinc with placebo (Azizollahi 2013; Wong 2002) and did not show evidence of increased sperm concentration (MD 5.51, 95% CI -4.00 to 15.01, 105 men, 2 RCTs, P = 0.26, I^2 = 0%).

1.21.11 Three studies compared zinc plus folic acid with placebo (Azizollahi 2013; Schisterman 2020; Wong 2002). As heterogeneity was high (84%), we have not reported the pooled analysis; individually their results were:

- Azizollahi 2013 did not show evidence of increased sperm concentration when compared with placebo (MD 17.70, 95% CI -1.88 to 37.28, 54 men, P = 0.08);
- Schisterman 2020 did not show evidence of increased sperm concentration when compared with placebo (MD -9.00, 95% CI -19.00 to 1.00, 853 men, P = 0.08);
- Wong 2002 did show an increase in sperm concentration when compared with placebo (MD 26.40, 95% CI 6.33 to 46.47, 49 men, P = 0.01).

1.21.12 Six studies (7 intervention arms) compared combined antioxidants to placebo or no treatment (Ardestani 2019; Busetto 2018; Gamidov 2019; Gopinath 2013; Kizilay 2019; Stenqvist 2018). As the heterogeneity was very high (91%), we have not reported the pooled analysis; individually their results were:

- Ardestani 2019 did not show evidence of increased sperm concentration when compared with placebo (MD 5.50, 95% CI -6.57 to 17.57, 60 men, P = 0.37);
- Busetto 2018 did show an increase in sperm concentration when compared with placebo (MD 7.70, 95% CI 2.41 to 12.99, 104 men, P = 0.004);
- Gamidov 2019 did not show evidence of increased sperm concentration when compared with placebo (MD 4.50, 95% CI -12.17 to 21.17, 80 men, P = 0.60);
- Gopinath 2013 did show an increase in sperm concentration when compared with placebo (MD 16.48, 95% CI 13.08 to 19.87, 125 men, P < 0.00001);
- Kizilay 2019 did show an increase in sperm concentration when compared with placebo (MD 2.00, 95% CI 1.06 to 2.94, 90 men, P < 0.0001);
- Stenqvist 2018 did not show evidence of increased sperm concentration when compared with placebo (MD -2.60, 95% CI -25.30 to 20.10, 75 men, P = 0.82).

There was evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 246.11, P < 0.00001).

1.22 Data not usable for meta-analysis

Analysis 1.22

One study (Saeed Alkumait 2020) provided data as percentage improvement and therefore could not be used in the forest plot. The percentage improvement was higher in the two intervention groups than in the placebo group (P = 0.01).

1.23 Sperm concentration at nine months; type of antioxidant

See Analysis 1.23.

We analysed this outcome using a fixed-effect model. We used only subtotals in this analysis.

1.23.1 Carnitines (three intervention arms) did not show evidence of increased sperm concentration when compared with placebo (Balercia 2005) (MD 4.17, 95% CI -1.71 to 10.06, 59 men, 1 RCT, 3 intervention arms, P = 0.16, I^2 = not applicable).

1.23.2 Three studies compared coenzyme Q10 with placebo (Balercia 2009; Safarinejad 2009a; Safarinejad 2012). As the heterogeneity was extremely high (95%), we have not reported the pooled analysis; individually their results were:

- Balercia 2009 did not show evidence of increased sperm concentration when compared with placebo (MD -5.40, 95% CI -15.75 to 4.95, 60 men, P = 0.31);
- Safarinejad 2009a did show an increase in sperm concentration when compared with placebo (MD 1.60, 95% CI 0.53 to 2.67, 194 men, P = 0.003);
- Safarinejad 2012 did show an increase in sperm concentration when compared with placebo (MD 6.20, 95% CI 5.17 to 7.23, 225 men, P < 0.00001).

1.23.3 Vitamin E did not show evidence of increased sperm concentration when compared with no treatment (Ener 2016) (MD 11.40, 95% CI -2.56 to 25.36, 45 men, 1 RCT, P = 0.11, I^2 = not applicable).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: Chi^2 = 1.10, P = 0.58).

1.24 Sperm concentration over time

See Analysis 1.24.

This analysis was only useful in directly comparing the same studies reporting at the three time points and not in comparing results of meta-analyses that included different subsets of studies.

1.24.1 Total sperm concentration at three months or less. We analysed this outcome using a fixed-effect model (MD 5.49, 95% CI 5.02 to 5.96, 2535 men, 35 RCTs, 47 intervention arms, P < 0.00001, I^2 = 91%) and used subtotals (Abbasi 2020; Amini 2020; Attallah 2013; Azizollahi 2013; Bahmyari 2021; Balercia 2005; Barekat 2016; Boonyarangkul 2015; Cavallini 2004; Conquer 2000; Cyrus 2015; Dimitriadis 2010; Ener 2016; Gamidov 2017; Gamidov 2019; Gonzalez-Ravina 2018; Gopinath 2013; Greco 2005; Haghighian 2015; Joseph 2020; Kopets 2020; Kumalic 2020; Martinez-Soto 2010; Mehni 2014; Morgante 2010; Nadjarzadeh 2011; Nouri 2019; Peivandi 2010; Popova 2019; Raigani 2014; Rolf 1999; Scott 1998; Steiner 2020; Stenqvist 2018; Zavaczki 2003).

1.24.2 Total sperm concentration at six months. We analysed this outcome using a fixed-effect model (MD 7.21, 95% CI 6.73 to 7.70, 2995 men, 19 RCTs, 28 intervention arms, P < 0.00001, I^2 = 92%) and used subtotals (Ardestani 2019; Azizollahi 2013; Balercia 2005; Balercia 2009; Boonyarangkul 2015; Busetto 2018; Cavallini 2004; Ener 2016; Gamidov 2019; Gopinath 2013; Kizilay 2019; Lenzi 2004; Safarinejad 2009; Safarinejad 2009a; Safarinejad 2011b; Safarinejad 2012; Schisterman 2020; Stenqvist 2018; Wong 2002).

1.24.3 Total sperm concentration at nine months or more. We analysed this outcome using a fixed-effect model (MD 3.95, 95% CI 3.22 to 4.69, 583 men, 5 RCTs, seven intervention arms, P < 0.00001, I^2 = 86%) and used subtotals (Balercia 2005; Balercia 2009; Ener 2016; Safarinejad 2009a; Safarinejad 2012).

2. Head-to-head antioxidants (natural conception and undergoing fertility treatment)

The studies included in this comparison did not report on adverse events.

2.1 Live birth; type of antioxidant

See Analysis 2.1.

2.1.1 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased live birth rate when compared with L-acetyl carnitine (Balercia 2005) (Peto OR 1.00, 95% CI 0.13 to 7.92, 30 men, 1 RCT, P = 1.00).

2.1.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased live birth rate when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (Peto OR 0.34, 95% CI 0.06 to 1.79, 30 men, 1 RCT, P = 0.20).

2.1.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased live birth rate when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (Peto OR 0.34, 95% CI 0.06 to 1.79, 30 men, 1 RCT, P = 0.20).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: $Chi^2 = 0.79$, P = 0.67)

2.2 Clinical pregnancy; type of antioxidant

See Analysis 2.2.

2.2.1. L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased clinical pregnancy rate when compared with L-acetyl carnitine (Balercia 2005) (Peto OR 1.00, 95% CI 0.13 to 7.92, 30 men, 1 RCT, P = 1.00).

2.2.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased clinical pregnancy rate when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (Peto OR 0.34, 95% CI 0.06 to 1.79, 30 men,1 RCT, P = 0.20).

2.2.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased clinical pregnancy rate when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (Peto OR 0.34, 95% CI 0.06 to 1.79, 30 men,1 RCT, P = 0.20).

2.2.4 L-carnitine versus coenzyme Q10. There was no evidence of the use of L-carnitine and increased clinical pregnancy rate when compared with coenzyme Q10 (Cheng 2018) (Peto OR 1.48, 95% CI 0.54 to 4.05, 156 men, 1 RCT, P = 0.44).

2.2.5 L-carnitine versus L-carnitine plus coenzyme Q10. There was no evidence of the use of L-carnitine and increased clinical pregnancy rate when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (Peto OR 0.62, 95% CI 0.27 to 1.46, 156 men, 1 RCT, P = 0.28).

2.2.6 Coenzyme Q10 versus L-carnitine plus coenzyme Q10. There was no evidence of the use of coenzyme Q10 and increased clinical pregnancy rate when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (Peto OR 0.43, 95% CI 0.18 to 1.06, 156 men, 1 RCT, P = 0.07).

2.2.7 Vitamin D plus calcium versus vitamin E plus vitamin C. There appeared to be an association between the use of vitamin D plus calcium and increased clinical pregnancy rate when compared with vitamin E plus vitamin C (Deng 2014) (Peto OR 5.13, 95% CI 1.21 to 21.79, 86 men, P = 0.03).

2.2.8 Combined antioxidants versus L-carnitine. There was no evidence of the use of combined antioxidants and increased clinical pregnancy rate when compared with L-carnitine (Tsounapi 2018) (Peto OR 1.93, 95% CI 0.20 to 19.08, 89 men, P = 0.57).

There was no evidence that different antioxidants had differing effects (test for subgroup differences: $Chi^2 = 12.59$, P = 0.08).

2.3 Sperm DNA fragmentation; type of antioxidant

See Analysis 2.3.

2.3.1 L-carnitine versus coenzyme Q10. There was no evidence of the use of L-carnitine and decreased DNA fragmentation when compared with coenzyme Q10 (Cheng 2018) (MD -0.80, 95% CI -2.22 to 0.62, 125 men, P = 0.27).

2.3.2 L-carnitine versus L-carnitine plus coenzyme Q10. There was no evidence of the use of L-carnitine and decreased DNA fragmentation when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (MD 0.40, 95% CI -1.14 to 1.94, 125 men, P = 0.61).

2.3.3 Coenzyme Q10 verus L-carnitine plus coenzyme Q10. There was no evidence of the use of coenzyme Q10 and decreased DNA fragmentation when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (MD 1.20, 95% CI -0.25 to 2.65, 126 men, P = 0.11).

2.3.4 L-carnitine versus vitamin B1. There was no evidence of the use of L-carnitine and decreased DNA fragmentation when compared with vitamin B1 (Cheng 2018) (MD -1.50, 95% CI -3.22 to 0.22, 136 men, P = 0.09).

2.3.5 Coenzyme Q10 versus vitamin B1. There was no evidence of the use of coenzyme Q10 and decreased DNA fragmentation when compared with vitamin B1 (Cheng 2018) (MD -0.70, 95% CI -2.34 to 0.94, 137 men, P = 0.40).

2.3.6 Vitamin B1 versus L-carnitine plus coenzyme Q10. There appeared to be an association between the use of vitamin B1 and increased DNA fragmentation when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (MD 1.90, 95% CI 0.16 to 3.64, 137 men, P = 0.03).

2.4 Total sperm motility at three months or less; type of antioxidant

See Analysis 2.4.

2.4.1 Coenzyme Q10 200 mg versus coenzyme Q10 400 mg. There was no evidence of the use of coenzyme Q10 200 mg/day and increased sperm motility when compared with coenzyme Q10 400 mg/day (Alahmar 2019) (MD -4.86, 95% CI -10.60 to 0.88, 65 men, P = 0.10).

2.4.2 Docosahexaenoic acid (DHA) 400 mg versus DHA 800 mg. There was no evidence of the use of DHA 400 g/day and increased sperm motility when compared with DHA 800 mg/day (Conquer 2000) (MD 7.40, 95% CI -11.35 to 26.15, 19 men, P = 0.44).

2.4.3 DHA versus DHA plus vitamin E. There appeared to be an association between the use of DHA and decreased sperm motility when compared with DHA combined with vitamin E (Eslamian 2020) (MD -3.77, 95% CI -5.42 to -2.12, 90 men, P < 0.00001).

2.4.4 DHA versus vitamin E. There was no evidence of the use of DHA and increased sperm motility when compared with vitamin E (Eslamian 2020) (MD -1.60, 95% CI -3.30 to 0.10, 90 men, P = 0.07).

2.4.5 DHA plus vitamin E versus vitamin E. There appeared to be an association between the use of DHA plus vitamin E and increased sperm motility when compared with vitamin E alone (Eslamian 2020) (MD 2.17, 95% CI 0.54 to 3.80, 90 men, P = 0.009).

2.4.6 Ethylcysteine versus vitamin E. There was no evidence of the use of ethyl cysteine and increased sperm motility when compared with vitamin E (Akiyama 1999) (MD -1.90, 95% CI -41.97 to 38.17, 10 men, P = 0.93).

2.4.7 L-acetyl carnitine plus L carnitine versus vitamin E plus vitamin C. There appeared to be an association between the use of L acetyl carnitine + L carnitine and increased sperm motility when compared with vitamin E + vitamin C (Li 2005) (MD 23.10, 95% CI 20.14 to 26.06, 138 men, P < 0.00001).

2.4.8 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm motility when compared with L-acetyl carnitine (Balercia 2005) (MD 3.40, 95% CI -3.73 to 10.53, 30 men, P = 0.35).

2.4.9 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 4.80, 95% CI -1.76 to 11.36, 30 men, P = 0.15).

2.4.10 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 1.40, 95% CI -6.42 to 9.22, 30 men, P = 0.73).

2.4.11 Selenium versus combined antioxidants. There was no evidence of the use of selenium and increased sperm motility when compared with combined antioxidants (Scott 1998) (MD 3.20, 95% CI -10.13 to 16.53, 46 men, P = 0.64).

2.4.12 Vitamin C 200 mg versus vitamin C 1000 mg. There appeared to be an association between the use of ascorbic acid 200 mg/day and decreased sperm motility when compared with ascorbic acid 1000 mg/day (Dawson 1990) (MD -43.00, 95% CI -67.10 to -18.90, 20 men, P = 0.0005).

2.4.13 Vitamin E plus "compound amino acids" versus vitamin E. There appeared to be an association between the use of vitamin E plus "compound amino acids" and increased sperm motility when compared with vitamin E only (Zhou 2016) (MD 11.90, 95% CI 8.71 to 15.09, 120 men, P < 0.00001). The authors of the study did not define the "compound amino acids" in more detail.

2.4.14 Zinc versus folic acid. Two studies compared zinc with folic acid and did not show evidence of an increased sperm motility (Azizollahi 2013; Raigani 2014) (MD -3.01, 95% CI -11.38 to 5.35, 124 men, P = 0.48, I^2 = 0%).

2.4.15 Zinc versus zinc plus folic acid. Two studies compared zinc with zinc plus folic acid and did not show evidence of an increased sperm motility (Azizollahi 2013; Raigani 2014) (MD -2.91, 95% CI -10.92 to 5.10, 125 men, P = 0.48, I^2 = 0%).

2.4.16 Zinc plus folic acid versus folic acid. Two studies compared zinc plus folic acid with folic acid only and did not show evidence of an increased sperm motility (Azizollahi 2013; Raigani 2014) (MD 0.24, 95% CI-6.17 to 6.66, 121 men, P = 0.94, I^2 = 0%).

2.4.17 Zinc versus zinc plus vitamin E. There was no evidence of the use of zinc and increased sperm motility when compared with zinc plus vitamin E (Omu 2008) (MD -1.00, 95% CI -15.00 to 13.00, 18 men, P = 0.89).

2.4.18 Zinc versus zinc plus vitamin E plus vitamin C. There was no evidence of the use of zinc and increased sperm motility when compared with zinc plus vitamin E plus vitamin C (Omu 2008) (MD -1.00, 95% CI -19.66 to 17.66, 12 men, P = 0.92).

2.4.19 Zinc plus vitamin E versus zinc plus vitamin E plus vitamin C. There was no evidence of the use of zinc plus vitamin E and increased sperm motility when compared with zinc plus vitamin E plus vitamin C (Omu 2008) (MD -0.00, 95% CI -18.97 to 18.97, 18 men, P = 1.00).

2.5 Total sperm motility at six months or less; type of antioxidant

See Analysis 2.5.

2.5.1 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm motility when compared with L-acetyl carnitine (Balercia 2005) (MD 4.10, 95% CI -2.70 to 10.90, 30 men, P = 0.24).

2.5.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 3.40, 95% CI -2.87 to 9.67, 30 men, P = 0.29).

2.5.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD -0.70, 95% CI -7.73 to 6.33, 30 men, P = 0.85).

2.5.4 N-acetylcysteine versus selenium plus NAC. There appeared to be an association between the use of NAC and decreased sperm motility when compared with selenium plus NAC (Safarinejad 2009) (MD -4.40, 95% CI -5.14 to -3.66, 234 men, P < 0.00001).

2.5.5 Selenium versus N-acetylcysteine (NAC). There appeared to be an association between the use of selenium and increased sperm motility when compared with NAC (Safarinejad 2009) (MD 1.30, 95% CI 0.56 to 2.04, 234 men, P = 0.0006).

2.5.6 Selenium versus selenium plus N-acetylcysteine (NAC). There appeared to be an association between the use of selenium and decreased sperm motility when compared with selenium plus NAC (Safarinejad 2009) (MD -3.10, 95% CI -3.85 to -2.35, 232 men, P < 0.00001).

2.5.7 Zinc versus folic acid. Two studies compared zinc with folic acid (Azizollahi 2013; Wong 2002) and did not show evidence of the use of zinc and increased sperm motility when compared with folic acid (MD -1.03, 95% CI -5.18 to 3.13, 125 men, P = 0.63, I^2 = 0%).

2.5.8 Zinc versus zinc plus folic acid. Two studies compared zinc with zinc plus folic acid (Azizollahi 2013; Wong 2002) and did not show evidence of the use of zinc and increased sperm motility when compared with zinc plus folic acid (MD -1.69, 95% CI -6.95 to 3.58, 127 men, P = 0.53, I^2 = 0%).

2.5.9 Zinc plus folic acid versus folic acid. Two studies compared zinc plus folic acid with folic acid (Azizollahi 2013; Wong 2002) and did not show evidence of the use of zinc plus folic acid and increased sperm motility when compared with folic acid only (MD 1.03, 95% CI -4.23 to 6.29, 126 men, P = 0.70, I^2 = 0%).

2.6 Total sperm motility at nine months or more; type of antioxidant

See Analysis 2.6.

2.6.1 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm motility when compared with L-acetyl carnitine (Balercia 2005) (MD 3.70, 95% CI -1.69 to 9.09, 30 men, P = 0.18).

2.6.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 5.30, 95% CI -0.73 to 11.33,30 men, P = 0.08).

2.6.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 1.60, 95% CI -3.29 to 6.49, 30 men, P = 0.52).

2.7 Progressive sperm motility at three months or less; type of antioxidant

See Analysis 2.7.

2.7.1 Coenzyme Q10 200 mg versus coenzyme Q10 400 mg. There was no evidence of the use of coenzyme 200 mg/day and increased progressive sperm motility when compared with coenzyme Q10 400 mg/day (Alahmar 2019) (MD -3.52, 95% CI -9.71 to 2.67, 65 men, P = 0.26).

2.7.2 Docosahexaenoic acid (DHA) versus DHA plus vitamin E. There appeared to be an association between the use of DHA and decreased progressive sperm motility when compared with DHA combined with vitamin E (Eslamian 2020) (MD -2.22, 95% CI -3.50 to 0.94, 90 men, P = 0.0007).

2.7.3 DHA versus vitamin E. There was no evidence of the use of DHA and increased progressive sperm motility when compared with vitamin E (Eslamian 2020) (MD -0.39, 95% CI -1.67 to 0.89, 90 men P = 0.55).

2.7.4 DHA plus vitamin E versus vitamin E. There appeared to be an association between the use of DHA plus vitamin E and increased progressive sperm motility when compared with vitamin E alone (Eslamian 2020) (MD 1.83, 95% CI 0.68 to 2.98, 90 men, P = 0.002).

2.7.5 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased progressive sperm motility when compared with L-acetyl carnitine (Balercia 2005) (MD 4.00, 95% CI -1.88 to 9.88, 30 men, P = 0.18).

2.7.6 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased progressive sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 5.00, 95% CI -0.68 to 10.68, 29 men, P = 0.08)

2.7.7 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased progressive sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 1.00, 95% CI -5.41 to 7.41, 29 men, P = 0.76).

2.7.8 L-carnitine versus vitamin B1. There was no evidence of the use of L-carnitine and increased progressive sperm motility when compared with vitamin B1 (Cheng 2018) (MD 1.70, 95% CI -1.54 to 4.94, 136 men, P = 0.30).

2.7.9 L-carnitine versus coenzyme Q10. There was no evidence of the use of L-carnitine and increased progressive sperm motility when compared with coenzyme Q10 (Cheng 2018) (MD 1.30, 95% CI -1.70 to 4.30, 125 men, P = 0.40).

2.7.10 L-carnitine versus L-carnitine plus coenzyme Q10. There appeared to be an association between the use of L-carnitine and decreased progressive sperm motility when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (MD -8.20, 95% CI -12.31 to -4.09, 125 men, P < 0.0001).

2.7.11 Coenzyme Q10 versus L-carnitine plus coenzyme Q10. There appeared to be an association between the use of coenzyme Q10 and decreased progressive sperm motility when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (MD -9.50, 95% CI -13.54 to -5.46, 126 men, P < 0.00001).

2.7.12 Coenzyme Q10 versus vitamin B1. There was no evidence of the use of coenzyme Q10 and increased progressive sperm motility when compared with vitamin B1 (Cheng 2018) (MD 0.40, 95% CI -2.75 to 3.55, 137 men, P = 0.80).

2.7.13 Vitamin B1 versus L-carnitine plus coenzyme Q10. There appeared to be an association between the use of vitamin B1 and decreased progressive sperm motility when compared with L-carnitine plus coenzyme Q10 (Cheng 2018) (MD-9.90, 95% CI -14.12 to -5.68, 137 men, P < 0.00001).

2.7.14 L-acetyl carnitine versus L-carnitine plus vitamin E plus vitamin C. There appeared to be an association between the use of L-acetyl carnitine and increased progressive sperm motility when compared with L-carnitine plus vitamin E plus vitamin C (Li 2005) (MD 13.30, 95% CI 11.21 to 15.39, 138 men, P < 0.00001).

2.7.15 L-carnitine versus vitamin E plus vitamin C. There appeared to be an association between the use of L-carnitine and increased progressive sperm motility when compared with vitamin E plus vitamin C (Li 2005a) (MD 30.50, 95% CI 27.70 to 33.30, 63 men, P < 0.00001).

2.7.16 L-carnitine versus vitamin E. There appeared to be an association between the use of L-carnitine and increased progressive sperm motility when compared with vitamin E (Sun 2018) (MD 1.90, 95% CI 1.31 to 2.49, 212 men, P < 0.00001).

2.7.17 L-carnitine plus vitamin E versus vitamin E. There appeared to be an association between the use of L-carnitine plus vitamin E and increased progressive sperm motility when compared with vitamin E (Wang 2010) (MD 14.10, 95% CI 10.11 to 18.09, 113 men, P < 0.00001).

2.7.18 Vitamin D plus calcium versus vitamin E plus vitamin C. There appeared to be an association between the use of vitamin D plus calcium and increased progressive sperm motility when compared with vitamin E plus vitamin C (Deng 2014) (MD 6.90, 95% CI 5.38 to 8.42, 86 men, P < 0.000001).

2.7.19 Vitamin E plus "compound amino acids" versus vitamin E. There appeared to be an association between the use of vitamin E plus "compound amino acids" and increased progressive sperm motility when compared with vitamin E only (Zhou 2016) (MD 6.10, 95% CI 3.87 to 8.33, 120 men, P < 0.00001). The authors of the study did not define the "compound amino acids" in more detail.

2.8 Progressive sperm motility at six months; type of antioxidant

See Analysis 2.8.

2.8.1 L-carnitine versus L-acetyl carnitine. There appeared to be an association between the use of L-carnitine and increased progressive sperm motility when compared with L-acetyl carnitine (Balercia 2005) (MD 6.30, 95% CI 0.42 to 12.18, 30 men, P = 0.04).

2.8.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of a difference in progressive sperm motility when L-carnitine was compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 5.70, 95% CI 0.10 to 11.30, 29 men, P = 0.05).

2.8.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of a difference in progressive sperm motility when L-acetyl carnitine was compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD -0.60, 95% CI -6.93 to 5.73, 29 men, P = 0.85).

2.9 Progressive motility at six months (data not suitable for meta-analysis)

Analysis 2.9

One study (Saeed Alkumait 2020) compared coenzyme Q10 versus glutathione and provided data as percentage improvement and therefore could not be used in the forest plot. The authors did not provide a P value of the head-to-head comparison.

2.10 Progressive sperm motility at nine months or more; type of antioxidant

See Analysis 2.10.

2.10.1 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased progressive sperm motility when compared with L-acetyl carnitine (Balercia 2005) (MD 3.80, 95% CI -1.50 to 9.10, 30 men, P = 0.16).

2.10.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased progressive sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 5.50, 95% CI -0.11 to 11.11,29 men, P = 0.05).

2.10.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased progressive sperm motility when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 1.70, 95% CI -4.17 to 7.57, 29 men, P = 0.57).

2.11 Sperm concentration at three months or less; type of antioxidant

See Analysis 2.11.

2.11.1 Coenzyme Q10 200 mg versus coenzyme Q10 400 mg. There was no evidence of the use of the use of coenzyme Q10 200 mg/day and increased sperm concentration when compared with coenzyme Q10 400 mg/day (Alahmar 2019) (MD 0.20, 95% CI -3.26 to 3.66, 65 men, P = 0.91).

2.11.2 Docosahexaenoic acid (DHA) 400 mg versus DHA 800 mg. There was no evidence of the use of DHA 400 mg/day and increased sperm concentration when compared with DHA 800 mg/day (Conquer 2000) (MD -6.80, 95% CI -41.87 to 28.27, 19 men, P = 0.70).

2.11.3 DHA versus DHA + vitamin E. There appeared to be an association between the use of DHA and decreased sperm concentration when compared with DHA combined with vitamin E (Eslamian 2020) (MD -1.45, 95% CI -2.47 to -0.43, 90 men, P = 0.005).

2.11.4 DHA versus vitamin E. There was no evidence of the use of DHA and increased sperm concentration when compared with vitamin E (Eslamian 2020) (MD -0.24, 95% CI -1.26 to 0.78, 90 men, P = 0.64).

2.11.5 DHA plus vitamin E versus vitamin E. There appeared to be an association between the use of DHA plus vitamin E and increased sperm concentration when compared with vitamin E alone (Eslamian 2020) (MD 1.21, 95% CI 0.28 to 2.14, 90 men, P = 0.01).

2.11.6 Ethyl cysteine versus vitamin E. There was no evidence of the use of ethyl cysteine and increased sperm concentration when compared with vitamin E (Akiyama 1999) (MD 2.20, 95% CI -16.65 to 21.05, 10 men, P = 0.82).

2.11.7 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with L-acetyl carnitine (Balercia 2005) (MD 1.70, 95% CI -10.97 to 14.37, 30 men, P = 0.79).

2.11.8 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 4.10, 95% CI -9.17 to 17.37, 30 men, P = 0.54).

2.11.9 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased sperm concentration when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 2.40, 95% CI -11.14 to 15.94, 30 men, P = 0.73).

2.11.10 L-carnitine versus vitamin E plus vitamin C. There appeared to be an association between the use of L-carnitine and increased sperm concentration when compared with vitamin E plus vitamin C (Li 2005a) (MD 15.50, 95% CI 12.49 to 18.51, 63 men, P < 0.00001).

2.11.11 L-carnitine versus vitamin E. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with vitamin E (Sun 2018) (MD 0.70, 95% CI -0.34 to 1.74, 212 men, P = 0.19).

2.11.12 L-carnitine plus vitamin E versus vitamin E. There was no evidence of the use of L-carnitine plus vitamin E and increased sperm concentration when compared with vitamin E (Wang 2010) (MD 1.90, 95% CI -10.52 to 14.32, 113 men, P = 0.76).

2.11.13 Selenium versus combined antioxidants. There was no evidence of the use of selenium and increased sperm concentration when compared with combined antioxidants (Scott 1998) (MD 14.70, 95% CI -6.51 to 35.91, 46 men, P = 0.17).

2.11.14 Zinc versus folic acid. Two studies compared zinc with folic acid (Azizollahi 2013; Raigani 2014) and did not show evidence of

the use of zinc and increased sperm concentration when compared with folic acid (MD -1.30, 95% CI -8.65 to 6.06, 124 men, P = 0.73, I^2 = 0%).

2.11.15 Zinc plus folic acid versus folic acid. Two studies compared zinc plus folic acid with folic acid (Azizollahi 2013; Raigani 2014) and did not show evidence of the use of zinc plus folic acid and increased sperm concentration when compared with folic acid only (MD 2.93, 95% CI -3.67 to 9.54, 125 men, P = 0.38, I^2 = 0%).

2.11.16 Zinc versus zinc plus folic acid. Two studies compared zinc with zinc plus folic acid (Azizollahi 2013; Raigani 2014) and did not show evidence of the use of zinc and increased sperm concentration when compared with zinc plus folic acid (MD -4.11, 95% CI -9.79 to 1.57, 121 men, P = 0.16, I^2 = 0%).

2.12 Sperm concentration at six months or less; type of antioxidant

See Analysis 2.12.

2.12.1 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with L-acetyl carnitine (Balercia 2005) (MD 5.90, 95% CI -8.92 to 20.72, 30 men, P = 0.44).

2.12.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 8.10, 95% CI -5.54 to 21.74, 30 men, P = 0.24).

2.12.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased sperm concentration when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 2.20, 95% CI -10.89 to 15.29, 30 men, P = 0.74).

2.12.4 N-acetylcysteine (NAC) versus selenium plus NAC. There appeared to be an association between the use of NAC and decreased sperm concentration when compared with selenium plus NAC (Safarinejad 2009) (MD -5.30, 95% CI -6.86 to -3.74, 234 men, P < 0.00001).

2.12.5 Selenium versus N-acetylcysteine (NAC). There was no evidence of the use of selenium and increased sperm concentration when compared with NAC (Safarinejad 2009) (MD 0.80, 95% CI -0.71 to 2.31, 234 men, P = 0.30).

2.12.6 Selenium versus selenium plus N-acetylcysteine (NAC). There appeared to be an association between the use of selenium and decreased sperm concentration when compared with selenium plus NAC (Safarinejad 2009) (MD -4.50, 95% CI -6.20 to -2.80, 232 men, P < 0.00001).

2.12.7 Zinc versus folic acid. Two studies compared zinc with folic acid (Azizollahi 2013; Wong 2002) and did show an association between the use of zinc and decreased sperm concentration when compared with folic acid (MD -10.10, 95% CI -19.12 to -1.08, 125 men, P = 0.03, I^2 = 0%).

2.12.8 Zinc plus folic acid versus folic acid. Two studies compared zinc plus folic acid with folic acid (Azizollahi 2013; Wong 2002) and did not show evidence of the use of zinc plus folic acid and increased sperm concentration when compared with folic acid only (MD -13.58, 95% CI -25.99 to -1.17, 127 men, P = 0.03, I^2 = 23%).

2.12.9 Zinc versus zinc plus folic acid. Two studies compared zinc with zinc plus folic acid (Azizollahi 2013; Wong 2002) and did not show evidence of the use of zinc and increased sperm concentration when compared with zinc plus folic acid (MD 1.78, 95% CI -9.93 to 13.49, 126 men, P = 0.77, I^2 = 0%).

2.13 Sperm concentration at six months (data not suitable for meta-analysis)

One study (Saeed Alkumait 2020) compared coenzyme Q10 with glutathione and provided data as percentage improvement, and therefore could not be used in the forest plot. The authors did not provide a P value for this head-to-head comparison.

2.14 Sperm concentration at nine months or more; type of antioxidant

See Analysis 2.14.

Pooling was not possible in this analysis as only one study reported on two subgroups.

2.14.1 L-carnitine versus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with L-acetyl carnitine (Balercia 2005) (MD 8.20, 95% CI -0.07 to 16.47, 30 men, P = 0.05).

2.14.2 L-carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-carnitine and increased sperm concentration when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD 6.10, 95% CI -3.74 to 15.94, 30 men, P = 0.22).

2.14.3 L-acetyl carnitine versus L-carnitine plus L-acetyl carnitine. There was no evidence of the use of L-acetyl carnitine and increased sperm concentration when compared with L-carnitine plus L-acetyl carnitine (Balercia 2005) (MD -2.10, 95% CI -10.24 to 6.04, 30 men, P = 0.61).

Funnel plot

We assessed publication bias by using a funnel plot. The outcomes live birth and clinical pregnancy included 12 and 20 studies, respectively.

For the outcome of live birth, there was suspected publication bias (Figure 5). The funnel plot shows a remarkable lack of studies in the left lower section. This could be due to the fact that relatively small studies that do not show an increase of live birth with antioxidants, were not published. For the outcome of clinical pregnancy, there was no clear evidence of publication bias (Figure 7). We did not have enough studies to look at each of the subgroups for publication bias.

The studies reporting on the primary outcome of live birth did not all have study characteristics in common. They differed in terms of sample size, type and age of studied population, treatment period, and intervention and control. The results of the semen parameters in these studies were similar to those from the other included studies; the great majority did not show a significant improvement in semen parameters.

DISCUSSION

Summary of main results

Effectiveness of antioxidants versus placebo or no treatment

Live birth

Evidence of low quality suggests that for subfertile men, the use of antioxidants may be effective in increasing a couple's chances of having a live birth when compared to placebo or no treatment. It was found within the studies that contributed to the analysis of live birth rate, that for subfertile men with a baseline live birth rate of 16%, with the use of an antioxidant this rate could increase to between 17% and 27%. However, there were only 12 studies with a total of 1283 couples reporting on live birth and the certainty of this evidence was considered to be very low (Summary of findings 1). The methods were not well explained in three out of 12 of these studies (Korshunov 2018; Omu 1998; Suleiman 1996), two studies had a significant number of participants who dropped out of the study (Joseph 2020; Suleiman 1996), and Joseph 2020, Korshunov 2018, and Omu 1998 used 'no treatment' as control which introduced a degree of performance bias. When these four high-risk studies were removed from the analysis, there was no evidence of association between the use of antioxidants and increased live birth.

The apparent benefit from antioxidants did not persist when analyses were restricted to placebo-controlled studies. There was no evidence of increased live birth with the use of antioxidants in studies enrolling men undergoing assisted reproductive techniques (ART) (in vitro fertilisation (IVF)/intracytoplasmic sperm injection(ICSI)).

Clinical pregnancy

The findings of this review also suggest that for subfertile men the use of antioxidants may be effective in increasing a couple's chances of clinical pregnancy rate when compared to placebo or no treatment. It was found that within the studies that contributed to the analysis of clinical pregnancy, the population of subfertile men had a baseline or expected clinical pregnancy rate of 15%,and with the use of antioxidants this would increase to between 20% and 30%. However, there were only 20 studies with a total of 1706 men reporting on clinical pregnancy and the certainty of this evidence was considered to be low (Summary of findings 1). The methods were not well explained in six of the 20 studies, with three of these studies having a significant number of participants who dropped out of the study (Barekat 2016; Joseph 2020; Suleiman 1996). Furthermore, five of the 25 analyses (one trial had three arms) crossed the line of no effect with wide confidence intervals.

The apparent benefit from antioxidants persisted when analyses were restricted to studies at lower risk of bias, placebo-controlled studies, studies of men not undergoing IUI, studies of men undergoing ART (IVF/ICSI), and studies of men post-varicocelectomy.

Adverse events

There is no evidence that antioxidants used by the subfertile male lead to an increased miscarriage risk when compared to placebo or no treatment. It was found that within this population of subfertile men with an expected miscarriage rate of 5%, the use of an antioxidant would increase the chances of having a miscarriage to between 4% and 13%. However, there were only six studies with a total of 664 men reporting on miscarriage and the certainty of this evidence was very low (Summary of findings 1). The event rate in this analysis was very low with only 39 miscarriages reported in six studies, furthermore there was a high risk of bias within these studies.

The use of antioxidants by subfertile men may increase the occurrence of mild gastrointestinal complaints when compared to placebo or no treatment. It was found that within this population of subfertile men with an expected gastrointestinal event rate of 2%, the use of an antioxidant would increase the chances of having gastrointestinal complaints to between 2% and 7%. However, there were only 16 studies with a total of 1355 men reporting on gastrointestinal complaints and the certainty of this evidence was low (Summary of findings 1). The event rate in this analysis was low with only 46 events reported; furthermore there was a high risk of bias within these studies.

There was no evidence that the risk of other adverse events, such as stillbirth and ectopic pregnancy, differed between antioxidant or control group.

Sperm DNA fragmentation

Thirteen studies (1813 men) reported on DNA fragmentation with suitable data for meta-analysis. Pooled analysis of these 13 studies was not possible due to high heterogeneity. Pooling of the results from the subgroups was not possible either because of heterogenic data. One study reported substantially higher DNA fragmentation rates (> 80%) compared to other included studies, which could be explained by enrolment of participants post-varicocelectomy (Barekat 2016).

Sperm parameters

The pooled results for total sperm motility, progressive sperm motility and concentration at three, six and nine months were unreliable as heterogeneity was extremely high in each analysis. Studies could be pooled in some antioxidant subgroups, with differing results per type of antioxidant and duration of treatment.

Effectiveness of antioxidants versus antioxidants (head-to-head)

In the head-to-head studies only four studies reported on live birth and/or clinical pregnancy; one study with different types of carnitines in multiple arms (versus placebo), one study comparing L-carnitine with coenzyme Q10, and a combination of these two, one study comparing vitamin D plus calcium with vitamin E plus vitamin C, and one study comparing combined antioxidants with L-carnitine (versus no treatment). Only vitamin D plus calcium showed an association. However, due to the small study size no direct conclusions can be drawn. The head-to-head studies did not report adverse events.

Overall completeness and applicability of evidence

Of the 90 studies included in this review, only 14 reported on the primary outcome of live birth, and only 22 reported on clinical pregnancy rate. Live birth and clinical pregnancy rate are the outcomes of most interest to subfertile couples and until these are robustly reported by all subfertility studies we will not be able to draw clear conclusions for the use of antioxidants

for subfertile men. We believe that the lower baseline rate for clinical pregnancy than the baseline rate for live birth could be due to the difference in included populations. In the clinical pregnancy analysis (20 studies) there were four studies including men with varicocele; those studies did not report live birth and were therefore not included in the live birth rate analysis (12 studies). Adverse events such as miscarriage, ectopic pregnancy, stillbirth, gastrointestinal side effects, euphoria, headache, upper respiratory infection, and nasopharyngitis appear to be poorly reported, and the evidence is of very low certainty. The high heterogeneity may be an artefact caused by some studies reporting very small and potentially erroneous standard deviations (SDs). This undermines the credibility of the data.

Three of the trials included in the analysis of the semen parameter outcomes (Haghighian 2015; Safarinejad 2009; Safarinejad 2009a) had consistently reported SDs very much smaller than those reported by most of the other included trials. The review authors considered that these were potentially erroneous, but an attempt to check with the study authors was unsuccessful. One other trial (Peivandi 2010), also had very small SDs when compared to data in the other trials, but the authors confirmed, when contacted, that they are indeed SDs and not standard errors (SEs). We tried to manage these analyses in two different ways: firstly by imputing SDs from studies of a similar size and secondly by treating the data as SEs and converting back to SDs, however heterogeneity remained high in both situations so for the final analyses we reverted to the SDs as reported in the studies. The low SDs may have been due to the strict inclusion and exclusion criteria indicating that the trial was homogenous in nature, however we were unable to carry out a sensitivity analysis on these trials as pooling was not possible due to high heterogeneity. For the analysis of sperm concentration at three months, the heterogeneity was low despite the small SDs reported in Haghighian 2015. After sensitivity analysis the heterogeneity remained low, however this resulted in a confidence interval crossing the line of no effect.

Eighteen of the 90 included trials were very small in size (randomising less than 50 men), 39 of 90 included trials were small in size (randomising between 50 and 100 men) and only 33 of 90 included trials included more than 100 men. The estimates of the intervention effect tend to be more beneficial in smaller studies. Smaller studies also may not be as rigorous as the larger studies in their methodology (Higgins 2011).

We tried to assess which type of antioxidant might have a beneficial effect on the outcomes of interest in this review, however only three studies at the most could be pooled in any antioxidant subgrouping. Eighteen studies (Ardestani 2019; Bahmyari 2021; Busetto 2018; Gamidov 2017; Gamidov 2019; Gopinath 2013; Joseph 2020; Kizilay 2019; Kopets 2020; Korshunov 2018; Micic 2019; Morgante 2010; Popova 2019; Scott 1998; Steiner 2020; Stenqvist 2018; Tsounapi 2018; Tremellen 2007) used combined antioxidants versus placebo or no treatment and were used in the meta-analysis. Ten of these studies reported on clinical pregnancy rate, showing an association between the use of combined antioxidants and increased clinical pregnancy rate. Only five of these studies reported on live births, showing no evidence of an increased live birth with the use of combined antioxidants. When the analysis of clinical pregnancy rate was restricted to these five studies reporting live birth, there was no evidence of increased clinical pregnancy rate with the use of combined antioxidants.

The head-to-head comparison does not provide constructive information as we could not pool direct comparisons. Subgrouping of antioxidants could be performed in 11 comparisons, each comparison pooling two studies. These were all studies comparing zinc with folic acid or a combination of the two.

There were 29 studies that contained data that were unusable in the analysis, with either some or all of their data (Alahmar 2020; Biagiotti 2003; Boonyarangkul 2015; Cheng 2018; Eslamian 2013; Eslamian 2020; Exposito 2016; Galatioto 2008; Haje 2015; Huang 2020; Kessopoulou 1995; Kumamoto 1988; Lenzi 2003; Lombardo 2002; Lu 2018; Martinez 2015; Nozha 2001; Omu 1998; Pourmand 2014; Poveda 2013; Pryor 1978; Saeed Alkumait 2020; Schisterman 2020; Sivkov 2011; Sofikitis 2016; Steiner 2020; Tsounapi 2018; Vinogradov 2019; Zalata 1998). The reasons for this were baseline imbalance, no report of the number of patients in whom outcome was assessed, and presentation of percentages or mean differences (Analysis 1.8; Analysis 1.10; Analysis 1.16; Analysis 1.20; Analysis 1.22). Attempts were made to contact these authors regarding the data. There was no clear evidence of publication bias.

Quality of the evidence

The evidence was graded as low to very low certainty. The main limitation was that out of the 67 included studies in the meta-analysis only 20 studies reported clinical pregnancy, and of those 12 reported on live birth. Other limitations included poor reporting of study methods, imprecision, the number of small studies, reporting bias, and lack of data about adverse events. Publication bias was suspected for the outcome of live birth.

Figure 3 shows the review authors' judgements about the risk of bias of the studies included in this review. All included studies were described as randomised, however only just over 50% gave information on how the randomisation was achieved. Allocation concealment was described in only 36% of the studies. Blinding was better described with over 57% of the studies being double-blinded or occasionally single-blinded; 7% of studies stated that there was no blinding, and 20% of included studies used no treatment as a control. Dropout rates were high in some studies and dropout rates tended to be higher in the control groups, which created a potential for differential follow-up with better reporting of clinical pregnancies in the intervention groups. Reporting bias was unclear in 68% of studies.

Potential biases in the review process

There may have been some potential for bias in the review process, as there were some changes in previous updates of the review compared to the protocol. These included additions and deletions to exclusion criteria such as the removal of pentoxifylline, and adding the new outcome progressive sperm motility. Some bias in the review process may have arisen due to the inclusion of studies that have had a dropout of participants of > 20%, with subsequent imbalances in the number of participants between the treatment and control groups.

Agreements and disagreements with other studies or reviews

The results of our review are in agreement with those of other published systematic reviews. Two other reviews described the effects of L-carnitine and L-acetylcarnitine on subfertile men. The systematic review and meta-analysis by Zhou and colleagues (Zhou

2007) compared L-carnitine and L-acetylcarnitine therapy versus placebo treatment and found improvements in pregnancy rate and total sperm motility. Zhang 2020 also found improved total sperm motility, progressive sperm motility, and pregnancy rates with the use of L-carnitine and L-acetyl carnitine. Our review was unable to pool the results of the carnitine studies due to inconsistencies between the studies and excluded biochemical and undefined pregnancy from the meta-analysis. The descriptive review by Patel and Sigman (Patel 2008) discusses the improvement in pregnancy rates with oral intake of antioxidants, however Patel states that randomised controlled trials (RCTs) have not shown an effect on sperm motility and that there is a need for more RCTs in men with oxidative stress. Furthermore, Garg 2016 discusses in a review the effect of antioxidants in men with varicocele. They conclude that antioxidant therapy is a potential option as primary treatment or adjunct after surgical repair of varicocele. Wang 2019 discussed antioxidant therapy in men with varicocele as well, and found no evidence of increased pregnancy rate.

Agarwal and colleagues discussed in both an overview of the literature (Agarwal 2004) and systematic review (Majzoub 2018), the effectiveness of antioxidants. In the 2004 overview Agarwal notes that vitamin E and a combination of vitamin E with other antioxidants such as N-acetylcysteine, vitamin A and fatty acids appear to improve pregnancy rates in men with asthenozoospermia. This is in agreement with our review. However, their conclusion that carnitines also appear to have an effect on pregnancy rates could not be confirmed. In the systematic review Majzoub 2018 included 29 studies, of which there were 19 RCTs and 10 prospective studies. In 26 studies they found a significant positive effect on basic semen parameters, advanced sperm function tests, ART outcomes or live birth rate. Specifically, a positive effect was seen on live birth rate and fertilisation rate when using vitamin E, vitamin C, carnitines, coenzyme Q10 and zinc. A difference between differing antioxidants was not seen in our review.

Another review (Ross 2010) showed improvement in pregnancy rate and sperm quality after antioxidant therapy. This is in agreement with our review, although we are uncertain of the sperm parameter outcomes due to the extreme heterogeneity. A systematic review (Lafuente 2013) looking at the effect of coenzyme Q10 and male subfertility found an association between this antioxidant and improved pregnancy rate, sperm concentration and motility. We did agree on the effect of coenzyme Q10 on sperm motility and concentration at six months, however we could not draw clear conclusions due to the heterogeneity in these analyses. A more recent systematic review with meta-analysis studied the effectiveness of folate and folate plus zinc on sperm parameters in subfertile men (Irani 2017). They concluded that folate alone was only effective on sperm concentration, and folate plus zinc only on sperm concentration and morphology. Both interventions did not have any effect on sperm motility. This effect of zinc plus folate or folate alone could be confirmed with our review. The review by Zhou and colleagues (Zhou 2021) focused on N-acetyl-cysteine (NAC) and men with idiopathic infertility and found an increased sperm concentration and total motility after use of NAC. We found a similar effect in the six months comparisons, however due to inclusion of other studies, we found no evidence of increased sperm parameters in the other comparisons including NAC.

A review on nutritional and medical therapies (Omar 2019) and male infertility reports no improvement of pregnancy rates following treatment with L-carnitine or L-carnitine combined with L-acetyl-carnitine, which is in line with our review.

It should be noted that some of these reviews are relatively outdated, given the newly published studies in the past decade.
The above-mentioned systematic reviews mainly reported on overall pregnancy rates, whereas this updated Cochrane Review reported specifically on clinical pregnancy rates (as confirmed by the identification of a gestational sac on ultrasound) so fewer studies were available for analysis.

A Cochrane Review of antioxidants for female subfertility has been published (Showell 2020) showing that there is limited evidence for a beneficial effect of antioxidants for subfertile women. Furthermore, a recent systematic review and meta-analysis looking at the effect of micronutrient supplementation, in both male and females, on IVF outcomes showed a positive influence on clinical outcomes in terms of pregnancy rate and/or live birth rate (Kofi Arhin 2017). However, only five RCTs could be included, with significant heterogeneity among the interventions and study designs.

AUTHORS' CONCLUSIONS

Implications for practice

In this review, there is very low-certainty evidence suggesting that antioxidant supplementation in subfertile males may improve live birth rates for couples attending fertility clinics. Low-certainty evidence suggests that clinical pregnancy rates may increase as well. Overall, there is no evidence of increased risk of miscarriage. Based on low-certainty evidence, antioxidants may be associated with more gastrointestinal discomfort. Subfertile couples should be advised that the current evidence is inconclusive based on serious risk of bias.

Implications for research

As opposed to previous updates of this review, we have now included several recently published clinical trials with live birth as an outcome. This shows that investigators acknowledge the need for more trials with clinical outcomes in this field. However, the proportion of well-powered trials with low risk of bias remains small. Hence, large well-designed placebo-controlled randomised trials, focusing on male factor infertility and with live birth as primary outcome, are urgently needed. Researchers should make an effort to register and report important confounding factors including the use of other supplements, lifestyle factors (e.g. diet, physical activity, smoking habits, and alcohol consumption), and living environment.

There is insufficient evidence supporting one type or dose of antioxidants versus another, or a single antioxidant versus a combination of antioxidants.

The side-effect profile of antioxidant supplements appears to be low and mild. However, conclusions cannot be drawn based on the limited research reporting this outcome. Future trials should include predefined adverse events of antioxidants, with a focus on clinical outcomes such as miscarriage, stillbirth and ectopic pregnancy.

ACKNOWLEDGEMENTS

Cochrane Gynaecology and Fertility group. I would like to make special mention of the editors who were very thorough and helpful in editing this review.

Many thanks to the translators of the non-English studies: Ichiro Omori, Shaofu Li, Ivan Sola, Pawel Kanturski, Dr Peviandi, Shaofu Li, Farhad Shokraneh, Taixiang Wu, Juliane Reid, Roberto D'Amico, Vasily Vlassov, Liu Qin, Jianping Liu, Guoyan Yang, Gustavo Porfi, Valter Silva, Maíra Parra, Dr Tomoko Kumaga, Tan Wantao, Andrew Dubovyi, Yue Wang, Yongchuan Gu, Catherine Jia-yun Tsai, Alyona Oryshchuk. A special thank you to Juliane Reid, Angela Beros and Helen Nagels for putting us in touch with many of our translators.

Thanks also to Stephan Bontekoe who kindly helped with some of the text in the original review.

We acknowledge comments sent by Tina Kold Jensen, Niels Erik Skakkebaek, Niels Jørgensen, Martin Blomberg Jensen, Anders Juul, Peter Gøtzsche, Department of Growth and Reproduction, and The Nordic Cochrane Centre, Rigshospitalet, Denmark. Our formal response was published in December 2011 and the points made have been addressed.

The authors of the 2018 review thank Professor Roger Hart for his contributions to all previous versions of this review.

The authors of the 2022 review thank Dr Yazdani and Dr Stankiewicz for their contributions to previous versions of this review.

The authors of the 2022 review thank Ms Liqing Yao, Ms Jeanette MacKenzie and Professor Andy Vail for providing peer review comments.

Further information for the studies was received from:

Dr N Adel (Adel 2015)

Dr Ovchinnikov (Gamidov 2017)

Dr Zavari (Gopinath 2013)

Dr Kabir (Cyrus 2015)

Professor Matorras (Exposito 2016)

Dr Balercia (Balercia 2005; Balercia 2009)

Dr Busetto (Busetto 2018)

Dr Nasr-Esfahani (Barekat 2016)

Dr Irge (NCT01520584)

Dr Dimitriadis (Sofikitis 2016)

Dr Agarwal and ms. Micic (Micic 2019)

Dr Norouzi (Sharifzadeh 2016)

Dr Hekmatdoost (NCT01846325)

Dr Mathieu-d'Argent (NCT01407432)

Dr Kamath (CTRI/2013/02/003431)

Dr Pinter (NCT02310087)

Dr Nematollahi-mahani (Azizollahi 2013),

Associate Professor Kelton Tremellen (Tremellen 2007).

Dr Kamath (CTRI/2013/02/003431)

Dr Peivandi (Peivandi 2010)

Dr El Gindy (Elgindy 2008)

Dr M Sigman (Sigman 2006)

Professor Niewchlag (Rolf 1999)

Dr Cavallini (Cavallini 2004)

Dr Wang (Wang 1983)

Dr Martinez-Soto (Martinez-Soto 2010)

Dr Morgante (Morgante 2010)

Dr Nadjarzadeh (Nadjarzadeh 2011)

Dr Safarinejad (Safarinejad 2009; Safarinejad 2009a)

Dr Korshunov (Korshunov 2018)

Dr Haidari (Haghighian 2015)

Dr Chakravarty (Goswami 2015)

Dr Huang (Steiner 2020)

Dr Stenqvist (Stenqvist 2018)

Dr Kizilay (Kizilay 2019)

Dr Ovchinnikov (Gamidov 2017; Gamidov 2019; Popova 2019)

Dr Zhivulko (Vinogradov 2019)

Dr Micic (Micic 2019)

Dr Nasr-Esfahani (Abbasi 2020)

Professor Kamath (Joseph 2020)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abbasi 2020

Study characteristics	
Methods	Triple-blinded controlled clinical study
	Duration of study: from 2018 to 2019

Abbasi 2020 *(Continued)*

Participants	Country: Iran Population: infertile men with varicocele, treated after microsurgical repair, N = 60 Mean age: 31.14 ± 5.54 years (alpha lipoic acid group) and 31.89 ± 5.06 years (placebo group) Inclusion criteria: men with uni/ bilateral grade II–III varicocele (confirmed by Doppler duplex ultrasonography if ambiguous on palpation). Exclusion criteria: azoospermia, occupational exposure to heat, radiation, and pesticides, a history of mumps, cryptorchidism, solitary testis, urogenital malignancies/infections, endocrinopathies, Sertoli cell only syndrome, leukocytospermia, scrotal trauma, high fever prior to sampling, recurrent varicocele, severe alcoholism and heavy smoking
Interventions	Alpha lipoic acid 600 mg, oral daily (n = 30) versus Placebo (n = 30) Both treatments were given after microsurgical repair of varicocele. Duration of treatment: 80 days
Outcomes	Semen analysis, protamine deficiency (CMA3 staining), sperm DNA fragmentation with SCSA and TUNEL test, sperm lipid peroxidation with BODIPY staining
Notes	E-mailed author nasr.royan@gmail.com on 15-03-2021 requesting information on population. Reply on 23-03-2021 and 10-04-2021: Quote: “In the first study, the infertile couples, with primary infertility, referred to our center for infertility treatment. Following the consultation with clinical andrologist they were recognized to have varicocele (grade II-III) and subsequently they were included in our study. Therefore, inclusion was based on infertile couples with varicocele.” “Our criteria was sole varicocele. But our center is an infertility center and therefore, all the couples referring to center are infertile, therefore, we could consider them to be also the male partner of the infertile couple.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The permutation block randomization method was used, applying nine blocks containing eight units (individuals) for the sample size, and a random sequence was built using all the possible permutations."
Allocation concealment (selection bias)	Low risk	Quote: "Drug and placebo packaging was identical, and medications were given to the participants according to the randomization sequence, to which the clinician, healthcare providers, individuals in charge of data collection and analysis, and statistician were all blinded. The codes were revealed only after the final analysis of the data."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Drug and placebo packaging was identical, and medications were given to the participants according to the randomization sequence, to which the clinician, healthcare providers, individuals in charge of data collection and analysis, and statistician were all blinded. The codes were revealed only after the final analysis of the data."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All samples were provided by masturbation after 3–4 days of abstinence, subsequently liquefied at room temperature, fixed and analysed based

Abbasi 2020 *(Continued)*

All outcomes		on the World Health Organization (WHO) criteria by an instructed operator who was blinded to the type of the treatment given to each donor."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 60 individuals met the inclusion criteria and were enrolled in the study. Of these, 41 – 22 men who had received placebo and 19 who had received ALA – attended the post-medication sampling." High percentage of withdrawals, reason unclear.
Selective reporting (reporting bias)	Low risk	All outcomes reported. Protocol available (IRCT20110804007223N10)

Akiyama 1999

Study characteristics	
Methods	Randomised single-centre cross-over trial Duration of study: 8 months
Participants	Country: Japan Population: infertile men, N = 10 Mean age: 36 years (treatment group age range 24 to 49 years, control age range 30 to 37 years) Inclusion criteria: male infertility (ROS > 5 x 10,000 counts/10,000,000 viable spermatozoa) Exclusion criteria: azoospermia, pyospermia
Interventions	Ethylcysteine 600 mg (n = 5) versus Vitamin E 600 mg (n = 5) Duration of treatment: 3 months, with a one month wash out, then cross-over for another 3 months. Only data from the first phase were used in data analysis
Outcomes	Sperm parameters, blood serum and seminal plasma levels of ethyl cysteine and vitamin E
Notes	In Japanese. Data extraction translated by Ichiro, a colleague of Samantha Roberts, 29.01.2009 Author contacted 'no further information is available'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were divided randomly"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	Not mentioned

Akiyama 1999 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Sperm parameters reported. No protocol available.

Alahmar 2019

Study characteristics	
Methods	Prospective randomised clinical trial Duration of study: from June 2018 to November 2019, treatment 3 months
Participants	Country: Iraq Population: patients with idiopathic OAT, N = 65 Mean age: 27.24±7.81 years Inclusion criteria: a history of infertility lasting for at least 12 months despite regular unprotected intercourse. OAT was diagnosed by semen analysis results showing abnormal sperm concentration (<15 million/mL), progressive motility (<32%), and total motility (<40%) as defined by the fifth edition of the WHO criteria for semen analysis and abnormal morphology (<30% normal morphology) as defined by the fourth edition of the WHO criteria. Exclusion criteria: azoospermia, varicocele, genital tract infection, cryptorchidism, testicular trauma or scrotal surgery, endocrine disorders, systemic illness including hepatic and renal diseases, smoking, recent intake of antioxidants, and the presence of female factor infertility.
Interventions	Coenzyme Q10 200 mg oral single dose daily (n = 35) versus Coenzyme Q10 400 mg oral single dose daily (n = 30) Duration of treatment: 3 months
Outcomes	Semen analysis, seminal total antioxidant capacity, seminal superoxide dismutase, seminal catalase activity
Notes	Coenzyme Q10 200 mg group is the same as Alahmar 2020

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned.

Alahmar 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label (clinicaltrials.gov)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers in outcome tables match randomised numbers. No lost to follow up mentioned.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. Study protocol published after completion of the study (NCT03850561).

Alahmar 2020

Study characteristics	
Methods	Prospective randomised study Duration of study: inclusions from June 2018 to January 2019
Participants	Country: Iraq Population: men with idiopathic infertility and oligoasthenoteratospermia, N = 70 Mean age: 25.4 ± 7.71 years Inclusion criteria: a history of infertility of at least 12 months despite regular unprotected intercourse. Oligoasthenoteratospermia was diagnosed according to the WHO guidelines (5th edition) by semen analysis showing abnormal sperm concentration (< 15 million/mL), progressive motility (< 32%), and total motility (< 40%). Abnormal morphology (< 30% normal morphology) was assessed by the WHO guidelines (4th edition). Exclusion criteria: azoospermia, varicocele, genital tract infection, cryptorchidism, testicular trauma or scrotal surgery, endocrine disorders like hypothalamic, pituitary, thyroid, diabetes mellitus, adrenal gland and exogenous medications, systemic illness, recent antioxidants intake, smoking, alcohol, relevant medications, and the presence of female factors.
Interventions	Coenzyme Q10 200 mg oral single dose daily (n = 35) versus Selenium 200 mcg oral single dose daily (n = 35) Duration of treatment: 3 months
Outcomes	Sperm parameters, seminal total antioxidant capacity, seminal superoxide dismutase activity, seminal catalase activity
Notes	Power calculation performed, not mentioned on which outcome parameter it is based Coenzyme Q10 (200 mg) group is the same as Alahmar 2019

Alahmar 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The selected patients who fulfilled the selection criteria were randomly assigned (using simple randomization)". Not clear what is meant with "simple randomization".
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label (from clinicaltrials.gov)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "In this prospective randomized study, seventy patients enrolled in the study (four patients did not complete the study)." Not clear to which group patients belonged.
Selective reporting (reporting bias)	Low risk	All outcomes reported. Protocol available (NCT03834831).

Amini 2020

Study characteristics	
Methods	Randomised controlled triple-blind trial Duration of study: unclear.
Participants	Country: Iran Population: infertile men under fertility treatment aged 20-45 years old, N = 72 Mean age: 34.86 ± 4.65 (placebo group) and 34.37 ± 4.83 (intervention group) Inclusion criteria: physical and mental health (ascertained based on the records of the case); BMI of 18.5–30; no vitamin D3 supplement consumption during the past 3 months; no use of drugs affecting the levels of vitamin D3 for example glucocorticoids and anticonvulsants; no use of medications that affect spermatogenesis during the past 3 months for example cimetidine, spironolactone; absence of azoospermia in the spermogram, suffering from idiopathic disruptive spermograms, no genital infection or history of taking medication for STDs (sexually transmitted disease) within the past 3 months for example ciprofloxacin and ofloxacin; absence of anatomical abnormalities of the reproductive system such as varicocele; no contact with pesticides, heavy metals and high levels of heat based on their job; no smoking of either cigarette or hookahs during the past 3 months, no use of alcoholic drinks and illicit drugs; serum vitamin D3 levels ≤30 ng/L; Iranian nationality; and fertility of the spouse. Exclusion criteria: no more than one dose of vitamin D3 intake per day during the study, the incidence of complications diagnosed by a urologist and a nutritionist which prevented the continuation of vitamin D3 intake, and the use of other supplements or drugs during the study which were banned in the inclusion criteria.

Amini 2020 *(Continued)*

Interventions	Vitamin D3 50,000 IU tablets once a week for 8 weeks and a maintenance dose of vitamin D3 50,000 once a month in the remaining 4 weeks (n = 35) versus Placebo (oral paraffin) (n = 37) Duration of treatment: 12 weeks
Outcomes	Spermogram, serum hormones, serum vitamin D3 level
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done in form of drawings: the placebo and vitamin D3 containers were identical and coded with numbers from 1 to 72 by a person who was not aware of the randomization process. All containers were placed in an opaque bag. The participants then received the containers that were randomly taken out of the bag."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done in form of drawings: the placebo and vitamin D3 containers were identical and coded with numbers from 1 to 72 by a person who was not aware of the randomization process. All containers were placed in an opaque bag. The participants then received the containers that were randomly taken out of the bag."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The subjects, researchers, and statistics specialists were not informed of the contents of the containers (and consequently, were not aware which subjects belonged to which study group) until the end of the data analysis."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The subjects, researchers, and statistics specialists were not informed of the contents of the containers (and consequently, were not aware which subjects belonged to which study group) until the end of the data analysis."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “We randomly assigned 35 patients to the intervention and 37 patients to the control group; however, as described in Fig. 1, five patients in the intervention group and five patients in the control group were excluded.” From figure 1: 2/37 in placebo group and 1/35 in intervention group “did not receive allocated intervention due to failure to see the results of the tests by the doctor”; 3/37 in placebo group and 4/35 in intervention group were lost to follow-up due to vitamin D3 above 30 ng/L and "Did not complete the tests at the end of the intervention".
Selective reporting (reporting bias)	Low risk	All outcomes reported. Protocol available (IRCT2016111830947n1, protocol does not mention vitamin D3 level and free androgen index (FAI) as outcomes).

Ardestani 2019

Study characteristics

Methods	Randomised, single-blind clinical trial

Ardestani 2019 *(Continued)*

	Duration of study: from January 2015 to December 2017, follow-up 6 months
Participants	Country: Iran Population: infertile patients with VC who underwent sub-inguinal VCT, N = 64 Mean age: : 30.27 ± 4.67 years (supplement group) and 30.47 ± 6.09 years (placebo group) Inclusion criteria: VC was proven by physical examination in a warm room after applying the Valsalva maneuver in the standing position. The abnormalities in sperm parameters including count, morphology and motility of sperm were evaluated in two separate semen analyses and patients with VC diagnosis and abnormal sperm parameters were planned for VCT. Exclusion criteria: were usage of supplements, vitamins or alcohol, tobacco smoking, addiction to opium or using opium during the follow-up period, diabetes mellitus, peptic ulcer history, hormonal disorders (based on clinical history and medical examination), chronic or active genitourinary infection (according to the history, medical examination, urine and semen analysis) and previous reaction to folic acid, selenium or vitamin E. As well, patients with missed follow-up, incorrect usage of drugs, presenting side effects, and delayed complications of VCT including recurrent VC, hydrocele or testicular atrophy were excluded from the study
Interventions	Subinguinal VCT followed by: Folic acid 5 mg + selenium 200 mcg + Vitamin E 400 IU orally daily (n = 32) versus No treatment (n = 32) Duration of treatment: 6 months
Outcomes	Semen analysis
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In this study, permuted block randomization was used to allocate interventions in a completely random manner to the two treatment groups. Six blocks of 4 were defined. Structure of each block was four-way combination of two methods of intervention in a perfectly balanced way. Random digits table was used for random assignment of blocks to each group. Additional matching did not take place."
Allocation concealment (selection bias)	High risk	Quote: "Accordingly, a list was prepared. Eligible participants were enrolled in the study according to the list, respectively."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "All subjects were aware of receiving VitE-Se-FA supplementation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Laboratory specialist and statistic consultant were blinded to treatment assignment." "All laboratory analyses were performed by specialists blinded to study protocol."
Incomplete outcome data (attrition bias)	Low risk	Quote: "During the study, four patients (n=4) were excluded due to lost to follow-up and thus, the data of 60 patients were evaluated."

Ardestani 2019 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes reported. Protocol available (IRCT2015091223855N2).

Attallah 2013

Study characteristics	
Methods	Randomised controlled open-label trial Duration of the study: unclear
Participants	Country: Egypt Population: men with isolated idiopathic athenozospermia, prior to intrauterine insemination (IUI), N = 60 Mean age: unknown, quote "both treatment groups were homogenous at the time of randomisation regarding the type and duration of infertility" Inclusion criteria: couples with idiopathic athenozospermia (progressive motility < 32%) with normal other seminal criteria and normal infertility workup for female partner Exclusion criteria: unclear
Interventions	N-acetylcysteine (NAC) 600 mg (n = 30) versus No treatment (n = 30) Duration of treatment: 12 weeks
Outcomes	Sperm concentration, progressive sperm motility, clinical pregnancy rate
Notes	Conference abstract, no full text. Attempted to contact authors 04.02.2014, unable to find e-mail address. Letter posted 12.02.2014

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Couples were randomised" Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-labelled"
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned

Attallah 2013 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Unknown - conference abstract

Azizollahi 2013

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: from May 2008 to November 2010
Participants	Country: Iran Population: infertile men with varicocele grade III, N = 160 (only 112 completed the study) Mean age: age range from 20 to 43 (mean ± SD: 29.07 ± 6.8) years Inclusion criteria: the presence of a grade III varicocele assessed by clinical parameters and was confirmed by Doppler ultrasound scanning Exclusion criteria: evidence of leukocytospermia, low testicular volume < 15 mL, congenital urogenital abnormalities and urogenital infections
Interventions	Zinc 66 mg (n = 32) versus Folic acid 5 mg (n = 26) versus Zinc 66 mg + Folic acid 5 mg (n = 29) versus Placebo (n = 25) Duration of treatment: 6 months, after varicocelectomy
Outcomes	Sperm parameters; number, morphology, halo formation rate, motility, forward progressive motility, chromomycin A3 positivity
Notes	Trial registration: IRCT138802261910N1 E-mailed the author 03.03.2014 (nematollahimahani@yahoo.com / nnematollahi@kmu.ac.ir). Author replied 06.03.2014 with information included in the ROB table. Author e-mailed again to ask about pregnancy data and dropouts from which group. The author informed us that Azizollahi 2011 was part of this trial and gave pregnancy and dropout data (there were originally 40 in each group). Quote: "At that time we observed 2 pregnancies in zinc/folic acid group, 1 pregnancy in zinc group, and no pregnancy in placebo and folic acid group. These data were just 6 months after the start of the trial."
Risk of bias	

Azizollahi 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For randomisation we used a table with 200 numbers (1 to 200). Before the trial we gave each group a number between 1 and 4 and allocated each group into the table. By this method the first, fifth, ninth, 13th and ... patients were allocated into the group 1 and the same manner was applied to the other groups"
Allocation concealment (selection bias)	Low risk	Quote: "We used sealed containers with the randomisation number on them. Drugs or placebo were in opaque capsules"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Our study was double blind. Neither the urologist nor the patient or examiner in the lab were aware of the arrangement of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Our study was double blind. Neither the urologist nor the patient or examiner in the lab were aware of the arrangement of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information gained from communication with the author explained the dropout numbers
Selective reporting (reporting bias)	Low risk	Clinical pregnancy rate data gained from email correspondence with the author. Protocol available.

Bahmyari 2021

Study characteristics	
Methods	Single-blind randomised controlled clinical trial Duration of study: from June 2016 to September 2018
Participants	Country: Iran Population: idiopathic infertile patients, patients with oligo, astheno, terato or oligoasthenoteratospermia, N = 70 Mean age: 37.23 ± 7.09 years (intervention group) and 36.65 ± 6.41 years (placebo group) Inclusion criteria: willingness to participate in the study; not being able to get pregnant after at least one year of regular unprotected sex; abnormal seminal analysis results (confirmed after two semen analyses within 3-4 week intervals done after the same sexual abstinence periods (3-5 days)); absence of underlying causes screened according to pre-testicular, testicular and post-testicular factors. We started antioxidant treatment for cases with a history of VCT at least 3 months later. Also, VC recurrence was ruled out again. Exclusion criteria: participant's unwillingness to continue, urogenital infection with antioxidant properties, symptom of an allergy to antioxidant therapy, diagnosis of pre-testicular, testicular or post-testicular factors.
Interventions	Selenium 200 mcg + Folic acid 5 mg + Vitamin E 400 IU per day, oral (n = 35) versus Matching placebo (sodium glycolate 100%) 250 mg per day, oral (n = 35)

Bahmyari 2021 *(Continued)*

	Duration of treatment: 3 months
Outcomes	Sperm parameters
Notes	Patients were also trained to change their lifestyle during the study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients who met the inclusion criteria were grouped as either intervention (n=35) or placebo group (n=35), through permuted block randomization method."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The placebo group received matching placebo (250 mg per day, oral) for three months." However: "single-blinded study", unclear if personnel was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Leaving the study intervention group: n = 5, leaving the study placebo group: n = 3. Reason not mentioned.
Selective reporting (reporting bias)	Low risk	All outcomes in methods section reported. Protocol available (IRCT2017012432153N1). Seminal white blood cell count in protocol not reported. Sperm motility index and functional sperm concentration not mentioned in protocol.

Balercia 2005

Study characteristics

Methods	Randomised double-blind trial Duration of study: 9 months, follow-up 3 months
Participants	Country: Italy Population: infertile men with idiopathic asthenozoospermia, N = 60 Mean age: 30 (range 24 to 38) years Inclusion criteria: primary infertility > 2 years after regular intercourse with a fertile woman, 20 to 40 years of age, normal rheologic characteristics, sperm count > 20 x 10^6 /mL, sperm motility < 50%, normal sperm morphological features > 30%, seminal WBC < 1 x 10^6 /mL, negative sperm culture and chlamydia and mycoplasma urealyticum, normal serum gonadotropins, T, E^2 and PRL, absence of infectious or genital disease, no anatomic abnormalities of the genital tract, absence of systemic diseases or treatment with other drugs within the 3 months before enrolment in the study, absence of smoking, alcohol or recreational drug use or of occupational chemical exposure

Balercia 2005 *(Continued)*

Interventions	L-carnitine 3g (n = 15) versus L-acetyl carnitine 3g (n = 15) versus L-carnitine 2g + L-acetyl carnitine 1g (n = 14) versus Placebo (n = 15) Duration of treatment: 6 months
Outcomes	Sperm parameters
Notes	2018: email sent on 07.03.2018 to author Balercia (g.balercia@aoumbertoprimo.marche.it: error, found new email: g.balercia@univpm.it) to ask if pregnancy rate were clinical pregnancies, how they were conceived, methods of randomisation and blinding Reply from author on 12.03.2018: Quote: "Pregnancies were clinical pregnancies, spontaneously conceived. I had at this time no data about the weekly progression, but the outcome of all pregnancies was newborn babies." New information added to RoB table. Added data in meta-analysis on clinical pregnancy, live birth and progressive motility ('Antioxidants vs placebo/no treatment' and 'head to head')

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from email): "The randomisation was made by blinded key"
Allocation concealment (selection bias)	Low risk	Quote (from email): "sealed opaque envelopes provided by the monitor" (reply email)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): "The randomisation was made by a blinded key, sealed opaque envelopes provided by the monitor, without any access for the researchers (except the hypothesis of adverse events). The key of randomization was available just at the end of the study." (reply email)
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 withdrawal from the L carnitine 2 g/day + L acetyl carnitine 1 g/day group Quote (from email): "as far your last question, I can confirm the results concerning the drop-out has not be considered in data analysis" (reply email) Conclusion: no ITT.
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Balercia 2009

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: 10 months, follow-up 3 months
Participants	Country: Italy Population: infertile men with idiopathic asthenozoospermia, N = 60 Mean age: 32 (range 27 to 32) years Inclusion criteria: age 20 to 40 years, infertility > 2 years, regular sexual intercourse with a potentially fertile female, normal rheologic characteristics (appearance, consistency and liquefaction) of semen and volume and pH in normal range, sperm count > 20 x 10^6 /mL, sperm motility < 50% (WHO 1999), normal morphology > 30%, seminal WBC < 1 x 10^6 /mL and a negative sperm culture and chlamydia and *Mycoplasma urealyticum* (*M.urealyticum*) detection, normal levels of gonadotropins, absence of genital disease and anatomical abnormalities of the genital tract including variocoele and antibodies, absence of systemic disease or treatment with other drugs within 3 months of being enrolled in the study, absence of smoking, alcohol and drug addiction and exposure to occupational chemicals Exclusion criteria: transient decrease in semen quality during run in and those who had sudden improvement in semen parameters during run in
Interventions	Coenzyme Q10 200 mg (n = 30) versus Placebo (n = 30) Duration of treatment: 6 months
Outcomes	Primary: sperm parameters, variations of coenzyme Q10 and ubiquinol concentrations in seminal plasma and spermatozoa Secondary: pregnancy rate
Notes	2018: added data on progressive sperm motility Email sent to author (g.balercia@staff.univpm.it) to ask if pregnancies were clinical and if he has live birth rates Reply of author Balercia on 29.03.2018: Quote: "Like the other study, I can confirm that pregnancies were clinical pregnancies, spontaneously conceived, but I had no data about the weekly progression (our outcome was another and we just reported the pregnancies as “collateral” data). All pregnancies gave newborn babies (patient/parent contacted us to share the joyful moment”)". Data added.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	At end of trial the paper mentions - quote: "after opening randomisation list" page 1789
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double blind". Placebo used.

Balercia 2009 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Semen quality was assessed by the same biologist" Blinding not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "5 patients dropped out of the study", 2 from the treatment group and 3 from the placebo group; this was discovered after opening the randomisation list at the end of the study. ITT was carried out
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Barekat 2016

Study characteristics	
Methods	Randomised clinical trial Duration of study: unclear, from 2011 to 2013
Participants	Country: Iran Population: subfertile men with varicocele grade 2-3, N = 40 Mean age: 30.1 ± 4.4 (range: 22-45) years Inclusion criteria: age < 45 years, primary infertility, left-sided varicocele (grade 2-3) diagnosed by palpation and Doppler duplex ultrasound. Female partner with age < 35 years, normal ovulatory cycles and patent tubes (confirmed by hysterosalpingography or laparoscopy). Exclusion criteria: varicocele grade I, azoospermia, recurrent varicocele, leukocytospermia, urogenital infections, testicular size discrepancy, abnormal hormonal profile, anatomical disorders, Klinefelter's syndrome, cancer, fever in the 90 days prior to surgery, seminal sperm antibodies, excessive alcohol and drug consumption, previous history of scrotal trauma or surgery, occupational exposure. Female partner with endometriosis, cycle irregularity, or gross anatomical abnormalities
Interventions	N-acetylcysteine (NAC) 200 mg (n = 20) versus No treatment (n = 20) Duration of treatment: 3 months, directly after varicocelectomy
Outcomes	Sperm parameters, DNA-fragmentation (TUNEL), protamine deficiency, ROS levels
Notes	Email sent to last author Nasr-Esfahani (mh.nasr-esfahani@royaninstitute.org) on 06.03.2018 to ask about the allocation concealment, sequence generation and definition of pregnancies and method of conceiving. Reply the same day from author (06.03.2018): Quote: "Clinical, spontaneous, pregnancies confirmed by heartbeat." Rest of information in RoB. Authors replied on 04.04.18 answering that data was presented with SEM

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

Barekat 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote (from email):"Randomisation done by table. We used computer-generated or random allocation software and with one block"
Allocation concealment (selection bias)	High risk	Quote (from email): "Dr would prescribe the NAC based on randomization table"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or health care providers (control is no treatment)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): “All parameters assessed in this study were carried out by a single trained individual unaware of treatment assignment.” "Lab collected the sample based on a table of allocation and handed the sample over to the researcher that carried out the semen analysis and sperm functional tests and was unaware to randomization. A third person called the patients and enquired about pregnancy and whether it was confirmed by heartbeat. Finally, the data gathered and analyzed independently of Dr or researchers"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “In this study, five individuals were excluded from the treatment group due to lack of compliance with NAC use, according to the study protocol" Lack of compliance directly related to treatment, furthermore 25% dropout is high. No ITT.
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Biagiotti 2003

Study characteristics	
Methods	Randomised trial Duration of study: unclear
Participants	Country: Italy Population: men with severe idiopathic oligoasthenospermia (sperm concentration < 5000 /µl), N = 42 Mean age: group A and B 35 (range 30 to 40) years, Group C 31 (range 24 to 34) years Inclusion criteria: severe idiopathic oligoasthenospermia (sperm concentration < 5000 /µl) Exclusion criteria: genomic, hormonal or inflammatory diseases
Interventions	Acetyl-carnitine 1 g + L-carnitine 2 g + Cinnoxicam (n = 14) versus Acetyl-carnitine 1 g + L-carnitine 2 g (n = 14) versus No treatment (n = 14) Duration of treatment: unclear

Biagiotti 2003 *(Continued)*

Outcomes	Sperm parameters
Notes	Conference abstract. No full text or data given. Contacted authors but no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised (1patient = 1 block) analysis of variance" Was this at the time of sequence generation or at data analysis?
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Unclear conference abstract

Blomberg Jensen 2018

Study characteristics

Methods	Randomised single-centre,triple-blinded, clinical trial Duration of study: from January 2011 to August 2014, follow-up 14 months
Participants	Country: Denmark Population: men part of an infertile couple with impaired semen quality, N = 307 Mean age: 34.8 ± 6.6 years Inclusion criteria: impaired semen quality (determined by WHO criteria) and vitamin D insufficient (25 OHD level #50 nmol/L) Exclusion criteria: serious comorbidities
Interventions	Vitamin D 1400 IU + calcium 500 mg (n = 151) plus vitamin D 300,000 IU oil once orally versus Placebo (n = 156) plus placebo oil once orally Duration of treatment: 150 days (5 months)

Blomberg Jensen 2018 *(Continued)*

Outcomes	Sperm parameters, reproductive hormones, live birth rate
Notes	Power calculation performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Infertile men were randomly assigned 1:1 (in blocks of 10) to either placebo or.." "Included men were given a specific trial identity number determined by minimization using the computer program Minim (21). Minimization was done using four groups based on serum 25OHD, sperm concentration, body mass index (BMI) and serum inhibin B"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization and manufacture of the high initial dose of vitamin D and placebo were performed by Glostrup Apotek."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "triple-blinded", "To avoid unblinding, the principal investigator gave the necessary clinical information to the sponsor, who had a list of numbers headed by X or Y. This ensured that both the principal investigator and the sponsor were unaware whether the patient was allocated to the vitamin D plus calcium (active) group or the placebo group (i.e., double blinding)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The trial remained blinded until all biochemical analyses, data handling, and statistical analyses by an independent statistician had been completed (i.e., triple blinding)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty men in the placebo group and 18 in the vitamin D plus calcium group were lost to follow-up. In total, 269 of 307 men (87.6%) completed the study (Fig. 1). By counting returned tablets, it was evident that one man in the vitamin D group and three in the placebo group were noncompliant; however, all data from these four men were included in all the analyses." Quote: "Twenty-nine of the 269 men completing the trial reported their partner was pregnant before start of the intervention, whereas five men lost their partner during the study period, leaving 235 with the possibility of effecting a pregnancy." ITT. No explanation given for lost to follow-up? Therefore unclear risk
Selective reporting (reporting bias)	Low risk	All the outcomes from the protocol were reported

Boonyarangkul 2015

Study characteristics	
Methods	Randomised double-blind controlled trial Duration of study: from May 2013 to October 2014
Participants	Country: Thailand Population: men with abnormal semen analysis, N = 68 Mean age: treatment group (folate only) 26.08 ± 0.76 years, control group 24.7 ± 10.84 years

Boonyarangkul 2015 *(Continued)*

	Inclusion criteria: abnormal semen analysis of at least one parameter according to WHO Criteria 2010(13) (concentration < 15 million/ml, motility < 40%, or morphology < 4%), failure of the female partner to conceive after one year of regular unprotected sexual intercourse, no history of tamoxifen and folate allergy Exclusion criteria: use of tamoxifen and folate within three months before recruitment, use of other medicines or vitamin during study period
Interventions	Placebo (n = 15) versus Tamoxifen citrate 20 mg (n = 15) versus Folate 5 mg (n = 15) versus Tamoxifen citrate 20 mg + Folate 5 mg (n = 15) Duration of treatment: 3 months
Outcomes	Sperm parameters, hyaluronan binding assay, hypo-osmotic swelling test and DNA damage (Comet assay, tail length)
Notes	Only folate and placebo arm included. Email sent to author on 06.03.2018 to Boonyarangkul (doctor_artit@yahoo.co.th) to ask about the randomisation process, blinding of outcome assessment, drop-out rate and funding of trial. Reminder email sent on 22.03.2018 to authors Boonyarangkul and Chiamchanya (doctor_artit@yahoo.co.th; charoenchai12@hotmail.com). No reply to date (19.04.2018) Data used in meta-analysis, however a sensitivity analysis was performed due to great baseline imbalance between these two groups, especially sperm concentration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	High risk	Baseline imbalance in concentration control versus folate group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Eight patients were excluded from the study (three patients declined to participate and five patients stop medication before completing the trial)" Unclear in which groups they participated. Data analysis by the authors was done without the 8 dropouts

Boonyarangkul 2015 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Busetto 2018

Study characteristics	
Methods	Randomised double-blind placebo-controlled study Duration of study: from December 2014 to June 2015, follow-up unclear
Participants	Country: Italy Population: infertile men with oligo- and/or astheno- and/or teratozoospermia, N = 104, divided in two clusters, 52 patients with varicocele grade I-III and 52 patients without varicocele Mean age: 32.5 ± 6.7 years Inclusion criteria: age 18 – 50 years, oligo-, astheno- and/or teratozoospermia, with or without varicocele, having a history of infertility for more than 12 months, varicocele patients were not surgically treated before and during the treatment, patients without varicocele were suffering from idiopathic male infertility, no other previous history of diseases affecting fertility. Fertile female partners were required with regular menstrual cycles, age <40 and couples not looking for fertility-related procedures (IVF/ICSI/IUI) for the next 90 days Exclusion criteria: known hypersensitivity to any of the treatment compounds, history of undescended testes or cancer, endocrine disorders, history of post-pubertal mumps, genitourinary surgery, obstructive azoospermia or obstructive pathology of the urogenital system, autoimmune disease, cystic fibrosis, history of taking any therapy affecting fertility within last 3 months, excessive consumption of alcohol or regular use of illicit or “recreational” drugs, positive serology for HIV, participants following any special diet, any condition which in the opinion of the investigator might put the participant at risk by participating in this study, participants involved in any other clinical trials
Interventions	Proxeed Plus 2 sachets (n = 52) (l-carnitine 1000 mg, fumarate 725 mg, acetyl-l-carnitine 500 mg, fructose 1000 mg, CoQ10 20 mg, vitamin C 90 mg, zinc 10 mg, folic acid 200 µg and vitamin B12 1.5 µg) versus Placebo 2 sachets (n = 52) Duration of treatment: 6 months
Outcomes	Sperm parameters, pregnancy rate
Notes	Power calculation performed. Email sent to author Busetto (gianmaria.busetto@uniroma1.it) on 07.03.2018 to ask about allocation concealment, blinding of outcome assessment and if the pregnancies were clinical and spontaneous conceived. Reply from author on 07.03.2018: Quote: "All natural pregnancies, spontaneously conceived, confirmed by ultrasound and we had just one abortion." See RoB.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The block randomisation method was used to randomise subjects into groups resulting in equal sample sizes to ensure a balance across the groups over time."

Busetto 2018 *(Continued)*

		Quote (from email): "Randomisation schedule (nQuery Advisor nTerim 2.0 (2012) program)"
Allocation concealment (selection bias)	Low risk	Quote (from email): "The randomization was done by an external company (non-pharmaceutical)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from email): "We used a double blind system and so researched didn't know anything about the randomization". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): "An external statistician evaluated everything external"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Ten patients dropped out from the study leaving 45 patients with varicocele and 49 without varicocele." "As for the ANCOVA, the p-values refer to the intention-to-treat population (ITT). The last observation carried forward (LOCF) method was used for replacing the missing data" Reasons for dropout not mentioned.
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Cavallini 2004

Study characteristics	
Methods	Randomised controlled trial Duration of study: follow-up 9 months
Participants	Country: Italy Population: idiopathic men with variocoele or idiopathic oligo-asthenospermia (OAT), N = 325 Mean age: 34 (range 27 to 40) years Inclusion criteria: men with OAT and with deficiencies in all sperm patterns whose chief complaint was primary couple infertility > 12 months with regular intercourse. Normal sperm appearance, consistency, liquefaction, volume, pH. Female partner without fertility problems. Varicoceles. Exclusion criteria: azoospermia, seminal WBC concentration more than 1000,000/mL, positive urethral chlamydia swab test, oligospermia < 5,000,000 /mL, hormonal alterations, age > 40 years, presence of anti-sperm antibodies, drug, tobacco or alcohol abuse, ongoing medical treatments, presence of hydrocoele, diabetes,hypertension, x-ray exposure in previous 8 months, peptic ulcer, unexplained gastric pain, previous hypersensitivity to NSAIDS or carnitines, carnitine metabolism deficiency, bilateral variocoele, prostate abnormalities, previous or current testicular pathology, testicle echographic abnormalities
Interventions	Placebo starch tablets 2 times/day + glycerine suppository (1 every 4 days) (n = 118) versus L-carnitine 1 x 2 g/day + acetyl-L-carnitine 500 x 2 mg/day + glycerine suppository (n = 101)

Cavallini 2004 *(Continued)*

	versus L-carnitine 1x 2 g/day + acetyl-L-carnitine 500 x 2 mg/day + glycerine suppository + cinnoxicam suppository 1 x 30 mg (every 4 days) (n = 106) Duration of treatment: 6 months
Outcomes	Primary: sperm parameters Secondary: pregnancy, side effects
Notes	Cinnoxicam is a NSAID, therefore the third arm was not included in meta-analysis as per protocol Author contacted regarding uneven numbers and missing placebo and continuous data Author replied that raw data were not available due to computer crash Data used from "Idiopathic oligoasthenoteratospermic males" in Table 2, calculated mean+SD from median+IQR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "casual random tables"
Allocation concealment (selection bias)	Low risk	Quote: "drug placebos identical in appearance", "anonymized carnitine and cinnoxicam and glycerine suppository containers; and filled and sealed anonymous color coded boxes", "the color code was disclosed to physicians by pharmacists and by IRB at the end of the research"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study personnel and participants were blinded to treatment assignment for the duration of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All study personnel and participants were blinded to treatment assignment for the duration of the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	325 randomised but only 185 accounted for; 55 dropouts from 185 (42%), 53 reasons given for the dropouts
Selective reporting (reporting bias)	Unclear risk	Sperm parameters as primary outcome. Intention to collect biochemical pregnancy data as secondary outcome recorded in the methods. No protocol available.

Cheng 2018

Study characteristics

Methods	Prospective, randomised, controlled study Duration of the study: from 12th of June 2013 to 2016
Participants	Country: China

Cheng 2018 *(Continued)*

	Population: infertile men with idiopathic OAT, N = 312 Mean age: 30.72 ± 5.2 years Inclusion criteria: • Sperm concentration <15 × 10^6 /ml and viability rate < 40% or sperm progressive motility < 32%; • Percentage of normal morphological sperm by Pap staining ≥ 4%; • No current or history of reproductive system infection, chronic disease or trauma; • Normal reproductive hormone levels and chromosome karyotype analysis; • Normal testicular volume, without cryptorchidism and varicocele; • Normal daily routine and no bad habits; • Spouse's age < 40 years old; • No use of spermatogenic drug in the past 6 months; • Receive the study treatment for 3 months Exclusion criteria: • Extremely severe oligospermia, asthenospermia (sperm concentration <2 × 10^6 /mL, viability rate <5%) or teratozoospermia; • Infertility caused by other factors has been identified; • Patients with alcoholism, smoking and other bad habits; • The treatment cycle has not been completed for 3 months
Interventions	L-carnitine 10 ml, oral twice daily (n = 78) versus Coenzyme Q10 20 mg, oral three times daily (n = 78) versus L-carnitine 10 ml twice daily + coenzyme Q10 20 mg three times daily (n = 78) versus Vitamin B1 (placebo group), dosage and frequency not mentioned (n = 78) Duration of treatment: 3 months
Outcomes	Semen analysis, sperm DNA fragmentation with sperm chromatin dispersion test, sperm acrosome reaction, clinical pregnancy, pregnancy rate, abortion rate
Notes	Article in Chinese, translated by Yue Wang, Yongchuan Gu, and Catherine Jia-yun Tsai. E-mailed authors Jiangh105@sina.com on 06-05-2021 requesting information on treatment in placebo group and additional outcome for all groups. No reply to date 03-09-2021.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using the computer-generated random number sequence"
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Cheng 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	262/312 completed the study, more drop outs in the intervention groups (16, 15, 15) compared to the vitamin B1 placebo group (4) . Most due to “protocol violation”. More lost to follow up in pregnancy data, not accounted for.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available.

Conquer 2000

Study characteristics	
Methods	Randomised placebo-controlled trial Duration of study: unclear
Participants	Country: Canada Population: healthy asthenozoospermic men who were patients of an infertility clinic, N = 28 Mean age: placebo group 35.2 years, treatment group 400 mg 38.3 years and treatment group 800 mg 34.4 years Inclusion criteria: asthenozoospermic, sperm motility < 50% of total sperm Exclusion criteria: unclear
Interventions	Docosahexaenoic acid (DHA) 400 mg (n = 9) versus Docosahexaenoic acid (DHA) 800 mg(n = 10) versus Placebo (n = 9) Duration of treatment: 3 months
Outcomes	Sperm parameters
Notes	Data with SEs converted to SDs. Placebo arms split

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The 28 subjects were randomly assigned to ..."

Conquer 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All men randomised were in the analysis, no dropouts.
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Cyrus 2015

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: from February 2010 to May 2011
Participants	Country: Iran Population:infertile men with palpable varicocele grade 2-3, N = 115 Mean age: 27.6 ± 5.3 years. Inclusion criteria: a palpable varicocele in physical examination and accompanying abnormalities in count, motility, or morphology of sperm in two separate semen analyses (according WHO criteria 1999), age range between 18 and 50, weight between 50 kg and 100 kg, being married Negative inclusion criteria**:** • absence of azoospermia, • diabetes mellitus, • hormonal disorders (according to medical history and clinical examination), • tobacco smoking, opium or recreational drugs addiction, • regular usage of vitamins or nutritional supplements, • active or chronic genitourinary infection (based on medical history, physical examination, semen and urine analysis), • history of peptic ulcer, • previous reaction to or intolerance to vitamin C. Exclusion criteria: missed follow-up, incorrect usage of the capsules, demonstrating side effects due to vitamin C, commencement of smoking or opium addiction during the follow-up period, delayed complications of varicocelectomy such as: hydrocele, recurrence of varicocele, and testicular atrophy.
Interventions	Vitamin C 500 mg (n = 46) versus

Cyrus 2015 *(Continued)*

	Placebo (n = 69) Duration of treatment: 3 months, after varicocelectomy
Outcomes	Primary: mean sperm count, motility (mean per cent of type A plus type B divided by all motility types) , morphology index (before and after surgery) Secondary: complications of surgery, varicocele grade, age and weight
Notes	Trial registration: IRCT201103042134N2 Email sent to author on 06.03.2018 to dr Kabir (aikabir@yahoo.com) to ask about funding and if the new matched cases were randomised. Reply on 23.03.2018 with all questions answered (see RoB)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomization method using Excel 2010 software (Microsoft Corporation, Washington, USA) by RANDBETWEEN(0;1000000)"function." Quote: "Five patients from the intervention group and eight patients from controls did not show-up for the follow-up visits and were substituted with matched new cases" Reply from authors by email: new cases were randomised
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was produced by our statistician and was delivered to our pharmacist. Participants were enrolled by the two executive urologists who were unaware of the results of the allocation table. Then based on the number in the sequence being odd or even each new patient after varicocele surgery was assigned to intervention or placebo group by our pharmacist who supplied the drugs. The ratio of placebo to intervention group was 1.5"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Analyzed in a reference laboratory (Sina Laboratory of Arak) by an experienced specialist in pathology and clinical laboratory medicine. Complications of surgery, varicocele grade, age and weight were determined" Reply from authors by email: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Five patients from the intervention group and eight patients from controls did not show-up for the follow-up visits and were substituted with matched new cases" Quote (from email): "We were able to have access to some of these drop-out cases. None of them mentioned disease-, medication-, or study-related causes for loss to follow up. Moving out from the city, changing their mind for participating in the study immediately after accepting to participate, personal secret causes and so on were among some of these reasons."
Selective reporting (reporting bias)	Low risk	Quote: "Our secondary complications were rare and they were excluded from the study and only those with clinically cured varicocele were selected for the final analysis. If there was any other unaccounted factor from Ivanissevich

Cyrus 2015 *(Continued)*

	method that could affect the results, since both groups had the same type of operation, it would be balanced in the two groups" All the outcomes from the aim of the study and methods were reported.

Dawson 1990

Study characteristics	
Methods	Randomised controlled trial Duration of study: 4 weeks
Participants	Country: USA Population: men with sperm agglutination, N = 30 Mean age: range 25 to 45 years Inclusion criteria: sperm agglutination over 25%, negative sperm antibodies, physically normal, no inflammatory disease Exclusion criteria: unclear
Interventions	Ascorbic acid (vitamin C) 1000 mg (n = 10) versus Ascorbic acid (vitamin C) 200 mg (n = 10) versus Placebo (n = 10) Duration of treatment: 3 weeks
Outcomes	Seminal parameters
Notes	Placebo numbers split by 2. Data were given in SE converted to SD New comment 2018: progressive forward motility instead of total motility, data total sperm motility moved to outcome progressive sperm motility

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "By random selection, three groups of 10 subjects each.."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each subject was told he was receiving AA and expected improvement in sperm quality"

Dawson 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	All specified outcomes were reported. No protocol available.

Deng 2014

Study characteristics	
Methods	Randomised controlled trial Duration of study: from January 2013 to February 2014
Participants	Country: China Population: men with idiopathic oligoasthenozoospermia (N = 86) Mean age: treatment group 31.5 ± 3.7 years, control group, 32.0 ± 4.1 years Inclusion criteria: 18 to 45-year-old male infertility patients, no contraception after marriage and infertility more than 12 months, normal sex life, no abnormal fertility of the women. According to WHO requirements 5 × 106/mL < sperm concentration < 20 × 106/mL, 10% < forward motility sperm percentage < 50%. Exclusion criteria: severe oligozoospermia; dead sperm disease due to erectile dysfunction (ED) or retrograde ejaculation or non-ejaculation; drug, uncontrolled bacterial prostatitis, fever and other factors affecting fertility; taking drugs that may affect sperm function; congenital malformations, fine tract obstruction, testicular atrophy; tuberculosis, liver, kidney and haematopoietic system of severe primary disease, mental illness.
Interventions	Vitamin D 200 IU + calcium 600 mg chewable tablet once daily (n = 43) versus Vitamin E 100 mg + vitamin C 100 mg three times a day (n = 43) Duration of treatment: 3 months
Outcomes	Sperm parameters, adverse reactions, pregnancy rate
Notes	Email sent on 23.07.2018 to Dr Deng (dengxiaolin@hsc.pku.edu.cn) with questions regarding the randomisation, blinding, outcome data assessment. No reply to date

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "86 patients were randomly divided into treatment group and control group"

Deng 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded: treatment A once daily chewable tablets, treatment B tablets three times a day
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Dimitriadis 2010

Study characteristics	
Methods	Randomised controlled trial Duration of study: unclear
Participants	Country: Japan Population: infertile men with oligoasthenospermia, N = 96 Mean age: unclear Inclusion criteria: unclear Exclusion criteria: unclear
Interventions	Vardenafil 10 mg (n = 23) versus Sildenafil 50 mg (n = 25) versus L-carnitine 1000 mg (n = 26) versus No treatment (n = 22) Duration of treatment: 12 weeks
Outcomes	Seminal parameters
Notes	Excluded were vardenafil (n = 23) and sildenafil (n = 25) Tried multiple times to contact authors for randomisation details and methods. No response. Last contacted in Feburary 2014. E-mail addresses tried: saitomo@kochi-u.ac.jp, akrosnin@hotmail.com

Dimitriadis 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control no treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or lost to follow-up mentioned.
Selective reporting (reporting bias)	Unclear risk	All data points accounted for. No protocol available.

Ener 2016

Study characteristics	
Methods	Randomised controlled trial Duration of study: unclear
Participants	Country: Turkey Population: infertile men with a left-sided clinical varicocele, N = 56 Mean age: 25.8 ± 4.6 years Inclusion criteria: males diagnosed with a left-sided clinical varicocele in the urology polyclinic, and for whom subinguinal varicocelectomy was planned Exclusion criteria: the use of alcohol, tobacco or any drugs including vitamins
Interventions	Vitamin E 600 mg (n = 22) versus No treatment (n = 23) Duration of treatment: 12 months, start after varicocelectomy
Outcomes	Sperm parameters, pregnancy rate
Notes	Power calculation performed

Ener 2016 *(Continued)*

	Email sent to author on 06.03.2018 to dr Ener (kemalener75@yahoo.com) to ask about funding, the randomisation process, blinding of outcome assessment and if the reported pregnancies were clinical pregnancies and how they were conceived. Reminder email sent to Ener and Ozayar (eozayar@yahoo.com.tr) on 22.03.2018. No reply to date (19.04.2018), data on pregnancy not used, unknown if clinical

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group is no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A total of 45 patients were included in the study." Quote: "Of note, our cohort was not without limitation. During the study set-up, the sample size was calculated as 56. However, 11 patients who could not use vitamin E regularly, or did not come to visit in control periods, were excluded from the study." Not clear in which groups drop-outs belonged
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Eslamian 2013

Study characteristics

Methods	Randomised controlled triple-blinded trial Duration of study: 12 weeks
Participants	Country: Iran Population: asthenozoospermic infertile men, N = 50 Mean age: unclear Inclusion criteria: patients interest in contribution aged 20-45 who have passed at least one year from the date they have decided to have a baby, not to using pregnancy protection methods, affected by idiopathic asthenozoospermia based on WHO criteria, normal serum gonadotropin, testosterone and prolactin values

Eslamian 2013 *(Continued)*

	Exclusion criteria: affected by genital system infection or taking drug for the infection during past three months, affected by anatomical anomalies in genital system such as varicocoele, surgical history on testicles and vas deferens
Interventions	Docosahexaenoic acid (DHA) 465 mg + vitamin E 600 IU (n = 25) versus Placebo (n = 25) Duration of treatment: 12 weeks
Outcomes	Sperm parameters, serum fatty acid concentration and sperm membrane fatty acid concentration
Notes	In Arabic, translated. Tried multiple times to contact authors for further study details with no response. Last tried to contact Feburary 2014: janati@avicenna.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified blocked randomisation
Allocation concealment (selection bias)	Low risk	Cans containing capsules marked as A1, A2, B1, B2 and patients, researchers and physician were unaware of the types of drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Cans containing capsules marked as A1, A2, B1, B2 and patients, researchers and physician were unaware of the types of drugs"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Triple-blinded" "Cans containing capsules marked as A1, A2, B1, B2 and patients, researchers and physician were unaware of the types of drugs"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and exclusions: **Intervention group (3 withdrawals)**: one man could not refer to the clinic in sixth week, the wife of the other one got pregnant, and another one was excluded because he have not taken more than 10% of the capsules **Control group (6 withdrawals)**: two men could not refer to the clinic in sixth week, one man could not refer to the clinic in 12th week. One man used complementary Coenzyme Q_{10}, and another one was excluded because he have not taken more than 10% of the capsules
Selective reporting (reporting bias)	Unclear risk	Sperm parameters reported. No protocol available.

Eslamian 2020

Study characteristics

Methods	RandomiSed, double-blind, placebo-controlled trial Duration of study: from April 2013 to May 2015, follow-up 12 weeks

Eslamian 2020 *(Continued)*

Participants	Country: Iran Population: idiopathic asthenozoospermic men, N = 180 Mean age: 32.67 ± 4.44 years (DHA + Vitamin E) 32.96 ± 4.17 years (DHA + placebo) 32.80 ± 4.13 years (Vitamin E + placebo) and 33.04 ± 4.08 years (placebo) Inclusion criteria: healthy, voluntary, idiopathic asthenozoospermic men, aged 20–45 years, unwanted childlessness for ≥1 year with the same female partner, normal endocrine function, and with the total number (or concentration) of spermatozoa, and percentage of morphologically normal spermatozoa, equal to or above the lower WHO reference limits Exclusion criteria: • To have abnormal testis, cryptorchidism, varicocele, had genital surgery, abnormal karyotypes, or endocrine hypogonadism detected via physical examination and para clinical testing; • A history of the use of antioxidant and ω-3 supplements within the previous 3 months; • A history of receiving radiation and/or chemotherapy, testosterone, and antiandrogens; • Genital tract infection or use of medication for this condition within the previous 3 months; • Being a candidate for intracytoplasmic sperm injection owing to severe sperm motility failure; • Exposure to extreme heat and/or pollutants such as pesticides, chemical solvents, heavy metals, and/or radioactive agents; and • Enrollment or planned enrolment in other research that might conflict with full participation in the current study or confound the observation or interpretation of the study findings.
Interventions	Docosahexaenoic acid (DHA) 465 mg + Vitamin E 600 IU daily, oral, frequency not mentioned (DE, n = 45) versus DHA 465 mg + Vitamin E resembling placebo (medium-chain triglycerides) (DP, n = 45) versus Vitamin E 600 IU + DHA resembling placebo (medium-chain triglycerides) (EP, n = 45) versus DHA resembling and Vitamin E resembling placebo (medium-chain triglycerides) (PP, n = 45) Duration of treatment: 12 weeks
Outcomes	Semen analysis, oxidative stress of seminal plasma (TAC, MDA, free 8 isoprostane), fatty acid analysis of blood serum and sperm membrane, serum vitamin E assay,
Notes	Power calculation provided based on progressive sperm motility.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomization"
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes opened at enrolment"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Placebo capsules contained medium-chain triglycerides, were shaped similarly to either DHA or vitamin E capsules" "Double blind"

Eslamian 2020 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Out of 180 participants, 41men in theDE group (91%), 42 men in the DP group (93%), 41 men in the EP group (91%), and 40 men in the PP group (89%) completed the protocol of the study." Figure 2 shows reasons: "discontinued treatment" and "lost to follow-up". Method of imputation provided.
Selective reporting (reporting bias)	Low risk	All outcome reported. Protocol available (NCT01846325). Only sperm motility and count mentioned in protocol.

Exposito 2016

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: quote: "from January 2010 to July 2014" (information from email)
Participants	Country: Spain Population: men from infertile couples participating in an IVF/ICSI program, N = 113 according to final manuscript and authors, grouped into three categories: normozoospermic, oligozoospermic and asthenozoospermic. Mean age: 37.6 ± 3.8 years Inclusion criteria: duration of infertility of at least 12 months and female age less than 40, as this a mandatory criterion in all Spanish public hospitals Exclusion criteria: quote: "the patient does not sign the informed consent" (information from email)
Interventions	Vitamin E (α-tocopherol) 400 mg (n = 55, n = 50 completed treatment) versus Placebo (n = 59, n = 51 completed treatment) Duration of treatment: 3 months
Outcomes	Sperm concentration, sperm count, progressive motility (A+B%), pregnancy rate
Notes	Conference abstract. Trial registration: EudraCT 2007-000960-25 Email sent to author Exposito (antonia.expositonavarro@osakidetza.eus;) and Matorras (JOSEROBERTO.MATORRASWEINIG@osakidetza.eus) on 20.02.2018 and 07.03.2018 to request full text or data regarding the outcomes in the OAT/azoospermic group Reply from author Matorras on 13.03.2018, received draft of manuscript.("we hope we are able to submit it for publication in two months") and asked some more questions about design/methods and data (means with SD) on the subgroup of men with male factor (so without the normospermic men). Reply on 24.03.2018: see RoB. Data not usable in meta-analysis due to the fact that is data for all the 3 categories (normozoospermic, oligozoospermic and asthenozoospermic) together.

Exposito 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from email): "To maintain the blindness to the investigator and the subject, the investigator receives the information of the treatment allocation number from the computer system." Computer randomisation
Allocation concealment (selection bias)	Low risk	Quote (from email): "To maintain the blindness to the investigator and the subject, the investigator receives the information of the treatment allocation number from the computer system. The subject receives his study medication package from the study site of the institution." Investigator receives a number belonging to a study medication package
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Placebo used. Quote (from email): "All the active and placebo capsules are identical in appearance, shape, smell and taste"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from email): "At the end 101 couples completed the treatment (placebo group N=51 and vitamin E group N=50). Nine couples withdrew from this study before completing their 3 months of treatment due to IVF cycle cancelled or a lack of continuing interest(8%) (five of the placebo group and four of the vitamin E group)(N=104) .Three couples achieved spontaneous pregnancy at 50, 60 and 90 days of treatment;two of them belonged to placebo group and the other belonged to the vitamin E group (2.7%)" Quote (from email): "The data analysis was done with the people who completed the study (n=101)" No ITT. Reasons for drop-out well explained and balanced.
Selective reporting (reporting bias)	Low risk	All the outcomes from the aim of the study and methods were reported

Galatioto 2008

Study characteristics

Methods	Randomised controlled, intention-to-treat, single-centre study. Duration of study: 12 months, from January 2003 to June 2005
Participants	Country: Italy Population: men with persistent oligospermia (5 to 20 m/ml), N = 42 Mean age: treatment group 32 (27.5 to 35.5) years, control 33 (23 to 36) years Inclusion criteria: having performed a retrograde embolization with concomitant oligospermia, persistent oligospermia and infertility > 12 months

Galatioto 2008 *(Continued)*

	Exclusion criteria: smoking, alcohol consumption, taking any fertility drugs within 3 months prior to the study, serious medical or psychiatric condition, abnormal hormonal profile, sperm infection
Interventions	N-acetylcysteine (NAC) 600 mg + vitamins-minerals (vitamin C, vitamin E, vitamin A, thiamine, riboflavin, pyridoxin, nicotinamide, pantothenate, biotin, cyanocobalamin, ergocalciferol, calcium, magnesium, phosphate, iron, manganese, copper, zinc) (n = 20) versus No treatment (n = 22) Duration of treatment: 90 days
Outcomes	Primary: seminal parameters Secondary: pregnancy (undefined) and adverse effects
Notes	Power calculation performed. Attempted to contact author regarding median data. No response yet (2014) 2018: motility reported as WHO Class A motile sperm instead of total motility, added to table 'data not usable for meta-analysis'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned to either antioxidant therapy or no medical therapy. Randomisation number was assigned by random allocation software using a block randomisation design"
Allocation concealment (selection bias)	Low risk	Quote: "All steps of randomisation process were performed blindly in the pharmacy of our hospital"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All ejaculate analysis was analyzed blindly with respect to the treatment groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "intention to treat"
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Gamidov 2017

Study characteristics

Methods	'Open perspective randomised' study Duration of study: unclear

Gamidov 2017 *(Continued)*

Participants	Country: Russia Population: men with varicocele, N = 114 Mean age: 34.1 ± 12.1 years Inclusion criteria: aged 25-45 years, participants' wives had not become pregnant in the last 12 months or more, despite regular unprotected sexual intercourse between the partners; oligo-,asteno- and/or teratozoospermia, varicocele evident upon palpation confirmed by Doppler ultrasonography of scrotum blood vessels, normal constitutional development as determined by the physical exam Exclusion criteria: previously established genetic causes of infertility (Klinefelter syndrome, micro deletions AZF, CFTR), azoospermia, clinical and laboratory evidence for inflammatory changes to sex glands, pyospermia, follicle-stimulating hormone (FSH) overproduction, immunologic infertility (MAR-test IgG > 10%), pronounces somatic pathology, psychosexual or ejaculatory disfunction
Interventions	SpermActin-forte (acetyl-L-carnitine, L-carnitine fumarate and alpha-lipoic acid) (n = 38) versus SpermActin-forte + Vitamin complex 'Man's formula' (n = 38) versus No treatment (n = 38) Duration of treatment: 3 months, after microsurgical varicocelectomy (MVE)
Outcomes	Sperm parameters, DNA fragmentation, side effects
Notes	Article in Russian, translated by Andrew Dubovyi. Ethical approval and obtaining informed consent not mentioned in text. Email sent to author Ovchinnikov (r_ovchinnikov@oparina4.ru) on 29.03.2018 to ask about the randomisation process, blinding of outcome assessors, drop-outs and which side-effects they aimed for ("No side effects related to the pharmacological treatment were observed."). Reply on 11.04.18, see RoB. Data on adverse events used. Data on sperm parameters (median+IQR) adjusted to mean+SD. Placebo arm split.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using adaptive dynamic randomization with stratification patients were assigned to one of three groups of 38 subjects" Quote (from email): "It was computer randomized block design"
Allocation concealment (selection bias)	Unclear risk	Quote (from email): "Randomization was done by the researchers"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment, furthermore group A uses 1 tablet, group B uses 2 tablets Quote (from email):"The study was not blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): question was the person who assessed the outcomes blinded? "Yes"

Gamidov 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from email):"There were no lost to follow-up participants (the samples were small)"
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available. Quote (from email) when asking about which adverse events were aimed for: "We have not registered any side effects, including gastro-intestinal, urological, neurological complications, etc"

Gamidov 2019

Study characteristics	
Methods	Open-label, prospective, randomised placebo-controlled study Duration of study: unclear
Participants	Country: Russia Population: infertile men aged 25-45 years with an increased level of sperm DNA fragmentation and oxidative stress, N = 80 Mean age: 34.9 years Inclusion criteria: • absence of pregnancy for more than 12 months with regular sex life without contraception; • miscarriage by a spouse in the presence of increased indicators of sperm DNA fragmentation and oxidative stress in a man; • repeated failures of ART programs in the presence of increased rates of sperm DNA fragmentation and oxidative stress in men; • normal development according to physical examination data. Exclusion criteria: • the presence of active inflammatory processes; • laboratory signs of inflammatory changes in the accessory gonads; • established genetic causes of infertility (Klinefelter's syndrome, AZF microdeletion, CFTR); • cryptozoospermia; • azoospermia; • necrozoospermia; • pyospermia; • hypergonadotropic and hypogonadotropic hypogonadism; • varicocele; • the presence of an immune form of infertility (MAR-test IgG > 50%); • severe somatic pathology; • psychosexual and ejaculatory dysfunction.

Gamidov 2019 *(Continued)*

Interventions	Spermactin Forte (dosage not described in report; l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + ascorbic acid 100 mg), oral once daily (n = 60) versus Placebo (n = 20) Duration of treatment: 180 days
Outcomes	Spermiogram, ROS concentration, sperm DNA fragmentation with TUNEL assay, pregnancy rate, live birth rate
Notes	Article in Russian, translated by Alyona Oryshchuk. E-mailed author Dr. Ovchinnikov r_ovchinnikov@oparina4.ru to request information. Reply on 18-05-2021 concerning RoB: "Investigators and outcome assessors were blinded". "No patients were lost to follow up or withdrawn". Reply on 31-05-2021 with information on pregnancies: "Spontaneous pregnancies. It is correct that the one case in group A was a clinical pregnancy (7-8 weeks) (with positive heartbeat on ultrasound). It is correct that the one case in group B was a clinical pregnancy (5-6 weeks) (with positive heartbeat on ultrasound). It is correct that the one case in group B (anembryonic pregnancy) was a biochemical pregnancy (no discernible heartbeat seen)." Results of sperm parameters expressed as median+IQR, data adjusted to mean+SD for meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Adaptive dynamic randomisation”, from e-mail: “computer randomised block design”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind”, see e-mail quote
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See e-mail quote
Incomplete outcome data (attrition bias) All outcomes	Low risk	See e-mail quote
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available.

Gonzalez-Ravina 2018

Study characteristics	
Methods	Prospective, randomised, double-blind and placebo-controlled intervention study Duration of study: unclear
Participants	Country: Spain Population: men between 18 and 50 years with a previous history of infertility of at least one year, N = 60 Mean age: unclear Inclusion criteria: men aged between 18 and 50 years with a previous history of infertility of at least one year and whose semen analysis met the following criteria: (a) sperm count greater than 10 million per mL; (b) sperm progressive motility of less than 60%; and (c) normal sperm morphology of less than 2% Exclusion criteria: not mentioned
Interventions	Docosahexaenoic acid (DHA) 0.5 g oral daily dose (n = 15) versus DHA 1 g oral daily dose (n = 15) versus DHA 2 g oral daily dose (n = 15) versus Placebo: 0.5 daily dose of primrose oil (n = 15) Duration of treatment: 3 months
Outcomes	Semen analysis, ROS, mitochondrial membrane potential (MMP), lipid peroxidation, DNA fragmentation with TUNEL assay
Notes	E-mailed author (manuel.fernandez@ivirma.com) on 10-03-2021 and 04-05-2021 to request SD of different results. No reply to date (03-09-2021).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization list was generated using Randomization.com [http://www. randomization.com] with randomly permuted blocks of 60 subjects randomized into four blocks."
Allocation concealment (selection bias)	Low risk	Quote: "The list was kept in a locked drawer in the administration office, to which the clinical staff who enrolled the participants in the study had no access; group allocation was requested by telephone."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Physicians and patients were blinded to the assigned study intervention."

Gonzalez-Ravina 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fig 1. No patients were lost to follow-up, and no patients discontinued the intervention. The outcome data for all patients who were randomized were included in the final data analysis."
Selective reporting (reporting bias)	Low risk	All outcomes reported. Protocol available (NCT02889341).

Gopinath 2013

Study characteristics	
Methods	Randomised placebo-controlled double-blind parallel three-arm multicentre trial Duration of study: follow-up 6 months
Participants	Country: India Population: Idiopathic oligoasthenozoospermia men, N = 138 (N = 125 completed the study) Mean age: 30.74 (range 24-45) years Inclusion criteria: age 21-50 years, infertility >1 year, sperm count less than 15 million/mL, sperm total motility < 40%, no history of taking therapy for infertility, no history of OAT, regular sexual intercourse with a potentially normal fertile female, willing to sign informed consent and likely to be available for all visits during follow-up period Exclusion criteria: primary testicular disease, any organic cause for infertility including varicocele, prostate-vesiculo-epididymitis,genital infectious disease,planning for any other ART during study period, serum follicle-stimulating hormone FSH >15 mIU/mL, abnormal serum levels of LH, testosterone, estradiol and prolactin, presence of antispermatozoa antibodies, severe oligospermia (< 2 million sperm/mL), azoospermia, seminal WBCs more than 1 x 10^6 mL, major hepatic and renal disease, myopathy, history of allergy to any ingredient of the formulation, not likely to be available for follow-up, have participated in another clinical trial in the past 3 months, female partners with anatomic or physiological alterations causing subfertility
Interventions	Fixed doses combination (FDC) 2 tablets (coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg) (n = 46) versus Fixed doses combination (FDC) 1 tablet + 1 Placebo tablet (n = 43) versus Placebo 2 tablets (n = 36) Duration of treatment: 180 days
Outcomes	Primary: improvement in sperm count, total sperm motility (90 and 180 days) Secondary: pregnancy rate, side effects
Notes	Email sent on 06.03.2018 to dr Zaveri (drhemantzaveri@gmail.com) to ask about the pregnancies (clinical? How conceived?), the randomisation process, blinding of outcome assessment and allocation of 13 dropouts. Reminder email sent on 27.03.2018. Reply on 30.03.2018 from author; see text in RoB.

Gopinath 2013 *(Continued)*

	Pregnancy data not used, distribution in groups unknown, only reply from author quote: "No pregnancies were not followed up to stage 12 weeks. So no pregnancy was clinical. 9 pregnancies were conceived through ART 3 Conceived spontaneous" Numbers from text: 6 in FDC 2, 7 in FDC 1, 2 in Placebo. Pregnancy data used in table 1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from email): "Procedures were computer"
Allocation concealment (selection bias)	Low risk	Quote: "Centrally randomised to one of three treatment arms (arm 1-3) in a 1:1:1 ratio" Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blinded". Placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): "Yes outcome assessment was blinded "
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 lost to follow-up (dropout), quote: "at different stage during the study" Asked by email in which groups or what reasons. Quote (reply email): "5 in paternia BID, 6 in placebo, 2 in paternia BID" Data-analysis only on the 125 who completed the study. Low risk because dropouts accounted for.
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Goswami 2015

Study characteristics

Methods	Prospective observational study Duration of study: from March 2013 to April 2015
Participants	Country: India Population: men with idiopathic male infertility with high reactive oxygen species (ROS), N = 175 Inclusion criteria: unclear Exclusion criteria: unclear
Interventions	Diet rich in antioxidants and lifestyle changes (n = 80) versus Combined oral antioxidant (n = 95)

Goswami 2015 *(Continued)*

	versus Placebo (n = 75) Duration of treatment: unclear
Outcomes	Semen parameters, antioxidant concentrations (CoQ-10, L-carnitine, zinc), plasma total antioxidant capacity (TAC), total glutathione (GSH), sperm DNA fragmentation (TUNEL assay)
Notes	Conference abstract only. Not clear if it is a randomised clinical trial. Email sent to authors Goswami and Chakravarty (bncirm@gmail.com; syednkabir@yahoo.com) on 20.02.2018 and 06.03.2018. Email sent to authors again on 30.06.2021, reply: "yes it was a randomised controlled trial among Infertile male without any reasonable or specific cause and were waiting for IUI or IVF treatment cycle." Requested clarification on randomisation of placebo group ("maintained in parallel") and information on study design, RoB and study results on 01.07.2021. No reply to date (03-09-2021).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "A placebo-controlled group was maintained in parallel", might even be non-randomised.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of drop-outs or lost to follow up not mentioned.
Selective reporting (reporting bias)	Unclear risk	Conference abstract. No protocol available.

Greco 2005

Study characteristics

Methods	Randomised controlled double-blind trial Duration of study: unclear
Participants	Country: France Population: infertile males, N = 64

Greco 2005 *(Continued)*

	Mean age: unclear Inclusion criteria: TUNEL assay showed a presence of fragmented DNA ≥ 15% of ejaculated spermatozoa Exclusion criteria: variocele, genitourinary inflammation, infection, smoking
Interventions	Vitamin C 1000 mg + Vitamin E 1000 mg (n = 32) versus Placebo (n = 32) Duration of treatment: 2 months
Outcomes	Sperm parameters
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was double-blinded with both the authors and the patients unaware of which of the patients was in the treatment or control arm of the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Haghighian 2015

Study characteristics

Methods	Randomised triple-blind placebo-controlled trial Duration of study: unclear, in 2014
Participants	Country: Iran Population: men with idiopathic asthenozoospermia, N = 48 Mean age: 33.56 ± 5.07 years

Haghighian 2015 *(Continued)*

	Inclusion criteria: unwilling childlessness at least 24 months in duration with a female partner, no medical condition that could account for infertility, normal fertile female partner according to investigations, all patients were needed to have stopped all medical therapy R12 weeks before study initiation Exclusion criteria: the history of epididymo-orchitis, prostatitis, genital trauma, testicular torsion, inguinal or genital surgery, urinary tract infection, or previous hormonal therapy, another genital disease (cryptorchidism, current genital inflammation or varicocele), severe general or central nervous system disease and endocrinopathy, use of cytotoxic drugs, immunosuppressants, anticonvulsants, androgens, or antiandrogens, recent history of sexually transmitted infection, psychologic or physiologic abnormalities that would impair sexual performance or the ability to provide semen samples, drug or alcohol abuse, hepatobiliary disease, significant renal insufficiency, occupational and environmental subjections to possible reproductive toxins, BMI of >30 kg/m^2, participation in another investigational study, unlikely availability for follow-up
Interventions	Alpha-lipoic acid (ALA) 600 mg (n = 23) versus Placebo (n = 21) Duration of treatment: 12 weeks
Outcomes	Sperm parameters, markers of oxidative stress (total antioxidant capacity (TAC) and malondialdehyde (MDA)), side effects
Notes	Email sent to last author Haidari (haidari58@gmail.com) on 06.03.2018 to ask what side effects they aimed for and reasons for lost to follow-up. Reminder email sent on 22.03.2018 to Haidari and Dadfar (mdadfar@yahoo.com). No reply to date (19.04.2018). E-mail sent to both authors to ask about small SDs, reply on 18.07.2021 that this was "due to the accuracy in sampling and selecting of infertile subjects and also accurate matching when grouping patients".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each eligible patient received a randomization number which was determined by a computer-generated schedule. Then a randomization table was generated by the method of random permuted blocks"
Allocation concealment (selection bias)	Low risk	Quote: "Persons who were operationally independent from the study investigator performed the study randomization"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigator, clinician prescriber, and patients were blinded to the treatment condition"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients'data collected during this trial were kept confidential and locked in a secure area. Randomization codes of the study were opened only after all participants had completed the study protocol"
Incomplete outcome data (attrition bias) All outcomes	Low risk	N = 48, quote: "44 completed the study, rest lost to follow-up: data analysis with 23 of 24 in ALA group, 21 of 24 in placebo group" Reasons lost to follow-up not mentioned.

Haghighian 2015 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Haje 2015

Study characteristics	
Methods	Randomised controlled trial Duration of study: from January 2013 to June 2014
Participants	Country: Iraq Population: infertile men with idiopathic oligozoospermia (OA), N = 128 (in flow chart "182") Mean age: 37.54 ± 2.46 years Inclusion criteria: repeated exhibition of OA without detectable cause (idiopathic OA) Exclusion criteria: leukocytospermia, altered testicular volume of a minimum of 20 ml as depicted by ultrasonography, varicocele as detected by clinical examination and ultrasonography, abnormal FSH levels, couples with combined male and female factors
Interventions	Tamoxifen 20 mg (n = 45) versus L-carnitine 1000 mg (n = 20) versus Tamoxifen 20 mg + L-carnitine 1000 mg (n = 34) versus Placebo (n = 29) Duration of treatment: 3 to 6 months followed by ICSI
Outcomes	Sperm parameters, fertility and pregnancy outcome following ICSI
Notes	Email sent to author Haje on 06.03.2018 (milathaji@yahoo.com) to ask about randomisation, dropouts, amount of pregnancies (instead of %) and if they were clinical, and to provide raw data specified for amount of months treatment used? Reminder email sent on 22.03.2018. No reply to date (19.04.2018). Data not usable: range of treatment 3 - 6 months, not specified as separates, pregnancy in % instead of numbers, unknown if clinical or not.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Haje 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not mentioned. Furthermore baseline characteristics not mentioned
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes are mentioned and provided. No protocol available.

Huang 2020

Study characteristics	
Methods	Double-blinded, randomised, controlled trial Duration of study: from March 2014 to September 2017, follow-up 90 days
Participants	Country: China Population: men suffering oligozoospermia, N = 769 Mean age: 31.6 ± 2.3 years Inclusion criteria: oligozoospermia was demonstrated in at least 3 semen analyses performed within a period of 6 months; infertility for at least 1 year; no medical treatment in the previous 6 months; no presence of varicocele; no smoking; no obesity; no infection of the accessory sex glands; no identifiable cytogenetic abnormalities. All of the wives received a complete infertility workup to rule out female factors. All partners ovulated regularly detected by transvaginal ultrasound scanning; no anatomic abnormalities detected by ultrasound scanning; no abnormal fallopian tube anatomy detected by hysterosalpingography. Exclusion criteria: not mentioned.
Interventions	Folic acid 0.8 mg orally per day (n = unclear) versus Placebo (starch-filled capsules), dose and frequency not mentioned (n = unclear) Duration of treatment: 3 months
Outcomes	Evaluation of MTHFR polymorphism to divide patients in genotype subgroups, semen analysis, MDA, sperm DNA fragmentation with TUNEL assay, biochemical pregnancy, clinical pregnancy, spontaneous pregnancy or with use or ART treatment, abortions, live birth, gestational week at birth
Notes	Outcomes reported for specific MTHFR polymorphism groups only. E-mailed author 06-04-2021 and 04-05-2021 to request data for all groups. No reply to date (03-09-2021).
Risk of bias	

Huang 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to simple randomization method using EXCEL 2010 software"
Allocation concealment (selection bias)	Low risk	Quote: "The statistician produced the allocation sequence and delivered it to the pharmacist. Specialist in this study was not known of the results of allocation table."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind" "Patients in folic acid treatment group received folic acid at the dose of 0.8 mg/day for 3 months, and the patients serving as the placebo group received starchfilled capsules for 3 months."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	High risk	Semen volume, abortions and gestational age at birth are not reported. Not all polymorphism group are reported. Protocol not available.

Joseph 2020

Study characteristics	
Methods	Open-label randomised, controlled trial Duration of study: from February 2013 to October 2019
Participants	Country: India Population: couples who were scheduled for ART owing to male factor subfertility, N = 200 Mean age: 37.28 ± 3.9 years (intervention group) and 37.48 ± 4.9 (control group) Inclusion criteria: abnormal semen analysis was defined as follows: mild oligozoospermia with a sperm concentration of more than 5 million/mL and less than 15 million/mL, and/or asthenozoospermia with sperm motility more than 25% and less than 32%, and/or teratozoospermia with sperm morphology of less than 4%. Exclusion criteria: - Couples in whom the female partner was over 37 years of age or those who were diagnosed with moderate or severe endometriosis. - Couples with a male partner whose semen analysis was suggestive of severe male factor, defined as a sperm concentration <5 million/mL. - Those who had taken oral antioxidants in the past 3 months.
Interventions	Antioxidant consisting of vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg once daily orally prior to ART treatment (ICSI) (n = 100) versus

Joseph 2020 *(Continued)*

	No treatment prior to ART treatment (ICSI) (n = 100) Duration of treatment: 3 months
Outcomes	Clinical pregnancy rate, miscarriage rate, fertilisation rate, ongoing pregnancy rate, live birth rate per embryo transfer, semen parameters
Notes	Data of semen parameters adjusted to mean+SD for meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using computer-generated random numbers at the time of ART booking."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was achieved using opaque sealed envelopes which were sequentially numbered and contained the group code."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, no placebo control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 65 couples (36 in antioxidant and 29 in the control arm) did not undergo ART, deviated from the protocol or had a cancellation of the treatment cycle before oocyte retrieval or embryo transfer." "The overall attrition rate was high (32.5%, 65/200)."
Selective reporting (reporting bias)	High risk	Certain secondary outcome parameters are only presented as per protocol analysis. Protocol available (CTRI/2013/02/003431)

Kessopoulou 1995

Study characteristics

Methods	Randomised double-blinded placebo cross-over trial Duration of study: unclear
Participants	Country: UK Population: men with high levels of reactive oxygen species (ROS) of a couple undergoing IVF, N = 30 Mean age: unclear, median age 32 years Inclusion criteria: attending fertility clinic, high levels of ROS in semen. Female partner has patent tubes and is ovulating Exclusion criteria: men with antisperm antibodies, > 20% spermatozoa with Ig (immunoglobulin A) or IgG antibodies and sperm concentration < 5 x 10^6 mL
Interventions	Vitamin E 600 mg (n = 15) versus

Kessopoulou 1995 *(Continued)*

	Placebo (n = 15) Duration of treatment: 3 months, 1 month wash-out, 3 more months after cross-over
Outcomes	Primary outcomes: sperm parameters Secondary outcomes: adverse effects, live birth
Notes	Power calculation performed. Attempted to contact author regarding median difference data, no response as yet (2014). Only first phase data used in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study was a randomised double blind placebo controlled trial". "The randomisation was performed by the manufacturer"
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation was performed by the manufacturer"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the code was blind for the researcher and patients. The code was broken at the end of the trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "30 patients completed the study over 2 years" Changed to unclear risk in 2018 (was low risk); not reported how many were randomised to start with, or how many drop-outs
Selective reporting (reporting bias)	Unclear risk	Outcomes reported as stated in the methods section. No protocol available.

Kizilay 2019

Study characteristics

Methods	Single-centre randomised trial Duration of the study: from January 2016 to January 2018, follow-up 6 months
Participants	Country: Turkey Population: infertile patients with low sperm counts (oligo- and/or astheno- and/ or teratozoospermia) and grade I-III varicocele, N = 93 Mean age: 32.86 ± 3.14 years (intervention group) and 32.18 ± 2.44 years (control group) Inclusion criteria: male patients older than 18 years and with infertility history ≥ 12 months; the participants' spouses were younger than 35 years old; their hormone profiles and menstrual cycles were regular; they had no known diseases that might cause infertility.

Kizilay 2019 *(Continued)*

	Exclusion criteria: patients who had previously undergone a genitourinary system and/or varicocele surgery; had idiopathic infertility; had a disease affecting fertility and received a medical treatment affecting fertility for the previous 3 months; had a history of undescended testis, testicular cancer, testicular trauma, post-pubertal mumps and endocrine disorder, or an obstructive urogenital disease; who followed a fertility-specific diet; who ingested excessive alcohol, cigarettes, drugs, opioids, or hallucinogens; whose HIV serology was positive; or who had an acute infection and another identified cause of infertility were not included in the study.
Interventions	Oral antioxidant supplement containing 1 g of L-carnitine fumarate, 0.5 g of Acetyl-Lcarnitine, 1 g of fructose, 50 mg of citric acid, 90 mg of vitamin C, 10 mg of zinc, 200 mcg of folic acid, 50 mcg of selenium, 20 mg of coenzyme Q-10, and 1.5 mcg of vitamin B12. Dosage was two sachets daily. (n = 64) versus No treatment (n = 29) Duration of treatment: 6 months
Outcomes	Semen analysis, clinical pregnancy rate, peroxidase positive leukocytes, adverse events
Notes	E-mailed author on 10-03-2021 and 04-05-2021: how was clinical pregnancy assessed? Reply on 05-05-2021: “1- Clinical pregnancies were defined by an obstetrician by demonstrating fetal heart rate by USG. 2- Clinical pregnancies were defined by the obstetricians. 3- All pregnancies occurred 6 months after varicocelectomy. However, there is no mean time data for these. 4- Unfortunately, data on live births are not available.” And on 01-06-2021: “4 pregnancies with assisted reproductive techniques were in the group that did not receive antioxidants.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "we used the simple random allocation method to allocate patients to antioxidant and non-antioxidant groups using Excel 2010 software"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo control group, participants had to pay for the treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During the study period, 2 patients left the study and 1 patient was lost in the follow-up" 2 patients in antioxidant group and 1 patient in control group.
Selective reporting (reporting bias)	High risk	Quote: "As there were only seven patients with grade 1 varicocele in both groups, they were not evaluated." No protocol available.

Kopets 2020

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, prospective, parallel arms study Duration of study: from September 2018 and August 2019, follow-up 6 months
Participants	Country: Ukraine Population: males aged 21-50 years with idiopathic male infertility and at least 1 of 3 abnormal values, N = 83 Mean age: 32.5 ± 6.1 years (verum group) and 32.7 ± 5.2 years (placebo group) Inclusion criteria: were informed consent form signed, age 21-50 years, idiopathic male infertility defined as absence of conception in a couple having a regular unprotected intercourse for 12 months with a woman without evident pathology that could cause infertility, oligo- (sperm concentration < 15 million/mL) and/or astheno- (<32% forms with progressive motility) and/or teratozoospermia (<4% of sperm cells with normal morphology), affirmed availability throughout the study period and a mobile phone. Exclusion criteria: allergy to any component of the TDS, known genetic, anatomical, endocrine, and inflammatory or traumatic testicular cause of male infertility; known or suspected genetic, anatomical, endocrine, and inflammatory cause of female infertility; inflammatory bowel disease; moderate-to-severe disease of any systems; sexually transmitted diseases; alcohol or drug addiction of any couple counterpart as suspected by investigator; difficulty understanding the study requirements as judged by an investigator; use of any investigational product within the previous 3 months before entering the study; and use of any drugs that stimulate or suppress spermatogenesis within previous 3 months.
Interventions	Verum TDS, (1990 mg of l-carnitine/ l-acetyl-carnitine, 250 mg of l-arginine, 100 mg of glutathione, 40 mg of coenzyme Q10, 7.5 mg of zinc, 234 mg of vitamin B9, 2 mcg of vitamin B12, 50 mcg of selenium and excipients), one oral dose daily (n = 42) versus Placebo TDS, containing the excipients orange/beta-carotene colourant, citric acid anhydride, sorbitol, silicium dioxide, magnesium stearate, and maltodextrin (n = 41) Duration of treatment: 6 months
Outcomes	Spermiogram, pregnancy rate, time to conception, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random numbers were generated online with no restrictions to randomization by the statistician using the web site Randomization.com."
Allocation concealment (selection bias)	Low risk	Quote: "The investigators and patients were concealed, which type of the TDS, verum or placebo, was selected."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigators and patients were concealed, which type of the TDS, verum or placebo, was selected." "Both placebo and verum boxes with sachets of the TDS looked the same, and their content was similar on smell, texture, and color."

Kopets 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers in outcome tables match randomised numbers. Quote from abstract: "All males finished the study".
Selective reporting (reporting bias)	High risk	Time to pregnancy is not reported. Protocol available (NCT03588949): "... couples will be screened for conception, pregnancy, and a newborn." Newborns not reported.

Korshunov 2018

Study characteristics	
Methods	Prospective randomised clinical trial Duration of study: from September 2015 to February 2017
Participants	Country: Russia Population: infertile couples with male factor (obstructive azoospermia), N = 46 Mean age: 42.6 ± 7.2 years (men) and 32.1 ± 5.5 years (women) Inclusion criteria: treatment with fresh TESA/ICSI Exclusion criteria: genetic anomaly (CBAVD: Congenital bilateral absence of the vas deferens)
Interventions	Antioxidant supplement (vitamin E 400 mg, vitamin C 1000mg, selenium 50 mcg once daily and L-carnitine 1000 mg) twice daily. (n = 24) versus No treatment (n = 22) Duration of treatment: 10 weeks
Outcomes	Fertilisation rate, implantation rate, clinical pregnancy rate, live birth rate per TESA/ICSI cycle. Also reported: embryo quality, early pregnancy loss.
Notes	Conference abstract, no published report available. E-mailed author m.korshunov@bk.ru on 16-03-2021 to ask for dosage, frequency and duration of treatment and method of assessing clinical pregnancy. Reply on 18-03-2021: "The treatment included: Vit C 1000 mg, vit E 400 mg, selenium 50 mkg — once a day, L-carnitin 1000 mg x 2 p/d — during 10 weeks. Clinical pregnancy was defined as a pregnancy observed sonographically by the visualization of a fetal heart beat by 7 weeks of gestation." Contacted author for data on early pregnancy loss / miscarriage to add to data analysis. Received reply on 16/7 with data on miscarriage (antioxidants: 4, no treatment: 6).

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

Korshunov 2018 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not mentioned, conference abstract
Allocation concealment (selection bias)	Unclear risk	Not mentioned, conference abstract
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned, conference abstract
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers in outcome tables match randomized numbers. No lost to follow-up reported,
Selective reporting (reporting bias)	Unclear risk	Conference abstract. No protocol available.

Kumalic 2020

Study characteristics	
Methods	Prospective randomised double-blind placebo-controlled trial Duration of study: from November 2014 to January 2019
Participants	Country: Slovenia Population: infertile men with OAT, N = 80 Mean age: 35.0 ± 5.2 years (intervention group) and 36.4 ± 5.5 years (placebo group) Inclusion criteria: patients were considered OAT after at least two previous semen analysis and andrological examination in the frame of their infertility treatment after their partner being unable to conceive for at least 12 months of unprotected sexual intercourse or after a failed assisted conception procedure. Semen quality was defined as OAT according to the WHO 2010 guidelines: oligospermia (O) – sperm concentration < 15 million/ml; asthenozoospermia (A) – progressive motility of spermatozoa < 32%; teratozoospermia (T) – < 4% spermatozoa with normal morphology. Exclusion criteria: smoking more than 20 cigarettes per day, genetic causes of infertility, endocrinopathies, genital tract infections, undescended testis, systemic diseases, history of testicular cancer and treatment with other drugs and food supplements, such as antioxidants, during the last three months before enrolling in this study.
Interventions	Astaxanthin 16 mg and 40 mg vitamin E oral daily (n = 40) versus Placebo (n = 40) Duration of treatment: 3 months

Kumalic 2020 *(Continued)*

Outcomes	Semen analysis, DNA fragmentation with TUNEL assay, MMP, FSH, adverse events
Notes	E-mailed authors bojana.pinter@guest.arnes.si on 16-03-2021 about daily dosage of vitamin E in astaxanthin capsules and availability of pregnancy related outcomes. Reply 17-03-2021: "One capsule contained 10 mg of vitamin E, the daily dosage of vitamin E was 40 mg. As a secondary aim we evaluated the outcome of the ART for 19 couples in the astaxanthin with vitamin E group and 17 couples in the placebo group who had the ICSI procedure within three months after the participants finished the intervention. The average age of participants female partner was 34.0 ± 3.6 years in the astaxanthin with vitamin E group and was not significantly different from those in the placebo group, 34.9 ± 5.0 years (p = 0.507). There was no significant difference between both groups in the pregnancy rates per cycle, spontaneous abortion rates per pregnancy and delivery rates per cycle after the transfer of fresh embryos." Data added to meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computerized randomization table was used for the purpose of randomization."
Allocation concealment (selection bias)	Low risk	Quote: "A random allocation sequence was generated and participants were enrolled and assigned to interventions by a third party, thus ensuring that both the enrolled participants and researchers were blinded."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A random allocation sequence was generated and participants were enrolled and assigned to interventions by a third party, thus ensuring that both the enrolled participants and researchers were blinded."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Eight patients in both groups (10%) dropped out for personal reasons during the treatment, and thus, 72 patients completed the trial." "Five patients were not included in the statistical analyses on changes in sperm total number and concentration and 27 patients were not included in the statistical analyses on the motility of spermatozoa as in these patients only a few mobile or immobile spermatozoa in the semen sample were present."
Selective reporting (reporting bias)	High risk	All outcomes in methods section reported. Protocol available (NCT02310087): “In the ART procedure (ICSI) the fertilization rate, the quality of embryos, pregnancy rates and miscarriages rates in 1st trimester will be compared between the study and control group.” These pregnancy outcomes are not reported.

Kumamoto 1988

Study characteristics

Methods	Randomised double-blind parallel trial

Kumamoto 1988 *(Continued)*

	Duration of study: from January 1985 to June 1986
Participants	Country: Japan, 25 centres Population: men with abnormal sperm count or motility, N = 375 Mean age: unclear, average 32.8 (SD 4.8) years Inclusion criteria: average sperm count ≤ 40 × 10^6 /mL measured on ≥ 2 occasions OR average sperm count ≥ 40 count ≤ 40 × 10^6 /mL measured on ≥ 2 occasions AND sperm motility < 50% Exclusion criteria: sperm count only measured at 1 occasion, average sperm count ≤ 2 × 10^6/mL, sperm motility = 0%, testicular size < 8 mL using orchidometer bilaterally, use of hormone or anti-hormone drug within preceding 3 months before the study period, WBC > 5/HPF in the semen or the presence of possible genito-urinary infection, presence of hypoganadism or endocrine disease, presence of undescended testes, genito-urinary tract obstruction, varicocele or any other serious associated condition also included concomitant use of anti-hormonal and hormonal treatment and the 2 patients with polypharmacy were excluded from the data analysis
Interventions	Mecobalamin (vitamin B12) 6.000 mcg (n = 125) versus Mecobalamin (vitamin B12) 1.500 mcg (n = 124) versus Placebo (n = 126) Duration of treatment: 12 weeks
Outcomes	Sperm concentration, sperm motility
Notes	Article in Japanese, translated by Dr Tomoko Kumaga and Tan Wantao. No contact details available for authors. No useable data available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 396 patients were divided into 3 groups (6000ug/day, 1500ug/day, placebo) by randomisation. The implementation of randomisation and allocation concealment was carried out by two people (Doctor Yamamoto, Doctor Shimizu)
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT. 21 lost to follow-up; 19 dropouts, 2 polypharmacy 2018 Change in RoB to unclear. Not sure in which groups dropouts belonged.

Kumamoto 1988 *(Continued)*

Selective reporting (reporting bias)	High risk	Subgroup analysis performed as an addition post-treatment

Lenzi 2003

Study characteristics	
Methods	Randomised placebo-controlled, double-blind cross-over trial Duration of study: 10 months
Participants	Country: Italy Population: infertile men with oligoasthenoteratozoospermia (OAT), N = 100 Mean age: unclear, range: 20 to 40 years Inclusion criteria: age between 20 to 40 years with infertility lasting longer than 2 years, regular sexual intercourse with a gynaecologically normal female partner with no female infertility, absence of endocrine disease, genital infections, obstructive cryptorchism, antisperm antibodies, normal sperm parameters with no significant differences after 3 tests, mild oligospermia with perm concentration 10 to 20 x 10^6/mL and motility 10% to 30% Exclusion criteria: unclear
Interventions	L-carnitine 2 g (n = 43) versus Placebo (n = 43) Duration of treatment: 2 months of washout, 2 months of therapy/placebo, 2 more months of washout, 2 more months of placebo/therapy
Outcomes	Sperm parameters, pregnancy rate
Notes	Power calculation performed First phase data: attempted to contact author regarding standard deviations, how many were in each group for the first phase and how many of the 4 who went to assisted reproduction did so in the first phase and what do they mean by 172 cycles. No response yet (2014). Added to outcome data 'not usable for meta-analysis'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blinded", "seemingly identical placebo"

Lenzi 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 withdrew - 4 went onto assisted reproduction, 6 did not return for second period and 4 due to pregnancy in first phase. Therefore should only be?4 at the most lost from first phase. No ITT All withdrawals accounted for whole trial however how many were lost in the first phase in first phase
Selective reporting (reporting bias)	Unclear risk	All outcomes are reported. No protocol available.

Lenzi 2004

Study characteristics	
Methods	Randomised placebo-controlled, double-blind trial Duration of study: 8 months
Participants	Country: Italy Population: infertile men with OAT, N = 60 Mean age: unclear, range 20 to 40 years Inclusion criteria: oligoasthenoteratospermia, age between 20 to 40 years, infertility > 2 years with regular intercourse, no endocrine disease, cryptorchidism, genital infections or obstructions, variocoele or testicular hypertrophy, antisperm antibodies Exclusion criteria: none
Interventions	L-carnitine 2 g + L-acetyl-carnitine 1000 mg (n = 30) versus Placebo (n = 26) Duration of treatment: 6 months
Outcomes	Sperm parameters, pregnancy rate
Notes	Power calculation performed Attempted to contact author regarding 8-month follow-up data. No reply as yet (2014)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Mentions coding: quote: "When codes were broken at the end of the study"

Lenzi 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 men withdrew from the placebo group. 60 randomised 56 analysed. No ITT
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Li 2005

Study characteristics	
Methods	Randomised double-blinded parallel trial Duration of study: 3 months
Participants	Country: Eastern China Population: infertile men with oligoasthenospermia, N = 150 Mean age: treatment group 30 ± 5.5 (23 to 45) years, control group 32 ± 3.5 (24 to 46) years Inclusion criteria: no smoking or alcohol use, any fertility medication needed to be stopped 2 weeks before Exclusion criteria: none
Interventions	L-carnitine 2 g + acetyl-L-carnitine 1 g (n = 85) (90 with ITT) versus Vitamin E 200 mg + vitamin C 200 mg (n = 53) (60 with ITT) Duration of treatment: 3 months
Outcomes	Sperm parameters, pregnancy rate
Notes	Article in Chinese, translated by Shaofu Li 10.11.2008. Contact author regarding methods of randomisation, concealment and whether SD or SEs used and query that this is the same trial as Li 2005a 2018: added data on progressive motility

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned

Li 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind" but unclear who is blinded as the control is another antioxidant i.e. not placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition explained. Withdrawal: 5 from treatment group and 7 from control
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Li 2005a

Study characteristics	
Methods	Randomised trial Duration: unclear
Participants	Country: Eastern China Population: infertile men with oligoasthenospermia, N = 80 Mean age: 29 ± 3.5 (23 to 40) years Inclusion criteria: no smoking or alcohol, any fertility medication needed to be stopped 2 weeks before Exclusion criteria: none
Interventions	L-carnitine 2 g (n = 40) versus Vitamin E 100 mg + Vitamin C 200 mg (n = 40) Duration of treatment: 3 months
Outcomes	Seminal parameters, pregnancy rate
Notes	Article in Chinese, translated by Shaofu Li 10.11.2008. Attempted to contact author re methods of randomisation, concealment and whether SD or SEs used and whether this is the same trial as Li 2005. Also asked whether there were any data on pregnancy rate. Translator replied 22.09.2009 no pregnancy data were available in the text of the trial

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

Li 2005a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawal: 8 from treatment (n = 32) and 9 from control (n = 31). 21% loss to follow-up. No ITT
Selective reporting (reporting bias)	Unclear risk	No protocol available.

Lombardo 2002

Study characteristics	
Methods	Randomised controlled cross-over trial Duration of study: 10 months
Participants	Country: Italy Population: infertile men with oligoasthenospermia, N = 100 Mean age: unclear, range 20 to 40 years Inclusion criteria: age 20 to 40 years,infertility > 2 years, 3 baseline semen analysis demonstrating concentration 10 to 20 10^6/mL, 10% to 30% total motility, forward progression < 15%, abnormal morphological forms < 70%, curvilinear velocity 10 to 30 /second + linearity < 4 Exclusion criteria: unclear
Interventions	L-carnitine 2 g (n = ?) versus Placebo (n = ?) Duration of treatment: 2 months
Outcomes	Sperm parameters
Notes	Abstract only Attempted to contact author re first phase data, outcomes, randomisation, concealment and whether there was a full publication of the trial

Lombardo 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	86 patients completed the trial out of 100. Need to see full trial for the reasons for withdrawals and ITT
Selective reporting (reporting bias)	Unclear risk	Abstract only

Lu 2018

Study characteristics	
Methods	Randomised, prospective, double-blind, placebo-controlled trial Duration of study: unclear
Participants	Country: China Population: patients with a left-sided clinical varicocele, who were mildly oligospermic(sperm count: 5–15 million) and could not have a child for at least 1 year, N = 54 Mean age: 32.76 years (intervention group) and 32.23 years (placebo group) Inclusion criteria: the diagnostic criteria for varicocele were the presence of two or more varicose veins in the relaxed state and retrograde flow for duration of more than 2 seconds during the Valsalva manoeuvre, patients for whom subinguinal VCT was planned. Exclusion criteria: the use of alcohol, tobacco or any drugs including vitamins
Interventions	Melatonin 400 mg oral daily (n = 27) versus Placebo (starch-filled capsules) (n = 27) Both treatments were given after subinguinal VCT. Duration of treatment: 3 months
Outcomes	Semen analysis, serum hormones (FSH, testosterone, inhibin B) and TAC and MDA in seminal plasma

Lu 2018 *(Continued)*

Notes	Not clear if mean+SEM or mean+SD provided. Unclear if outcomes were assessed in all randomised patients. E-mailed author Dr. Zhang on 11-05-2021 and 17-05-2021 with e-mail addresses zjmxhxy@163.com and jmzwfhl@163.com. Both not functioning. E-mail to Jun-Ming.Zhang@uc.edu, zjmlwsz@sina.com and qljiangjie@sdu.edu.cn on 28-05-2021. No reply to date (03-09-2021).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomisation method using Excel 2010 software"
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was produced by our statistician and was delivered to our pharmacist. Participants were enrolled by the two executive urologists who were unaware of the results of allocation table."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind and placebo-controlled mentioned in the title but blinding of participants and personnel not mentioned in the report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear from results in how many patients the outcomes were assessed.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available.

Martinez 2015

Study characteristics

Methods	Randomised double-blind controlled trial Duration of study: from July 2009 to September 2010
Participants	Country: Mexico Population: men with idiopathic oligoasthenozoospermia, N = 54 Mean age: unclear Inclusion criteria: patients between the ages of 20 to 45 years with a diagnosis of idiopathic oligoasthenozoospermia. The diagnosis of oligoasthenozoospermia was reached by performing two semen analyses on different dates with an interval of three weeks between them. Exclusion criteria: infertile patients with normal findings on semen analysis, chronic smokers, antioxidants use in the last 6 months prior to the study, chronic degenerative diseases such as diabetes or high blood pressure

Martinez 2015 *(Continued)*

	Hormonal abnormalities
Interventions	Resveratrol (3,5,4´-trihydroxystilbene) 25 mg + 725 mg microcrystalline cellulose (n = 18) versus SG1002 (hydrogen sulphide) 750 mg (n = 18) versus Placebo 750 mg microcrystalline cellulose (n = 18) Duration of treatment: 75 days
Outcomes	Sperm parameters (with A+B type sperm motility)
Notes	SG1002 (hydrogen sulphide) excluded because it is a gaseous transmitter Email sent to second author Sordia-Hernandez (luissordia@telmexmail.com) on 22.03.2018 to ask details about the randomisation process and for him to provide more data (SDs). Inconsistence in sentence about adverse events: 3 side effects in SG1002 group, however in the sentence before only 2 in this group? Data not usable, no SD's. No reply to date (19.04.2018).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Quote: "Bottles and capsules for each treatment were identical and identified by a code unknown to the researchers or subject." Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Sperm analysis performed by lab technicians, blinded to the treatment group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the seven subjects who did not complete the study (3 from the placebo group, 2 from the resveratrol treatment group and 2 from the SG1002 treatment group), none returned for follow-up visits and therefore no data on sperm count, motility or abnormality was available and an intent to treat analysis could not be carried out. Four of these subjects were lost in follow-up while the other three withdrew due to unpleasant smelling sweat (SG1002 treatment group), nausea and flatulence (SG1002 treatment group), and inconvenience (SG1002 treatment group)." Quote: "All study subjects who did not comply with medication given as prescribed, who discontinued the drug or were hypersensitive to it were eliminated"

Martinez 2015 *(Continued)*

		Reasons enough explained, all 3 in SG1002 due to side effects, however we did not include this arm
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Martinez-Soto 2010

Study characteristics	
Methods	Randomised double-blind controlled trial Duration of study: 10 weeks
Participants	Country: Spain Population: infertile men, N = 42 (abstract), N = 64 (from author) Mean age: treatment group 35.23 years, placebo 36.10 years, overall average age 35 years Inclusion criteria: men suffering from male factor infertility, according to the WHO guidelines (WHO 1999), and who were undergoing infertility evaluation during the period 2009 to 2011 Exclusion criteria: oncological patients, those suffering from metabolic disease, chromosomal or genetic alterations, and patients on anticoagulant treatment
Interventions	Brudy Plus 1500 mg of DHA-enriched oil (DHA 1000 mg + eicosapentaenoic acid (EPA) 135 mg) (n = 35) versus Placebo (n = 29) Duration of treatment: 10 weeks
Outcomes	Sperm DNA fragmentation, seminal parameters, lipid composition, antioxidant capacity
Notes	Conference abstract only. Contacted author multiple times by e-mail (JuanCarlos.Martinez@ivi.es) for further study details. Clarified that the abstract details were different from that in the final study, a copy of the unofficial manuscript was submitted to the review authors. Last contact was on 26.02.2014 2018: added data on progressive sperm motility

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random list with a computer program
Allocation concealment (selection bias)	Low risk	Closed and numerated envelopes with allocation group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants knew that they was included in group A or B but only Brudy technology knew the assignation to the control group or experimental group

Martinez-Soto 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Mehni 2014

Study characteristics	
Methods	Randomised double-blind, placebo-controlled trial Duration of study: from May 2008 to August 2012
Participants	Country: Iran Population: infertile men with idiopathic OAT, N = 235 Mean age: treatment (L-carnitine) group 30 ± 1.7 years, control group 30 ± 4.6 years Inclusion criteria: age 25 – 40 years, infertile men with OAT, healthy fertile wives Exclusion criteria: existence of genital abnormalities (undescended testes, varicocele, atrophy of testes), occupational chemical exposure history, systemic diseases, abnormal semen volume, pH, agglutination or viscosity, serum hormonal abnormalities (FSH, LH, testosterone, estradiol, prolactin), wives with known fertility risk factors confirmed by gynaecologist
Interventions	Pentoxifylline 800 mg + L-carnitine 1000 mg (n = 58) versus Pentoxifylline 800 mg + Placebo (n = 59) versus L-carnitine 1000 mg + Placebo (n = 59) versus Placebo (n = 59) Duration of treatment: 3 months
Outcomes	Sperm parameters (progressive sperm motility), selection of type of assisted reproductive techniques (ART)
Notes	Only data from L-carnitine and placebo arm used. Email sent to author (dr.ketabchi@gmail.com) on 06.03.2018 to ask about the randomisation process and blinding of the outcome assessment Reminder email sent to Ketabchi on 22.03.2018. No reply to date (19.04.2018).
Risk of bias	

Mehni 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized by Bloch method to four groups" Bloch (block?) method, does this mean computerised? Insufficient explanation
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "After intervention 23 patients excluded from study (3 patients for drug intolerance in group I, and 20 patients for uncooperative in group II and III)" Data-analysis only with for those who completed the study (N = 212) According to figure 1: 5 patients (instead of 3 mentioned in text) dropped out due to drug intolerance in group I? Type error? Reasons and exact numbers for dropout not given for L-carnitine arm specifically.
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Micic 2019

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: from December 2014 to January 2016, follow-up 6 months
Participants	Country: Serbia Population: men with idiopathic oligoasthenozoospermia, N = 175 Mean age: 31.5 years Inclusion criteria: men visiting the Andrology centre, (18-50 years) and with difficulty in conceiving > 12 months; one semen analysis that demonstrated either total sperm number ≤15 million per mL; progressive motility < 32%; normal viscosity and normal leucocytes number (<1 × 106/mL); total ejaculate volume 1.0 mL; sperm vitality ≤58% live; normal sperm morphology <4% (according to WHO, 2010). The following female partners were included in the study: • fertile partners with regular menstrual cycles, and younger than 40 years; • infertile partners provided no fertility-related procedures such as artificial insemination (AI), in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) were planned for the next 90 days. Exclusion criteria: motility < 5%; sperm concentration <1 × 106/mL; history of undescended testes; subjects with known hypersensitivity to ingredients in Proxeed Plus; endocrine disorders affecting the hypothalamic–pituitary axis; history of post-pubertal mumps; presence of anti-sperm antibodies; history

Micic 2019 *(Continued)*

	of endocrine disease; autoimmune disease, cystic fibrosis, or testicular cancer; leucocytospermia, leucocyte count >1 × 106/mL; use of antioxidant agents or vitamins within the 8 weeks prior to inclusion in the study (for subjects using vitamin supplementation, an 8-week wash-out period was required prior to inclusion in the study); use of vitamin or natural treatment for infertility at any time; history of taking any therapy for infertility within the last 2 months including over-the-counter treatment and vitamin supplementation; history of excessive consumption of alcohol 90 days prior to the start of the trial; subjects involved in other clinical trials.
Interventions	Proxeed Plus (L-carnitine 1 g, acetyl-L-carinitine 0.5 g, fumarate 0.725 g, fructose 1 g, critic acid 50 mg, zinc 10 mg, coenzyme Q10 20 mg, selenium 50 mcg, vitamin C 90 mg, folic acid 1.5 mcg, vitamin B12 1.5 mcg), oral twice daily (n = 125) versus Placebo made with the exipients of the supplementation without the active substances, oral twice daily (n = 50) Duration of treatment: 6 months (and 2 months wash-out)
Outcomes	Semen analysis, DNA fragmentation with Halosperm assay, alfa glucosidase activity, seminal plasma L-carnitine
Notes	Email sent to last author Agarwal (AGARWAA@ccf.org) on 20.02.2018. Answer on 21.02.18 "this study is not published in a journal at this time" New email on 06.03.2018 to ask raw data (means with SD) and more information about randomisation/blinding outcome/dropout rates. Reply on 22.03.18 from Agarwal & Micic (savamicic2016@gmail.com) with more information in a word document. Only medians with IQR. See RoB. Full report added in 2021. Data on semen parameters provided as median+IQR. Data adjusted to mean+SD for meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from email): "Random list was made using the nQuery Advisor nTerim 2.0 (2012) program"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from email): "This is a double blind study. Neither the patient, providers, nor investigators responsible for collecting data or analyzing laboratory specimens have been knowledgeable regarding the assignment of active or placebo product. A file has been maintained at each of the sites under the responsibility of the primary investigator which will provide product identification for each subject. Upon entry into the study, subjects have been assigned a unique study identification number."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): "Neither the patient, providers, nor investigators responsible for collecting data or analyzing laboratory specimens have been knowledgeable regarding the assignment of active or placebo product. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from email): "From the treated group (total 125) drop out was 6 subjects; 2 of them got flu with high temperature, 2 went form Serbia (new job), 2 stopped without reason. And from the placebo group (total 5o) drop out was

Micic 2019 *(Continued)*

		4; 2 drop out without explanation, 1 underwent abdominal surgery, and 1 divorced"
Selective reporting (reporting bias)	High risk	Sperm concentration not reported. No protocol available.

Morgante 2010

Study characteristics	
Methods	Randomised controlled trial Duration of study: 3 months
Participants	Country: Italy Population: infertile men with asthenospermia, N = 180 Mean age: range 25 and 49 years Inclusion criteria: age between 28 and 45, sperm concentration < 20 x 10^6 spermatozoa /mL, sperm progressive motility < 30%, normal morphology < 30%, leucocyte < 1 x 10^6 /mL, no infections Exclusion criteria: men younger than 28 and over 45, sperm concentration > 20 x 10^6 spermatozoa / mL, sperm progressive motility > 30%, normal morphology > 30%, leucocyte > 1 x 10^6 /mL, current infections, history of testicular pathology: cryptorchidism, varicocele, surgical operations, radiotherapy or chemotherapy, use of anabolic steroids, deficiency of hypothalamic-pituitary-gonadal axis, genital tract infections
Interventions	L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg in one vial (n = 90) versus No treatment (n = 90) Duration of treatment: 3 months
Outcomes	Sperm parameters, sexual satisfaction
Notes	Article in Italian, translated by Roberto D'Amico. Contacted author by email (giuseppe.morgante@unisi.it) to clarify study details, recruitment, randomisation, blinding, ethics approval, study population, withdrawals and to clarify progressive mortality. Last response was on 12.03.2014 Quote: "Total motility and progressive motility are similar terms for the same definition: all the spermatozoa that have progressive or not linear motility" 2018: motility data included as progressive motility

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned

Morgante 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Nadjarzadeh 2011

Study characteristics	
Methods	Randomised controlled trial Duration of study: 3 months
Participants	Country: Iran Population: infertile men with OAT who have been trying for pregnancy for > 1 year unprotected intercourse, N = 60 (analysed N = 47) Mean age: 34 years Inclusion criteria: seminal WBC < 1,000,000 /mL, absence of anatomical abnormalities of the genital tract, absence of infectious genital diseases or systemic diseases, absence of treatment with other drugs and dietary supplement during the 3 months before enrolling in the study, at last absence of smoking, drug, and alcohol use or occupational chemical exposure Exclusion criteria: seminal WBC > 1,000,000 /mL, presence of anatomical abnormalities of the genital tract, presence of infectious genital diseases or systemic diseases, presence of treatment with other drugs and dietary supplement during the 3 months before enrolling in the study, currently smoking, using drug, or alcohol use or occupational chemical exposure
Interventions	Coenzyme Q10 (CoQ10) 200 mg (n = 23) versus Placebo (n = 24) Duration of treatment: 3 months
Outcomes	Sperm motility and concentration, progression, total antioxidant capacity (TAC)
Notes	Power calculation performed Contacted regarding methods, randomisation, allocation concealment, recruitment, blinding and dropouts.

Nadjarzadeh 2011 *(Continued)*

Response from Azadeh Nadjarzadeh (azmm1383@yahoo.com)in October 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from email):"Participants were randomised using block randomisation. It was done by Dr Motevallian who is epidemiologist and it has done before study"
Allocation concealment (selection bias)	Low risk	Quote (from email): "Before the trial a colleague, that had not role in the study, coded the bottles of Coenzyme Q10 and placebo (that were similar) in A and B and give them to one of the staff of Avicenna Research centre. Only that person has a list of randomisation and give A or B bottles to the participants according to their code"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (from email): "Both participants and investigators blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (from email): "The appearance and the bottles of capsules were similar and none of outcome assessors knew group, because everyone had a code after being allocated group A and B"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "13 dropped out for personal reasons" - 22%: 7 from treatment group and 6 from the control group
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Nouri 2019

Study characteristics

Methods	Randomised, double-blind, clinical trial Duration of study: from January 2018 to October 2018
Participants	Country: Iran Population: men who had a history of primary and secondary infertility for at least 5 years, N = 44 Mean age: 32.89 ± 2.33 years (lycopene group) 32.15 ± 2.16 years (placebo group) Inclusion criteria: infertile men aged between 25 and 45 years, a sperm count of less than 20 million per millilitres, normal sperm of < 65% and spermia of <3.0 mL, and average motility of < 60% while receiving no treatments. Exclusion criteria: history of disorders (urinary tract infection, testicular atrophy, testicular torsion, azoospermia, asthenospermia, inguinal and genital surgery, genital trauma, and other genital diseases, such as current genital inflammation and cryptorchidism), anatomical disorders, endocrinopathy, previous hormonal therapy, use of androgens, antiandrogens, anticoagulants, cytotoxic drugs, or immunosuppressants, patients with physiological and psychiatric disorders that could affect sperm and sexual performance, alcohol and drug abuse, and body mass index of ≥ 30 kg/m^2.
Interventions	Lycopene 25 mg oral once daily (n = 22)

Nouri 2019 *(Continued)*

	versus Placebo (n = 22) Duration of treatment: 12 weeks
Outcomes	Semen analysis, seminal TAC, MDA and glutathione peroxidase
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned, "convenience sampling"?
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients and the clinician that prescribed the supplements were blind to the treatment. In order to guarantee the blindness, lycopene and placebo were prepared similar in appearance."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/22 in lycopene and 3/22 in placebo group lost to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in methods are all reported. Protocol available (IRCT20171105037249N1). Depression mentioned in protocol not reported.

Nozha 2001

Study characteristics

Methods	Randomised comparative study Duration of study: unclear
Participants	Country: Tunisia Population: infertile males with OAT, N = unclear Mean age: unclear Inclusion criteria: males with OAT. Exclusion criteria: unclear
Interventions	Vitamin E 400 mg + Selenium 200 µg (n = 12) versus

Nozha 2001 *(Continued)*

	Vitamin B_2, B_6 and B_{12} (n = 8) Duration of treatment: 3 months
Outcomes	Seminal parameters
Notes	Abstract only Attempted to contact authors regarding methods of randomisation and data. No reply as yet (2014). No extractable data from the abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In a prospective randomised comparative study"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Omu 1998

Study characteristics

Methods	Randomised controlled open trial Duration of study: follow-up 12 months
Participants	Country: Kuwait Population: men with asthenozoospermia attending infertility and andrology clinic, N = 100 Mean age: treatment group 37.8 ± 7.9 years, control group 38.1 ± 8.2 years Inclusion criteria: men with asthenozoospermia, spermatozoa motility impaired with > 4 0% non-motile sperm, have been trying to conceive for at least one year plus no obvious female factor Exclusion criteria: none mentioned
Interventions	Zinc 500 mg (n = 49)

Omu 1998 *(Continued)*

	versus No treatment (n = 48) Duration of treatment: 3 months
Outcomes	Sperm parameters
Notes	Attempted to contact authors regarding methods randomisation and concealment questioned. No reply as yet (2014). Data on sperm count/motility not used; only percentage of increase/decrease given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	100 men randomised, 97 analysed, dropouts are not accounted for
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Omu 2008

Study characteristics

Methods	Randomised controlled open trial Duration of study: unclear
Participants	Country: Kuwait Population: men with asthenozoospermia attending infertility clinic in Kuwait, N = 45 Mean age: 35 ± 1 years Inclusion criteria: asthenozoospermia with normal sperm concentration (20 to 250 million/mL) but with 40% or more immotile sperm Exclusion criteria: asthenozoospermia but sperm concentration of < 20 million/mL

Omu 2008 *(Continued)*

Interventions	Zinc 400 mg (n = 11) versus Zinc 400 mg + Vitamin E 20 mg (n = 12) versus Zinc 400 mg + Vitamin E 20 mg + Vitamin C 10 mg (n = 14) versus No treatment (n = 8) Duration of intervention: 3 months
Outcomes	Sperm parameters
Notes	Attempted to contact author regarding methods of randomisation, it states that quote: "8 men served as non- therapy control". No reply as yet (2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is another antioxidant or no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes are reported. No dropouts
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Peivandi 2010

Study characteristics

Methods	Randomised double-blind cross-over trial Duration of study: unclear, from 2005 to 2006
Participants	Country: Iran

Peivandi 2010 *(Continued)*

	Population: infertile men, N = 30 Mean age: 29.5 (SD 5.48) years Inclusion criteria: at least two abnormal spermograms based on WHO criteria with a two-week interval during four weeks, normal range of gonadotropins, testosterone an prolactin concentrations Exclusion criteria: variocoele, testicular atrophy, ejaculatory disorders, use of medications, azoospermia, endocrinological disorders, ICSI candidacy or other causes of infertility
Interventions	L-carnitine 2 g (n = 15) versus Placebo (n = 15) Duration of treatment: 8 weeks, washout period of 8 weeks, changed intervention and use for 8 more weeks
Outcomes	Sperm parameters
Notes	Abstract in English, full text in Arabic. Contacted the author and he is filling out the data extraction sheets. Author responded but data queries remain contacted again re SDs and pregnancies in first phase of cross-over. Author responded saying that the data were given in SDs and there were 3 pregnancies in the first phase 2018: added data on progressive motility for first phase (2 months).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Low risk	Quote: "sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "outcome assessor was blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "loss to follow up was not accounted for"
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Popova 2019

Study characteristics

Popova 2019 *(Continued)*

Methods	Comparative, randomised, prospective, controlled study Duration of study: unclear
Participants	Country: Russia Population: men aged 25 to 45 years planning an ART program, N = 80 Mean age: 34 ± 3.2 years Inclusion criteria: • No pregnancy despite having frequent, unprotected sex for > 12 months. • Abnormal sperm quantity and quality (oligo-,asteno- and/or teratozoospermia) • Absence of inflammatory changes in accessory glands of the reproductive system • Absence of varicocele and other conditions having negative impact on spermatogenesis • Absence of immunity associated infertility (MAR-test IgG <10%) • Absence of somatic pathologies Exclusion criteria: • Established genetic causes of infertility (Klinefelter's syndrome, AZF microdeletions, CFGR); • Azoospermia, • Pyospermia, • Secretory disorders (inadequate production of FSH); • The presence of an immune form of infertility (MAR-test lgG > 10%) • Severe somatic pathology; • Psychosexual and ejaculatory dysfunction.
Interventions	Androdoz (4 capsules contain: l-arginine 720 mg, l-carnitine 240 mg, l-carnosine 92 mg, coenzyme Q10 10 mg, glycyrrhizic acid 6 mg), oral, 2 capsules twice daily (n = 60) versus No treatment (n = 20) In both groups patients were also treated with ART. Duration of treatment: 3 months
Outcomes	Spermiogram, sperm hyaluronan binding assay (HBA), clinical pregnancy, adverse events
Notes	Article in Russian, translated by Alyona Oryshchuk. E-mailed authors Dr. Ovchinnikov (r_ovchinnikov@oparina4.ru) to request additional information on RoB, definition of pregnancy outcome and results of all semen parameters. Reply on 18-05-2021: "It was computer randomized block design (the adaptive dynamic randomization with stratification)." “No one in this study was lost to follow-up.” “All reported pregnancies in this study were confirmed by ultrasound.” From e-mail: outcome assessors were blinded and allocation was concealed. Data on sperm parameters (total sperm motility, progressive motility, concentration) used for data analysis.
Risk of bias	

Popova 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from e-mail): "It was computer randomized block design (the adaptive dynamic randomization with stratification)."
Allocation concealment (selection bias)	Low risk	From e-mail, see notes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From e-mail, see notes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote (from e-mail): “No one in this study was lost to follow-up.”
Selective reporting (reporting bias)	High risk	Not all outcomes are reported, results on semen parameters are missing.

Pourmand 2014

Study characteristics	
Methods	Randomised trial with add-on intervention Duration of study: unclear
Participants	Country: Iran Population: men with male factor infertility and varicocele, N = 100 Mean age: treatment group 26.73 ± 6.25 years, control group 27.52 ± 5.23 years Inclusion criteria: left-sided clinical or subclinical varicocele plus one of these factors: primary infertility, secondary infertility, or impaired semen analysis. Exclusion criteria: right- sided isolated varicocele, bilateral varicocele, and each side varicocele that did not decompress in lying position, or any medical or surgical history of male factor infertility - Medical: opium or drug abuse, any prior medical treatment for infertility, recurrent urinary tract infection, sexually transmitted disease, prostatitis, mumps in childhood, epididymo-orchitis, and so forth - Surgical: cryptorchidism, orchiopexy, prior varicocelectomy repair, inguinal hernia repair, other inguinal surgeries, and so forth
Interventions	L-carnitine 750 mg (n = 50) versus No treatment (n = 50) Duration of treatment: 6 months, after varicocelectomy

Pourmand 2014 *(Continued)*

Outcomes	Sperm parameters, DNA damage (TUNEL, PDA test), adverse effects
Notes	Email sent to last author Noori (m_noori560@yahoo.com) on 06.03.2018: Asked about the SD's for sperm motility (A+B%), concentration and DNA fragmentation. Asked about allocation concealment and blinding of outcome assessment. Reminder email sent to Noori and Pourmand (n.pourmand@yahoo.com) on 22.03.2018. Only data on adverse events used. No reply to date (19.04.2018).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomization was performed for controlling less probable variation in varicocelectomy technique or surgeon within the time of study" Not specified how block randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group is no treatment after varicocelectomy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	See appendix, none lost to follow-up
Selective reporting (reporting bias)	Unclear risk	All the outcomes from the aim of the study and methods were reported. No protocol available.

Poveda 2013

Study characteristics

Methods	Randomised double-blind placebo-controlled trial Duration of study: from January 2012 to March 2013
Participants	Country: Panama Population: infertile healthy men, N = 60 (quote: "60 patients completed the study", how may were randomised?) Mean age: unclear Inclusion criteria: infertile healthy men without previous treatments, non smokers, no alcoholics or drug users Exclusion criteria: varicocele and leukocyte-spermia were excluded
Interventions	L-carnitine 1 g/12 hours (n = ?)

Poveda 2013 *(Continued)*

	versus Spermotrend (Catalysis) 1 x /8 hours (n = ?) versus Maca extract 1 g/12 hours (n = ?) versus Placebo 1x/12 hours (n = ?) Duration of treatment: 13 weeks
Outcomes	Sperm motility, sperm concentration, normal sperm morphology
Notes	Conference abstract only. Letter written and posted regarding methods and data 12.02.2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Pryor 1978

Study characteristics

Methods	Randomised double-blind cross-over trial Duration of study: unclear
Participants	Country: UK (two centres) Population: men with severe oligozoospermia, N = 64 Mean age: unclear

Pryor 1978 *(Continued)*

	Inclusion criteria: sperm count of less than 10 million per ejaculate on each of 2 occasions immediately preceding the trial, no uncorrected varicoceles or testicular maldescent, testicular biopsy already performed (Johnsen 1970), no drugs taken in past 3 months which were known to affect spermatogenesis, no history of biliary disease owing to a suggestion that arginine might interfere with the metabolism of bile salts, the wives of all these men had been fully investigated with regard to fertility Exclusion criteria: men with varicocoele
Interventions	Arginine 4 g (n = 35) versus Placebo (n = 29) Duration of treatment: 12 weeks, than cross-over without intervening wash-out period
Outcomes	Total sperm motility, hormone levels
Notes	No data available for sperm parameters. Unable to contact author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 participants withdrew reasons were given but unsure from which group, the paper stated that they used ITT but data not presented. The study did not report the outcomes for the different phases of the trial (i.e. not separated into phase 1 phase 2). Pregnancy data are separated into phase one data but probably biochemical and will be used in biochemical pregnancy table.
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. Pregnancy not stated in the methods section as an outcome of interest but reported in the results. No protocol available.

Raigani 2014

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: unclear

Raigani 2014 *(Continued)*

Participants	Country: Iran Population: men from infertile couples with proved male factor infertility, N = 83 Mean age: unclear Inclusion criteria: infertile men (OAT) with sperm concentrations of < 20 x 10^6 mL^{-1}, sperm motility < 50% (grades a, b, c) and sperm normal morphology < 30% Exclusion criteria: unclear
Interventions	Folic acid 5 mg + Placebo (n = 20) versus Folic acid 5 mg + Zinc sulphate 220 mg (n = 21) versus Zinc sulphate 220 mg + Placebo (n = 24) versus Placebo + Placebo (n = 18) Duration of treatment: 16 weeks
Outcomes	Sperm concentration, motility (grade A+B+C), morphology, sperm viability, sperm mitochondrial function, sperm chromatin status (DNA damage measured by staining methods), semen and blood folate/zinc/B12, total antioxidant capacity (TAC) and malondialdehyde (MDA) concentration
Notes	Trial registration: IRCT138706091079N2 Email sent to last author Sadeghi (Sadeghi@avicenna.ac.ir) on 06.03.2018 to ask about the mean age, exclusion criteria, if there are means+SD instead of medians of the sperm concentration and sperm motility, randomisation process, dropouts/lost to follow-ups Reminder email sent to Sadeghi on 22.03.2018. No reply to date (19.04.2018). Data on DNA fragmentation used (means+SD). Other sperm parameters are provided as median+IQR and were therefore converted to mean+SD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated into four treatment groups with different supplementations."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blinded". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Semen analysis and sperm function assays were assessed individually and blindly by two laboratory experts"

Raigani 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	Reported all the outcomes from the methods and protocol; trial registration (IRCT138706091079N2)

Rolf 1999

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: 8 weeks
Participants	Country: Germany Population: men with infertility for over one year, N = 33 Mean age: treatment group 36.1 ± 5.0 years, control group 35.2 ± 4.8 years Inclusion criteria: asthenozoospermia (< 50% motile) diagnosed after 2 examinations, normal or reduced sperm concentration (> 20 x 10^6 per ejaculate) and without infection of access glands Exclusion criteria: unclear
Interventions	Vitamin C 1000 mg + Vitamin E 800 mg (n = 15) versus Placebo (n = 16) Duration of treatment: 8 weeks
Outcomes	Primary: sperm parameters Secondary: pregnancy rate and adverse effects
Notes	Power calculation performed. Contacted author about the allocation concealment and pregnancy and adverse effects were outcomes in their protocol. Author Rolf replied saying that pregnancy and adverse effects were stated in the protocol 2018: progressive forward motility instead of total motility, data total sperm motility moved to outcome progressive sperm motility

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with random numbers without further stratification by the pharmacist and the code was withheld from researchers and patients"
Allocation concealment (selection bias)	Unclear risk	Pharmacist performing randomisation and code withheld from patients and researchers. However no mention of type of containers or envelopes

Rolf 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind - patients and researchers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported, 2 patients withdrew from the trial: quote: "results from two patients were rejected from analysis." 1 from the treatment group due to poor compliance and 1 from the placebo group due to genital tract infection. No ITT
Selective reporting (reporting bias)	Unclear risk	All semen outcomes reported and author states (e-mail 22.09.09) that pregnancy and adverse effects were set a priori in the protocol. No protocol available.

Saeed Alkumait 2020

Study characteristics	
Methods	Randomized placebo-controlled clinical trial Duration of study: from January 2016 to December 2018
Participants	Country: Iraq Population: infertile male participants, N = 151 Mean age: 32.2±10.2, 31.4±11.6 and 30.1±7.6 in the coenzyme Q10, glutathione and placebo group respectively Inclusion criteria: normal female factor with idiopathic OAT Exclusion criteria: with a chronic disease like mumps, hydrocele, neoplasm, trauma from prolonged riding, hypospadias, vas deferens obstruction, varicocele, and genital tract infection were excluded from this study, also those who received treatment recently.
Interventions	Coenzyme Q10 200 mg orally, frequency not mentioned (n = 50) versus Glutathione 250 mg orally, frequency not mentioned (n = 51) versus Placebo (oral sugar sachets) (n = 50) Duration of treatment: 6 months
Outcomes	Semen parameters
Notes	Data on semen parameters provided as percentage improvement. Email sent to first author (malkumait@yahoo.com) several times. No reply to date (03-09-2021).
Risk of bias	

Saeed Alkumait 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned if sachets look identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients randomised to placebo group not mentioned in methods section.
Selective reporting (reporting bias)	High risk	Baseline characteristics not mentioned in outcomes table (marriage time, job type, social habits). Only % of improvement reported. No protocol available.

Safarinejad 2009

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: 56 weeks
Participants	Country: Iran Population: men with idiopathic oligoasthenoteratospermia, asthenospermia or teratospermia of 2 years duration, N = 468 (548 recruited) Mean age: 31 (25 to 48) years Inclusion criteria: sperm count > 5 x 10^6 /mL, over 2 years of failed conception, no female fertility problems, no history of possible cause for male infertility Exclusion criteria: abnormal testes, history of cancer or chemotherapy, testosterone or antiandrogen use, use of selenium or N-acetylcystine supplements, abnormal hormone levels, genital disease, genital inflammation or variocoele, history of genital surgery, major surgery, central nervous system injury, a known sperm defect or retrograde ejaculation. Y chromosome abnormalities, sexually transmitted disease, genitourinary infection, leukocytospermia, smoking, any environmental exposures to reproductive toxins. Medical, neurological or psychological problems. A history of drug or alcohol abuse, hepatobiliary disease or significant renal insufficiency. Any endocrine abnormality, a b BMI of 30 kg/m^2 or over, participation in another investigational study and a likelihood of being unavailable for follow-up
Interventions	Selenium 200 µg (n = 116) versus N-acetylcysteine (NAC) 600 mg (n = 118) versus

Safarinejad 2009 *(Continued)*

	Selenium 200 µg + N-acetylcysteine (NAC) 600 mg (n = 116) versus Placebo (n = 118) Duration of treatment: 26 weeks or 6.5 weeks
Outcomes	Primary outcome: sperm parameters Secondary outcomes: spontaneously reported adverse events
Notes	Power calculation performed. Attempted to contact authors regarding side effect data that had not yet been added to the review due to the query of multiple comparisons. Also to ask whether data are in SD (as reported in the text) or SE, as requested by statistician 24.09.2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation table generated by the method of random permuted blocks. Patient randomisation numbers were allocated to each site in ascending sequence in blocks."
Allocation concealment (selection bias)	Low risk	Quote: "Assignment to treatment groups was performed using a sealed envelope technique."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Eligible patients were randomly assigned to double blind.." Quote: "Placebo pills were coated with titanium oxide to ensure an identical appearance and smell."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed: n = 105 in selenium group (loss 11), n = 106 in placebo group (loss 12), n = 105 in N-acetylcysteine group (loss 13) and n = 104 in selenium + N-acetylcysteine group (loss 12) All withdrawals were accounted for in each treatment group. Withdrawal was mainly due to withdrawal of consent followed by lost to follow-up and lastly for reasons of missing data. No ITT
Selective reporting (reporting bias)	Unclear risk	The published report includes all expected outcomes. No protocol available.

Safarinejad 2009a

Study characteristics

Methods	Randomised double-blind controlled trial Duration of study: from February 2005 until October 2006, follow-up 14 months
Participants	Country: Iran

Safarinejad 2009a *(Continued)*

	Population: infertile men with idiopathic oligoasthenoteratospermia, N = 212 (recruited 268) Mean age: treatment group 28 ± 9 years, placebo group 28 ± 10 years Inclusion criteria: minimum 2 years unprotected intercourse with 2 years unwilling childlessness. male infertility diagnosed if 1 or more standard semen parameters were below cutoff levels accepted by WHO. A fertile female partner. No known medical condition that could account for infertility, testicular volume 12 mL or greater. No medical therapy for at least 12 weeks before the study begins. Only patients seeking medical attention for infertility were included Exclusion criteria: azoospermia or severe oligospermia (sperm count less than 5 million/mL. An history of epypidymo-orchitis, prostatitis, genital trauma, testicular torsion, inguinal or genital surgery. Any genital or central nervous system disease, endocrinopathy, cytotoxic drugs, immunosuppressants, anticonvulsives, androgens, antiandrogens, a recent history of Sexually transmitted disease. Psychological or physiological abnormalities that would impair sexual functioning or ability to produce sperm samples. Drug, alcohol or substance abuse. Liver disease, renal insufficiency or chromosome abnormalities. occupational and environmental exposures to reproductive toxins. A BMI of 30 kg/m^2 or over, participation in another investigational study and a likelihood of being unavailable for follow-up
Interventions	Coenzyme Q10 (CoQ10) 300 mg (n = 106) versus Placebo (n = 106) Duration of treatment: 26 weeks or 6.5 months
Outcomes	Primary outcomes: sperm parameters and testicular volume Secondary outcomes: adverse effects and hormone levels
Notes	Power calculation performed. Attempted to contact authors to ask whether data is in SD (as reported in the text) or SE, as requested by statistician 24.09.2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each eligible patient received a randomisation number, which was determined by a computer generated schedule. Therafter a randomisation table was generated by the method of random permuted blocks. Individuals who were geographically and operationally independent of the study investigator performed the study randomisation"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The clinician prescriber and the patients were blinded to the treatment condition. To maintain and guarantee blinding CoQ10 and placebo were identical in appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participant data collected during this trial were kept confidential and locked in a secure office area. Randomisation codes were opened only after all patients had completed the whole study protocol."

Safarinejad 2009a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who dropped out of the trial were accounted for - 8 from treatment group and 10 from placebo group for reasons such as withdrawal of consent, missing data and loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Safarinejad 2011b

Study characteristics	
Methods	Double-blind randomised study Duration of study: January 2007 to June 2008
Participants	Country: Iran Population: men with primary infertility and idiopathic oligoasthenoteratospermia, N = 238 Mean age: treatment group 32 ± 9 years, placebo group 32 ± 10 years Inclusion criteria: unwanted childlessness of at least 24 months with same female partner; no known medical condition that could account for their infertility; and total testicular volume ≥ 12 ml. The female partner had to be diagnosed normal. Exclusion criteria: patients who were determined to have abnormal testes, cryptorchidism, varicocele and genital surgery via physical examination and clinical testing were excluded. Y chromosome deletions, abnormal karyotypes; patients with azoospermia or any hormonal abnormality; a history of use of cancer chemotherapy, testosterone, anti-androgens or anti-oxidants; tobacco use; concomitant medical problems known to be associated with diminished fertility; hepatobiliary disease; significant renal insufficiency; body mass index (BMI) ‡ 30 and occupational and environmental exposures to potential reproductive toxins.
Interventions	Omega-3 (DHA 1.12 g and EPA 0.72 g / day) (n = 119) versus Placebo (with 1% fish oil) (n = 119) Duration of treatment: 32 weeks (after a 5 week wash-out period)
Outcomes	Sperm parameters, fatty acid composition of red blood cells, spermatozoa and seminal plasma, seminal plasma antioxidant status, adverse events
Notes	Power calculation performed. Adverse events not added to gastrointestinal upsets, risk to count doubles. Attempted to contact author for data.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation table was generated by the method of random permuted blocks [...]. The randomisation process was carried out by another member of staff independent of the study and blind to the assessment."

Safarinejad 2011b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "matching placebo", "The placebo was corn oil, selected as it minimally alters the fatty acid composition of the typical diet. To preserve the double-blind status in the proposed study, a small amount of fish oil (1%) was added to the placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	106/119 in omega-3 group and 105/119 in placebo group completed 32 weeks study period, reasons for all dropouts are provided, ITT.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available.

Safarinejad 2012

Study characteristics	
Methods	Randomised controlled trial Duration of study: from June 2010 to January 2011
Participants	Country: Iran Population: infertile men with primary infertility for at least 2 years, N = 228 Mean age: treatment group 31 years, control group 32 years Inclusion criteria: history of primary infertility of more than 2 years, abnormal sperm count and motility according to WHO criteria, wife age between 20 and 40 years, documentation of fertile female partner, no known medical or surgical condition which can result in infertility Exclusion criteria: history of cancer chemotherapy or radiotherapy, history of genital disease such as cryptorchidism and varicocoele, history of genital surgery, BMI 30 kg/m^2 or greater, any endocrinopathy, Y chromosome microdeletion or karyotype abnormalities, leukocytospermia (more than 106 WBC per mL), drug, alcohol or substance abuse, tobacco use, use of anticonvulsants, androgens or antiandrogens, significant liver (serum bilirubin greater than 2.0 mg/dL) or renal function (serum creatinine greater than 2.0 mg/dL) impairment, occupational and environmental exposure to reproductive toxins, severe oligozoospermia (less than 5 x 10^6 /mL), azoospermia and testicular volume less than 12 mL
Interventions	Coenzyme Q10 (Ubiquinol) 200 mg (n = 114) versus Placebo (n = 114) Duration of treatment: 26 weeks
Outcomes	Sperm volume, sperm density, sperm motility, sperm morphology, seminal plasma antioxidant status
Notes	Power calculation performed

Safarinejad 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	The randomisation codes were centrally assigned by the co-ordination centre after checking the main eligibility criteria
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators and study staff were blinded to treatment allocation during the whole study period, All of the participants were naive for treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators and study staff were blinded to treatment allocation during the whole study period, All of the participants were naive for treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	228 were randomised of 264 eligible Ubiquinol group – 13 excluded at end of treatment (3 protocol violations, 4 withdrawal of consent and 6 lost to follow-up). At 12 weeks follow-up a further 5 were lost to follow-up Placebo group – 12 excluded at end of treatment (4 protocol violations, 4 withdrawal of consent, 6 lost to follow-up. At 12 weeks follow-up a further 7 were lost to follow-up
Selective reporting (reporting bias)	High risk	The authors do not pre-specify which outcome measures will be reported. The primary outcome is a % change from baseline at the end of the treatment period

Schisterman 2020

Study characteristics

Methods	Multicentre, double-blind, block-randomised, placebo-controlled clinical trial
Participants	Country: USA Population: male partner of couples planning infertility treatment, N = 2370 Mean age: 32.5 ± 5.7 years (intervention group) and 32.7 ± 6.0 years (placebo group) Inclusion criteria: men aged ≥18 years and women aged 18-45 years, recruitment also included couples planning ovulation induction and IUI Exclusion criteria: couples were ineligible if they were planning use of donor sperm or a gestational surrogate, were pregnant at enrolment, or if the male had obstructive azoospermia or other known infertility causes unlikely to benefit from supplementation. Men were instructed to abstain from dietary supplements containing folic acid or zinc, as well as medications known to interact with folic acid or zinc. Men with poorly controlled chronic diseases (e.g. heart disease, diabetes, hypertension, cancer) were excluded. Men were excluded initially for anaemia (haemoglobin concentration <13 g/dL) using a point-of-care haemoglobin meter to avoid enrolling men with vitamin B12 deficiency. After October 30, 2015, men

Schisterman 2020 *(Continued)*

	with haemoglobin concentrations less than 13 g/dL were enrolled, with a follow-up serum vitamin B12 and methylmalonic acid measurement.
Interventions	Folic acid 5 mg + zinc 30 mg oral daily (n = 1185) versus Placebo (n = 1185) Duration of treatment: 6 months, a minimum of 4.5 to 6 weeks before the ovulatory phase of the first infertility treatment cycle.
Outcomes	• Live birth rate, • Semen parameters, • Pregnancy (beta HCG detected pregnancy, clinical pregnancy, ectopic pregnancy, early pregnancy loss, multiple gestation), • Pregnancy outcomes (caesarean delivery, preeclampsia, gestational diabetes, gestational age at delivery, preterm birth, birth weight, small for gestational age, severe postpartum maternal morbidity (including post-partum haemorrhage, anaemia requiring transfusion, sepsis, seizure, HELLP syndrome, pre-eclampsia with pulmonary oedema), major neonatal complications (including structural malformations, chromosomal anomalies, bronchopulmonary dysplasia, necrotizing enterocolitis, severe intraventricular haemorrhage, periventricular leukomalacia, and retinopathy of prematurity), still birth, neonatal death.) • Embryonic development parameters (in IVF stratum): fertilisation rates and method, number of cells and embryo morphology on day 3 and day 5, number and proportion of good quality embryos on day 5, number and quality of embryos transferred, number of embryos cryopreserved, and sperm penetration assay results. When available, information regarding the chromosomal complement of embryos was assessed. • Reproductive hormones and other biomarkers • Adverse events
Notes	Power calculation provided. Only data used from supplementary eTable 3, with data of a subgroup “restricted to men with known male factor infertility or poor semen quality at baseline”. Male factor infertility diagnosis was self-reported. E-mailed author Dr. Schisterman (schistee@mail.nih.gov) on 02-06-2021 to request data on pregnancies in the “male factor infertility” subgroup. No reply to date (03-09-2021). Some participants used multivitamins within 3 months of enrolment in the trial (40% in the intervention group, 38% in the placebo group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computerized randomization algorithm"
Allocation concealment (selection bias)	Low risk	Quote: "... permuted block design with block sizes of 2, 4, or 6 (in random order) within each infertility treatment stratum and study site and was implemented by blinded study coordinators."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, trial staff, and investigators were blinded to treatment throughout the trial."

Schisterman 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, trial staff, and investigators were blinded to treatment throughout the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	315/1185 lost to follow-up in intervention group, 282/1185 lost to follow-up in placebo group, "missed six month visit". Sample not collected for semen analysis and DNA fragmentation in 76/870 in intervention group, 68/903 in placebo group. Additional exclusions for morphology, TMSC and DNA fragmentation assessment due to "Insufficient quantity or quality". All patients included in primary analysis of live birth rate.
Selective reporting (reporting bias)	High risk	Progressive motility, reproductive hormones and biomarkers not reported. Protocol available (NCT01857310).

Scott 1998

Study characteristics	
Methods	Randomised double-blind trial Duration of study: 3 months and two weeks
Participants	Country: UK Population: men attending subfertility clinic with low sperm motility, N = 64 (recruited N = 69) Mean age: 33.3 ± 0.64 years Inclusion criteria: low sperm motility Exclusion criteria: not mentioned
Interventions	Selenium 100 µg (n = 16) versus Selenium 100 µg + Vitamin A 1 mg + Vitamin C 10 mg + Vitamin E 15 mg (n = 30) versus Placebo (n = 18) Duration of treatment: 3 months
Outcomes	Primary outcome: sperm parameters Secondary outcome: pregnancy rates
Notes	Uneven numbers, multivitamin numbers are double the other groups Asked author if they have separate numbers for pregnancy data. Currently have 5 pregnancies in the 2 treatment groups and none in placebo Furthermore; who was blinded, was the placebo identical when group 2 contained so many different vitamins. Was there any allocation concealment? Author has retired and is not able to be contacted. Data not added to table 'data for undefined or biochemical pregnancy'

Scott 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "As the patients entered the trial they were randomly allocated to one of three treatments, which had in turn been randomised within each block of four numbers and 'blinded' using a numeric code." Unclear as to why the uneven nature of the numbers in the groups i.e. 30 in multivitamin group and 16 in selenium, 18 in placebo
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of withdrawals and reasons (non compliance) were reported
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Sharifzadeh 2016

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: from March 2015 to November 2015
Participants	Country: Iran Population: Idiopathic subfertile men, N = 114 Mean age: Inclusion criteria: Idiopathic subfertile male with sperm rates 5 - 20 million cells/mL, and according to failure of female to conceive after one year regular and unprotected intercourse Exclusion criteria: chromatically fertility disorder (Y chromosome deletions), use of zinc three months before recruitment
Interventions	Zinc sulphate 10 mL solution of 0.5% (n = 61) versus Placebo 10 mL (n = 53) Duration of treatment: 3 months

Sharifzadeh 2016 *(Continued)*

Outcomes	Sperm parameters, side-effects, serum and semen plasma levels of zinc
Notes	Trial registration: IR.IUMS.REC.1394.26155 Email sent to second author Norouzi (sr.norouzi@yahoo.com) on 06.03.2018 to ask if they can provide mean+SD instead of median, and if the motility is total motility or progressive motility. Reply on 11.03.2018: "yes we use SD for motility and total concentration, for both of them instead of a median. Motility means group A+ B (progressive motility)" New email on 12.03.2018 to ask if they can then provide mean + SD. Reply on 04.04.18 answering "In this study we used the SPSS software (SPSS, Inc., Chicago, IL, USA, version 20) for statistical analyses. After normality testing confirmed by Shapiro-wilk test, quantitative data were reported as mean ± SD. Unfortunately there are some spelling and statistical errors in the final version of article. In the review process, some changes have been made in the manuscript and subtitle of the tables have been deleted. So all outcome are Mean ± SD."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In the current study males were divided into groups A and B by block randomized sampling." Quote: "sub fertile males were assigned according to a simple computer schedule into two groups to receive zinc sulfate or placebo."
Allocation concealment (selection bias)	Low risk	Quote: "Solutions were coded from 1 to 120 according to the randomization list by hospital pharmacy. Each code was given to one participant to receive one container of solution that according to their group called participates took zinc sulfate (0.5) or placebo."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind" Quote: "Containers of zinc solution and placebo were similar, and all of them had zinc syrup label. The secretary of infertility unit did not know about the box content and patients by showing their groups label could receive the medicine."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "seven subjects in the zinc group withdrew because of adverse gastrointestinal side effects, and three subjects in the zinc group and four subjects in the placebo group withdrew because of lack of motivation" Dropouts accounted for and reasons mentioned. No ITT
Selective reporting (reporting bias)	Low risk	Reported all the outcomes from the methods section and according to the protocol: trial registration (IR.IUMS.REC.1394.26155)

Sigman 2006

Study characteristics

Methods	Randomised double-blind trial

Sigman 2006 *(Continued)*

	Duration of study: 24 weeks, follow-up unclear
Participants	Country: USA Population: infertile men aged 18 to 65 years, N = 26 Mean age: 36.2 ± 5.8 years, 35.3 ± 7.5 years Inclusion criteria: males 18 to 65 years with infertility of at least six months duration, sperm concentration of at least 5 million sperm/mL, motility of 10% to 50%, absent pyospermia and normal FSH and testosterone levels Exclusion criteria: history of post-pubertal mumps, cryptorchism, vasal or epididymal surgery, history of medication or chemotherapy. recent alcohol, chronic marijuana. Use of testosterone or steroids. Exposure to environmental toxins. Recent history of fever or diabetes, liver failure, renal failure, endocrine disorder, untreated variocoele, urogenital infection, or prior vasectomy reversal
Interventions	L-carnitine 2000 mg + L-acetylcarnitine 1000 mg (n = 12) versus Placebo (n = 9) Duration of treatment: 4 months
Outcomes	Primary outcome: sperm parameters Secondary outcomes: pregnancy rate
Notes	Author replied 21.09.2009 saying: Quote "The published 2006 trial is the published version of the 2003 abstract (Pryor 2003)" and giving details of randomisation and concealment. Author says he will try and find out about the 5 patients that dropped out. Why did - "5 additional patients entered the study but dropped out before completion" - when did these patients enter and were they randomised? Quote: "One of these 5 dropped out because of pregnancy three months after starting carnitine" Pryor paper excluded as it is the same study as Sigman, author also gave details of randomisation and allocation concealment, author will try to find info on 5 patients who dropped out.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to receive carnitine or placebo" Quote: "The randomisation was done by a third party a company that oversaw the trial. We sent the patient number of new recruited patients in to them, they assigned them a study number that was associated with a collection of medication/placebo." The author replied to randomisation query 23.09.09 saying that the protocol stated that - "treatments will be assigned randomly to a subject number. The numbers will range from 1-84 for study centre 1 and 85-168 for study centre 2. Randomisation of treatments for each centre will be done independently. One half of subject numbers will be placebo, the other half, active ingredient."
Allocation concealment (selection bias)	Low risk	Quote: "The investigators and study sites had the study medication/placebo packets identified by number only. They were blinded to what was in the medication/placebo packets. We were sent the code at the conclusion of the trial." The author replied to a query on allocation concealment on 23.09.09 saying that the protocol stated that - " Integrated Data Solutions, Inc. will keep the randomisation code in a separate sealed envelope for each site until the end of

Sigman 2006 *(Continued)*

		the study. The randomisation lists will be provided to the packaging company for packaging of the packets into patient medication boxes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the investigators and the patient were blinded to the treatment arm assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "5 additional patients entered the study but dropped out before completion. One of these dropped out because of pregnancy three months after starting carnitine." Author replied to query re drop outs, quote: "I have data on one drop out at my site - the drop out occurred after randomisation to carnitine. The drop out occurred before the first follow-up study visit. The other four drop outs were from the other study site - I am trying to get that data for you" (23.09.09)
Selective reporting (reporting bias)	Unclear risk	All outcomes of interest were reported. No protocol available.

Sivkov 2011

Study characteristics	
Methods	Randomised controlled open-label trial Duration of study: unclear, from 2008 to 2009
Participants	Country: Russia Population: men with chronic prostatitis and abnormal fertility for more than 6 months, N = 30 Mean age: unclear, range 18 to 40 years
Interventions	Selznic (selenium + zinc + vitamins) (n = 15) versus Placebo (n = 15) Duration of treatment: 3 months
Outcomes	Sperm motility, sperm concentration
Notes	Article in Russian, translated by Vasya Vlassov. No SD available. Need to contact authors regarding methods, standard deviations, type of control and any pregnancy data. Author Vasya 17.02.14 saying that the control was placebo and SD's not given. Emailed the institution 18.02.2014 regarding methods and data, no reply as of 07.03.2013.

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

Sivkov 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	No allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Open labelled". However placebo used, might be a translation problem
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Sofikitis 2016

Study characteristics	
Methods	Randomised controlled trial Duration of study: unclear
Participants	Country: Greece Population: oligoasthenospermic infertile (OAI) men, N = 39 Mean age: unclear Inclusion criteria: unclear Exclusion criteria: unclear
Interventions	Avanafil 150 mg (n = 13) versus L-carnitine 1.5 g (n = 14) versus No treatment (n = 12) Duration of treatment: 12 weeks
Outcomes	Sperm parameters, length of sperm midpiece (LMP), outcome of hypoosmotic swelling test (%HPST), seminal plasma citrate concentration
Notes	Abstract only. Email sent to Dimitriadis (helabio@yahoo.gr) on 21.02.2018 to ask for data/full text, reply the same day from the author: Quote: "This work has not been published as a full paper".

Sofikitis 2016 *(Continued)*

New email sent on 26.02.2018 to ask if we could receive data (mean+SD) for the L-carnitine and placebo group.

Reminder email sent on 22.03.2018. No reply received to date (19.04.2018).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control is no treatment group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Unclear, only abstract available

Steiner 2020

Study characteristics

Methods	Multicentre, randomised clinical trial Duration of study: from December 2015 to December 2018, follow-up 6 months
Participants	Country: USA Population: male partner with at least one abnormal semen parameter on a semen analysis, N = 171 Median (IQR) age: 34.0 years (30.0-38.0) in intervention group and 34.0 years (30.0-37.0) in placebo group Inclusion criteria: heterosexual couples with at least 12 months of infertility were eligible. Male partners were 18 years of age or older with at least one abnormal semen parameter on a semen analysis in the preceding 6 months: sperm concentration ≤ 15 million/mL (oligospermia), total motility ≤ 40% (asthenospermia), normal morphology ≤ 4% (teratospermia), or DNA fragmentation ≥ 25%. Female partners were between 18 and 40 years of age with regular menstrual cycles (defined as 25 to 35 days in duration), evidence of ovulation (by biphasic basal body temperature, ovulation predictor kits, or luteal serum progesterone level ≥ 3 ng/ mL), and a normal uterine cavity with at least one patent fallopian tube. Women over the age of 35 had a normal ovarian reserve, defined as an early follicular phase follicle stimulating hormone (FSH) level of ≤10 IU/L, an anti-mullerian hormone (AMH) level of ≥ 1.0 ng/mL, or antral follicle count >10.

Steiner 2020 *(Continued)*

	Exclusion criteria: male partners were excluded if they had a sperm concentration <5 million/mL on the screening semen analysis or if they were taking fertility medication or testosterone. Men were required to refrain from taking any vitamins for 4 weeks before randomisation.
Interventions	Antioxidant formulation (500 mg of vitamin C, 400 mg of vitamin E, 0.20 mg of selenium, 1000 mg of L-carnitine, 20 mg of zinc, 1000 mg of folic acid, 10 mg of lycopene, and 2,000 IU of vitamin D) oral daily (n = 85) versus Placebo (n = 86) Antioxidant or placebo added to treatment with IUI with ovulation induction with Clomid. Duration of treatment: at least 3 months and up to 6 months
Outcomes	Live births, pregnancy (defined as a positive home pregnancy test), semen parameters, DNA fragmentation with SCSA test, adverse events, pregnancy loss, still birth, plasma vitamin levels
Notes	Power calculation provided. Only the change in semen parameters are reported. “Because we failed to reject the null hypothesis for the internal pilot, further enrolment in the trial was stopped based on the recommendation of the data and safety monitoring board; all enrolled couples completed the study protocol.” E-mailed authors anne.steiner@duke.edu and hao.huang@yale.edu to request outcome data expressed as mean+SD and data on clinical pregnancy rate. Reply on 18-03-2021 with requested data. Data from supplementary table 5 were used for “live births-as treated”- analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization scheme was generated using a computer-generated random number sequence in randomly varying blocks of four and six stratified by site and female age (<35 years andR35 years of age) with allocation 1:1 by the data-coordinating center through a Web-based, secured randomization service."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study medications were assigned in a double-blind fashion."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	18/85 in antioxidant group withdrawn (1 lost to follow up, 2 medication side effects, 6 no longer interested in participating, 4 unable to contact patient, 2 possible zika exposure, 1 moving out of the area, 1 not responding to Clomid, 1 other).

Steiner 2020 *(Continued)*

		9/86 in placebo group withdrawn (1 100% globozoospermia, 2 no longer interested in participating, 2 patient non-compliant to protocol, 1 patient and spouse separated, 1 unable to continue study due to personal constraints, 1 rest cycle needed due to right ovary cyst, 2 other). However in the results section there is additional missing data, reason are not mentioned.
Selective reporting (reporting bias)	High risk	Time to pregnancy not reported. Protocol available (NCT02421887).

Stenqvist 2018

Study characteristics	
Methods	Double-blind, randomised, placebo-controlled study Duration of study: from June 2015 to August 2016
Participants	Country: Sweden Population: men who had been referred for infertility – defined as at least one year of unsuccessful attempt to achieve pregnancy, in whom previously performed semen analysis showed DFI ≥ 25%, N = 79 Mean age: 38.0 ± 5.2 years (antioxidant group) and 37.3 ± 4.9 years (placebo group) Inclusion criteria: • Age: 18–50 years, • Non-smoking, • Not being treated with antihypertensive drugs, hormones, statins, psychotropic drugs or oral cortisone for the last six months, • No history of anabolic steroids use, • Not taking antioxidant supplementation for the last six months. Exclusion criteria: • Body mass index (BMI) ≥30, • FSH outside the normal range of 2–8 IU/L, • LH outside the normal range of 2–10 IU/L, • Testosterone < 10 nmol/L, • DFI <25% in a repeated semen sample
Interventions	Antioxidant supplement (vitamin C 30 mg, vitamin E 5 mg, vitamin B12 0.5 mcg, l-carnitine 750 mg, coenzyme Q10 10 mg, folic acid 100 mcg, zinc 5 mg, selenium 25 mcg), oral twice daily (n = 37) versus Placebo (maltodextrin, calcium carbonate, citric acid, steviol glycoside, flavours, beta-carotene and silicon dioxide), oral twice daily (n = 40) Duration of treatment: 6 months
Outcomes	Pregnancy (defined as positive urine test), adverse events, semen analysis, DNA fragmentation with SCSA
Notes	Power calculation is conducted prior to study.

Stenqvist 2018 *(Continued)*

E-mailed authors ameliestenqvist@icloud.com on 23-03-2021.

Reply on 24-03-2021 and 11-05-2021:

Tables with means and SDs of sperm concentration, total motility, progressive motility and DFI at the different time points, are provided.
"In total, 28 men in the placebo group and 29 men in the antioxidant group had abnormal semen parameters at baseline according to WHO 2010 criteria. Unfortunately, we do not have any data on pregnancy outcomes. We only have data if pregnancy occurred or not during the study period."

"Pregnancy was not our primary outcome, so we do not have any data on ultrasound. We defined pregnancy as positive urine test."

Pregnancy data not used due to biochemical pregnancy.

Data on sperm parameters adjusted from median+IQR to mean+SD for meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were pre-packed in identical boxes and numbered according to a randomization list, by the pharmaceutical company that supplied with the products."
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed from patients, health care providers, data collectors and researchers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled", "They were pre-packed in identical boxes...", "The allocation sequence was concealed from patients, health care providers, data collectors and researchers."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The allocation sequence was concealed from patients, health care providers, data collectors and researchers."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the remaining 77 men, 37 were randomized to antioxidant treatment and 40 to placebo. Two men missed three months visit, and two other men missed six months visit. The reason in all four cases was that the subjects, due to lack of time, missed the 2 days time window for the visit." Not clear to which group the patients belong.
Selective reporting (reporting bias)	Low risk	All outcomes reported. Protocol available. Pregnancies not mentioned in protocol.

Suleiman 1996

Study characteristics

Methods	Randomised double-blind controlled trial Duration of study: 6 months, follow-up unclear
Participants	Country: Saudi Arabia Population: asthenozoospermic men attending a fertility centre, N = 110

Suleiman 1996 *(Continued)*

	Mean age: treatment group 34.8 (27 to 52) years, control group 33.2 (22 to 45) years Inclusion criteria: asthenospermic (≥ 20 x 10^6 /mL). sperm motility ≤ 40%, normal sperm count, leucocyte concentration < 5%, normal fructose concentration, normal female Exclusion criteria: unclear
Interventions	Vitamin E 300 mg (n = 52) versus Placebo (n = 35) Duration of treatment: 6 months
Outcomes	Primary outcome: motility and MDA concentration Secondary outcome: live birth, pregnancy, miscarriage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Either 100mg vitamin E or a placebo was prescribed in a random double blind fashion". Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:"Double blinded". Placebo used. Quote: "If the semen sample improved and the patient's spouse became pregnant, the treatment was stopped; otherwise it was continued for 6 months. The placebo was given for 6 months" This could suggest that the investigators or clinicians had knowledge of whether the patients were in the placebo or antioxidant group, therefore this trial was rated as high risk.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	The exact dropout figures for each group is unclear. Quote: "A total of 110 patients were enrolled in the study, but some of the patients dropped out and some left the region and failed to continue. When the experiment was terminated, 52 patients were found to have taken vitamin E and 35 patients to have taken the placebo." Assuming the groups were equal initially then the placebo group lost 20 men and the intervention lost 3. A dropout rate of >20%
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the methods were reported in results. No protocol available.

Sun 2018

Study characteristics

Sun 2018 *(Continued)*

Methods	Randomised controlled trial Duration of study: from February 2017 to April 2018
Participants	Country: China Population: male infertility patients with low acrosin activity, N = 232 Mean age: 30.67 ± 0.39 years (L-carnitine group) and 31.36 ± 0.78 years (control group) Inclusion criteria: all the patients had conceived for more than 1 year after marriage without contraception; sexual life is normal; did not take any medication for 3 months before treatment. Exclusion criteria: cryptorchidism, genitourinary tract infection, endocrine disease, testicular dysplasia, varicocele, failure to receive treatment or funding as prescribed, patients with other systemic diseases. Semen exclusion criteria: oligoasthenospermia with sperm concentration <15 × 10^6 /mL and progressive motility < 32%
Interventions	L-carnitine 1 g, oral suspension three times daily (n = 173) versus Vitamin E (placebo) 100 mg, oral capsules 3 times daily (n = 59) Duration of treatment: 3 months
Outcomes	Semen analysis: sperm concentration and progressive motility, sperm acrosome activity
Notes	Article in Chinese, translated by Yue Wang, Yongchuan Gu, and Catherine Jia-yun Tsai. Ethical approval and informed consent not mentioned in text. Abstract mentions 180 patients in L-carnitine group, full report mentions 173. E-mailed author mahuagang@126.com on 06-05-2021 for additional data for Risk of Bias assessment. No reply to date (03-09-2021).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned, unclear if L-carnitine and placebo look identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 lost to follow-up, 11 did not take medication as indicated. Results for 156 patients in l-carnitine group and 56 in placebo group are reported, that means 21 patients missing. Unclear to which group the withdrawals belonged.

Sun 2018 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available.

Tremellen 2007

Study characteristics	
Methods	Randomised double-blind controlled trial Duration of study: 1.5 years, follow-up 13 weeks
Participants	Country: Australia Population: infertile men, couple undergoing IVF, N = 60 (recruited N = 82) Mean age: treatment group 37.1 ± 5.1 years, placebo group 35.5 ± 4.3 years Inclusion criteria: men with sperm samples showing oxidative stress and a significant level of DNA fragmentation (> 25% TUNEL positive) Exclusion criteria: female partner with diminished ovarian reserve or if the female partner is aged over 39 years
Interventions	Menevit (folate 0.5 mg + garlic 1000 mg + lycopene 6 mg + vitamin E 400 IU + vitamin C 100 mg + zinc 25 mg + selenium 26 µg + palm oil) (n = 40) versus Placebo (containing palm oil) (n = 20) Duraton of treatment: 3 months, prior to IVF cycle
Outcomes	Primary outcome: embryo quality Secondary outcomes: pregnancy, multiple pregnancy, fertilisation rate, side effects
Notes	Power calculation performed Associate Professor Tremellen provided live birth data in December 2014 "Only one pregnancy failed in the Menevit arm after 13 weeks (late miscarriage 19 weeks of male infant). All other pregnancies, including the twin pregnancies went on to live birth and all babies appear to be doing well from the records". There were three sets of twins in the combined antioxidants group and nil in the placebo group. Each twin pregnancy and live birth was counted as one event in the data analyses due to the protocol specifications of the review

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote:"The randomisation schedule was computer generated in blocks of six by Bayer Consumer Care Australia". Using a 2:1 ratio Quote: "There were no significant differences between the active and the placebo group in terms of important baseline prognostic characteristics..."
Allocation concealment (selection bias)	Low risk	Quote: "the appropriately numbered bottles of capsules delivered to the clinical site without any participant knowing the treatment sequence. Patients

Tremellen 2007 *(Continued)*

		were allocated the next numerical treatment package (one to sixty as they became eligible for enrolment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind". Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All withdrawals were accounted for, 2 from the intervention group, 4 from placebo all due to the couples not going through to embryo transfer
Selective reporting (reporting bias)	Unclear risk	All specified outcomes are reported. No protocol available.

Tsounapi 2018

Study characteristics	
Methods	Randomised controlled trial Duration of study: unclear
Participants	Country: Greece Population: infertile men with idiopathic oligoasthenospermia with normal serum testosterone levels, N = 217 Mean age: unclear Inclusion criteria: unclear Exclusion criteria: unclear
Interventions	Profertil (content not mentioned in report, from www.profertil.eu: for 2 capsules: l-carnitine 440 mg, l-arginine 250 mg, coenzyme Q10 15 mg, vitamin E 120 mg, zinc 40 mg, folic acid 800 mcg, glutathione 80 mg, selenium 60 mcg), oral twice daily (n = 45) versus L-carnitine 1000 mg oral daily (n = 44) versus Profertil twice daily + avanafil 25 mg oral twice daily (n = 43) versus Avanafil 25 mg oral twice daily (n = 43) versus No treatment (n = 42) Duration of treatment: 90 days

Tsounapi 2018 *(Continued)*

Outcomes	Serum hormones (FSH, LH, testosterone), semen analysis, sperm capacity to undergo hyperactivation, hypo-osmotic swelling test, sperm DNA integrity with SCSA, zinc level in seminal plasma, clinical pregnancy
Notes	Obtainment of informed consent not mentioned in report. Data presented as mean + SD: “as we previously described Dimitriadis et al., 2010”. Number of drop-outs unclear. E-mailed author Dr. Sofikitis akrosnin@hotmail.com on 23-03-2021 and 04-05-2021. Sent e-mail to co-author Dr. Dimitriadis helabio@yahoo.gr on 28-05-2021. No reply to date (03-09-2021). Data on clinical pregnancies used except for the avanafil groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo control, different types of medication and frequency of intake.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only mentioned for seminal zinc level: "blind fashion and duplicates".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients not mentioned in results tables.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No protocol available.

Vinogradov 2019

Study characteristics

Methods	Randomised, multi-centre, double-blind, placebo-controlled study Duration of study: unclear
Participants	Country: Russia Population: infertile men, N = 109 Mean age: unclear Inclusion criteria: "diagnosis of infertility was made on the basis of absence of pregnancy during 1 year of regular sexual intercourse without contraception. All patients had one or more abnormal semen parameters" from e-mail.

Vinogradov 2019 *(Continued)*

	Exclusion criteria: • Immune infertility, viscosipathy • tumours, acute and chronic inflammatory diseases or antibiotic therapy over the last 3 months • oligospermia • necrozoospermia • varicocele (with or without its treatment over the last 3 months) • cryptorchidism and its treatment in anamnesis, hydrocele • genetic diseases
Interventions	Brudy plus (docosahexaenoic acid 350 mg, omega-3 fatty acids up to 500 mg, antioxidants (mixture of tocopherols) 0.45 mg), one oral tablet three times daily (n = 59) versus Vegetable oil, one oral tablet three times daily (n = 50) Duration of treatment: 90 days
Outcomes	Semen analysis, DNA fragmentation (assay unclear), mixed antiglobulin reaction(MAR)-test, cryotolerance test, electron microscopic analysis of spermatozoa
Notes	Full report available in Russian, translation by Alyona Oryshchuk. Ethical approval not mentioned in report. E-mailed author Dr. Zhivulko a.zhivulko@yandex.ru on 03-05-2021 requesting information on population. Reply on 05-05-2021: "Diagnosis of infertility was made on the basis of absence of pregnancy during 1 year of regular sexual intercourse without contraception. All patients had one or more abnormal semen parameters" E-mail 06-05-2021 requesting results of semen parameters (only data available on parameters after cryotolerance test).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed using envelopes. On the day of randomization, the investigator selected the lowest numbered randomization envelope. The patient was given a dietary supplement with the number indicated inside the envelope." Not mentioned how sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Generation of sequence not mentioned, so concealment is unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned

Vinogradov 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Due to the loss of follow-up with the patients and failure to appear for control tests, 4 patients were excluded from the study". From figure: 1 withdrawal in placebo group, 3 withdrawals in Brudy plus group.
Selective reporting (reporting bias)	High risk	No results on semen analysis, only results after cryotolerance test reported. No protocol available.

Wang 2010

Study characteristics	
Methods	Randomised controlled trial Duration of study: from August 2007 to August 2009
Participants	Country: China Population: infertile men with asthenozoospermia, N = 135 Mean age: unclear, range 23 to 26 years Inclusion criteria: male asthenozoospermia patients, aged 23 to 26 years old, with a history of infertility for about 1 to 10 years, and with no contraception measures after marriage at least 12 months, has normal sex life, the wife's fertility is normal., semen analysis for at least twice based on WHO criteria (Forward mobile sperm (a + b level) < 50%, and fast forward movement sperm (a level) < 25%, sperm density > 20 x 10^6 /mL), tests for peripheral blood chromosome and reproductive hormones (FSH, LH, PRL, T) were normal, the tests for semen ureaplasma mycoplasma and chlamydia trachomatis were negative, semen WBC < 1 x 10^6 /mL Exclusion criteria:cryptorchidism, testicular dysplasia, varicoceles, reproductive tract infection
Interventions	L-carnitine 2 g + Vitamin E (n = 68) versus Vitamin E (n = 67) Duration of treatment: 3 months
Outcomes	Pregnancy rates, adverse effects, % forward motile sperm, sperm density, % sperm normal morphology
Notes	Article in Chinese, translated by Liu Qi. E-mailed Qi (translator) regarding pregnancy and adverse event data, then may need to write to the authors. No reply to date. 2018: added data on progressive sperm motility

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A total of 135 patients with asthenozoospermia were randomly divided into Groups".

Wang 2010 *(Continued)*

		Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 dropouts. Numbers from each group are given but no reasons are provided for the withdrawals. ITT not used in the trial analysis
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Wong 2002

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial Duration of study: from July 1997 to August 1998
Participants	Country: the Netherlands Population: fertile and subfertile men, N = 103 (recruited subfertile N = 258) Mean age: 34.3 ± 3.9 years Inclusion criteria for subfertile group: failure of the woman to conceive after 1 year regular unprotected intercourse and sperm concentration of 5 to 20 million/mL Exclusion criteria for subfertile group: chromosomal disorders, cryptorchidism, vasectomy, use of folic acid or zinc supplements in the previous 3 months, vitamin B deficiency
Interventions	Folic acid 5 mg (n = 22) versus Zinc sulphate 66 mg (n = 23) versus Zinc sulphate 66 mg + Folic acid 5 mg (n = 24) versus Placebo (n = 25) Duration of treatment: 26 weeks
Outcomes	Sperm parameters

Wong 2002 *(Continued)*

Notes	Data in median and range. Use of fertile and subfertile men. Adjusted data to mean+SD for meta-analysis. Placebo arm split.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible fertile and subfertile men were randomly assigned according to a simple computer-generated randomisation schedule in four blocks to receive folic acid and placebo, zinc sulphate and placebo, zinc sulphate and folic acid, or placebo and placebo, which resulted in eight subgroups." "At the end of the trial, the research fellow received the randomisation list that matched the codes from the hospital pharmacy."
Allocation concealment (selection bias)	Low risk	Quote: "capsules were coded by the hospital pharmacy according to the randomisation list."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind" Quote: "Neither the research fellow and the participants knew whether the participants received folic acid, zinc sulphate or placebo capsules" Quote: "Folic acid and placebo capsules were yellow and identical in appearance. Zinc sulphate and placebo capsules were white and identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 men withdrew from the subfertile arm of the trial, 1 due to side effects (gastrointestinal) and 8 due to lack of motivation. It is unclear which treatment groups these men were randomised to
Selective reporting (reporting bias)	Unclear risk	Outcomes reported. No protocol available.

Zalata 1998

Study characteristics

Methods	Randomised pilot study Duration of study: unclear
Participants	Country: Belgium Population: men attending andrology clinic, N = 22 Mean age: unclear Inclusion criteria: unclear Exclusion criteria: unclear
Interventions	Acetyl-cysteine 600 mg (n = 5)

Zalata 1998 *(Continued)*

	versus Mixture of essential fatty acid (EFA) (DHA 1 g + y-linolenic acid + arachidonic acid 100 mg) + α-tocopherol (vitamin E) + β-carotene (n = 12) versus Acetylcysteine + essential fatty acid (EFA) + antioxidants (n = 5) Duration of treatment: 4 to 6 months
Outcomes	Sperm parameters, DNA damage (oh8dG)
Notes	Abstract only. No extractable data. Attempted to contact authors re availability of data as means, if published?, methods of randomisation and allocation concealment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Abstract only

Zavaczki 2003

Study characteristics

Methods	Randomised, placebo-controlled trial Duration of study: 3 months
Participants	Country: Hungary Population: subfertile men, N = 20 (recruited N = 26) Mean age: treatment group 29.6 years, placebo group 28.3 years

Zavaczki 2003 *(Continued)*

	Inclusion criteria: unsuccessful attempt at pregnancy for over one year. A healthy female partner examined by a gynaecologist. Sperm volume < 2 mL and/or sperm concentration < 20 million/mL and/or morphology ratio < 30% and/or motility < 50%. No genital tract infection, no bacteria or fungi in urine or semen. Hormones are within physiological range. Intact renal function. No excessive magnesium intake Exclusion criteria: unclear
Interventions	Magnesium 3000 mg (n = 10) versus Placebo (n = 10) Duration of treatment: 90 days
Outcomes	Primary: sperm parameters Secondary: clinical pregnancy and side effects
Notes	Attempted to contact authors regarding methods of randomisation and allocation concealment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The members of Group P received the same number of placebo tablets which closely resembled the Magnerot tablets." Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 were randomised and 14 were analysed. Quote: "To date 26 patients have participated in the study and 20 men (10 in both groups) have completed the program of treatment. Six patients (2 in group M and 4 in group P were excluded from the program, including five cases for poor compliance, since they did not attend the control meeting at the end of treatment. One patient from Group M experienced severe diarrhoea and so his treatment was halted."
Selective reporting (reporting bias)	Unclear risk	All sperm data for outcomes in the trial were given, however clinical pregnancy only reported in the results section and not mentioned in methods. No protocol available.

Zhou 2016

Study characteristics	
Methods	Randomised controlled trial

Zhou 2016 *(Continued)*

	Duration of study: from January 2014 to February 2015
Participants	Country: China Population: patients with idiopathic asthenospermia, N = 120 Mean age: 32.5 years (treatment group) and 31.7 years in control group Inclusion criteria: • The couple has lived together for more than 1 year after marriage, the sex life is normal without taking any contraceptive measure; • The woman's reproductive function check is normal; • Sperm activity (PR + NP) ＜40%; • Sexual intercourse or masturbation can be obtained • Not any varicocele, prostatitis, etc. that affects sperm quality • Absence of diseases with abnormal reproductive hormone levels • Not taking drugs that affect sperm 4 weeks before the test • Age between 23 and 44 years old and voluntary participation Exclusion criteria: unclear
Interventions	Vitamin E 100 mg, oral twice daily (n = 50) versus Vitamin E 100 mg, oral twice daily + compound amino acid capsules 3 capsules twice daily Duration of treatment: 90 days
Outcomes	Semen analysis: total sperm motility and progressive motility, pregnancy (definition of pregnancy unclear), adverse events
Notes	Article in Chinese, translated by Yue Wang, Yongchuan Gu, and Catherine Jia-yun Tsai. E-mailed author sunzhy199481@hotmail.com on 06-05-2021 to request information on "compound amino acids" and definition of pregnancy outcome. No reply to date (03-09-2021). Pregnancy data in Table 1 because of unclear definition.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	SAS software was used to generate random serial number
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned

Zhou 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers in results tables match randomised numbers.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported. No study protocol available.

AI: artificial insemination; **ALA:** alpha-lipoic acid; **ART:** assisted reproductive technique; **BMI:** body mass index; **DFI:** DNA fragmentation index; **DHA:** docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **FSH:** follicle-stimulating hormone; **GSH:** glutathione; **HBA:** hyaluronan binding assay; **HCG:Human chorionic gonadotropin; ICSI:** intracytoplasmic sperm injection; **IgG:** immunogobulin G; **ITT:** intention-to-treat; mg: milligram; **IQR:** interquartile range; **IU:** international unit; **IUI:** intrauterine insemination; **IVF:** in vitro fertilisation; **LH:** luteinizing hormone; **mcg**; microgram; **MDA:** malondialdehyde; **mg:** milligram; **MMP:** mitochondrial membrane potential; **NSAID:** non-steroidal anti-inflammatory; **OAT:**oligoasthenoteratozoospermia; **PRL:** prolactin; **RoB:** risk of bias; **ROS:** reactive oxygen species; **SCSA:** sperm chromatin structure analysis; **SD:** standard deviation; **SE:** standard error; **SEM:** standard error of the mean; **STD:** sexually transmitted disease; **TAC:** total antioxidant capacity; **TESA:** Testicular sperm aspiration; **TUNEL:** Terminal deoxynucleotidyl transferase dUTP nick end labeling; **VC:** varicocele; **VCT:** varicocelectomy; **WBC:** white blood cell; **WHO:** World Health Organization.

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

Study	Reason for exclusion
Adel 2015	Ineligible based on intervention: main intervention is oral Vitamin E. However there was also an in vitro Berberine wash added to the collected sperm in 10 random participants from both groups (treatment group with oral Vitamin E or untreated group)
Akdeniz 2017	Ineligible based on study population: women
Alahmar 2017	Ineligible based on study design: "prospective randomised trial", however there was no control group, only comparison before and after treatment with antioxidants
Alizadeh 2018	Ineligible based on intervention: Curcumin Nanomicelle is a herbal product
Alsalman 2018	Ineligible based on control: subfertile men with zinc treatment versus fertile men without treatment
Anarte 2012	Ineligible based on study population: normozoospermic men and donors
Anarte 2013	Ineligible based on study population: normozoospermic men and donors
Azizollahi 2013a	Ineligible based on outcome: seminal antioxidant levels and endocrine parameters. Furthermore, same study population/group as Azizollahi 2013 which was already included in the 2014 update
Busetto 2020	Post hoc analysis of same study group as Busetto 2018, included in the 2018 update of the review.
Cai 2012	Ineligible based on study population: not subfertile men
Calogero 2015	Ineligible based on population: idiopathic infertile men, not male factor
Canepa 2018	Ineligible based on study design: not a randomized controlled trial
Capece 2017	Ineligible based on intervention: treatment with myo-inositol plus herbal extracts (Tribulus Terrestris, Alga Ecklonia Bicyclis)
Chattopadhyay 2016	Ineligible based on study design: not a randomised controlled trial

Study	Reason for exclusion
Chen 2012	Ineligible based on intervention: includes fertility drugs like tamoxifen. Group A tamoxifen + vitamin E, Group B tamoxifen
Ciftci 2009	Ineligible based on population: includes men with idiopathic infertility and normal sperm parameters
Comhaire 2005	Ineligible based on study design: used non-randomised controls recruited from another unrelated trial
Ebisch 2003	Ineligible based on study population: inappropriate population, polymorphisms
Elgindy 2008	Ineligible based on study population: antioxidant given to the women
Garcia-Baquero 2020	Ineligible based on study design: review article
Ghafarizadeh 2018	Ineligible based on intervention: in vitro selenium, no oral intake
Ghanem 2010	Ineligible based on intervention: clomiphene + vitamin E versus placebo, fertility enhancing drug
Gulati 2015	Ineligible based on study design: prospective cohort study, not a randomised controlled trial
Gulino 2016	Ineligible based on control: healthy fertile patients with intervention or control group of healthy patients undergoing IVF for a female factor
Hafeez 2011	Ineligible based on intervention: plant extracts, herbal formulation
Iacono 2014	Ineligible based on intervention: fertility enhancing drug, protocol exclusion criteria. Group A Tamofixfen citrate with antioxidant, group B tamoifen alone and group C placebo
Jawad 2013	Ineligible based on study design: not randomised quote: "men were classified into groups". Numbers of men in the groups were uneven
Kanta Goswami 2017	Ineligible based on study design: prospective study, not randomised
Keskes-Ammar 2003	Ineligible based on population: includes infertile men who are normospermic, oligospermic or azoospermic. No subpopulation with extraction data
Kim 2010	Ineligible based on study population: women
Korosi 2017	Ineligible based on intervention: oral myo-inositol supplement with treatment of the semen with myo-inositol incubation. The control group did not receive any form of treatment (no oral, no incubation). Not able to differentiate between effect due to oral supplement or incubation
Kumar 2011	Ineligible based on intervention: used a herbo-mineral supplement
Lenzi 1993	Ineligible based on intervention: route of supplementation was intramuscular not oral
Lu 2010	Ineligible based on study population: women
Martinez-Soto 2016	Ineligible based on study population: also included infertile men with normospermic parameters. No subgroup analysis
Merino 1997	Ineligible based on intervention: pentoxifylline no longer included, fertility enhancing drug
Micic 1988	Ineligible based on intervention: pentoxifylline no longer included, fertility enhancing drug

Study	Reason for exclusion
Micic 2001	Ineligible based on study design: not randomised, 105 men in the treatment group and 35 in control. Abstract only
Movahedin 2014	Ineligible based on (repetitive) study population: same study as Pourmand 2014, second author Movahedin
Nadjarzadeh 2014	Ineligible based on (repetitive) study population: exact same population, including the baseline characteristics and period of inclusion, as Nadjarzadeh 2011. Different outcome parameters (seminal plasma levels of antioxidant enzymes and oxidative stress)
Nashivochnikova 2014	Ineligible based on study design: no RCT, full text received from first author by email, after translation of full text (in Russian) to English found out there was no control group
Nasurullah 2020	Ineligible based on control: control group was treated with ferrous sulphate. This is not an antioxidant so not suitable for head-to-head comparison
NCT01075334	Ineligible based on no data to publish: study was terminated, not being able to recruit enough participants (contact with author)
NCT01520584	Ineligible based on no data to publish: recruiting participants not successful (contact with author)
NCT04585984	Ineligible based on intervention: treatment with probiotics
Nematollahi-Mahani 2014	Ineligible based on outcome: endocrine parameters and seminal antioxidant level. Furthermore, same study population as Azizollahi 2013 (included in update 2014)
Niederberger 2011	Ineligible based on study design: a commentary on Ghanem 2010
Nikolova 2007	Ineligible based on study design: not randomised, allocation method is by alternation. Translated from Bulgarian by Ivan Sola. Quote; "50 of them were randomly invited to participate depending on their order of attendance to the clinic"
Oliva 2020	Ineligible based on study population: women were treated with vaginal suppositories
Ovchinnikov 2018	Same study as Gamidov 2017, included study in 2018 update of the review
Pawlowicz 2001	Ineligible based on study design: not a randomised controlled trial
Polak 2013	Ineligible based on study population: women
Safarinejad 2011	Ineligible based on intervention: pentoxifylline no longer included, fertility enhancing drug
Safarinejad 2011a	Ineligible based on intervention: saffron, herbal not a supplement
Singh 2016	Ineligible based on study design: not randomised, based on conference abstract
Soylemez 2012	Ineligible based on study population: not subfertile men
Stanislavov 2009	Ineligible based on study design: not randomised, the study uses alternate allocation, odd and even numbers. Appears to be a report of the study Nikolova 2007
Stanislavov 2014	Ineligible based on intervention: L-arginine combined with herbal extract
Tang 2011	Ineligible based on intervention: tamoxifen, protocol exclusion criteria (tamoxifen + Q10 versus tamoxifen). Quote: “trials that included men taking other fertility enhancing drugs”

Study	Reason for exclusion
Verzeletti 2012	Ineligible based on intervention: Spirulina platensis (4 g) and Resveratrol (500 mg) are plant extracts not antioxidant supplements
Vicari 2001	Ineligible based on control: inappropriate control (anti-inflammatory) group. Treatment is not compared to placebo or another antioxidant
Vicari 2001a	Ineligible based on control: Inappropriate comparison. The same antioxidant is compared at different times - L-carnitine + acetyl-carnitine versus L-carnitine + acetyl-carnitine
Vicari 2002	Ineligible based on control: inappropriate control (anti-inflammatory). Treatment is not compared to placebo or another antioxidant
Wang 1983	Ineligible based on intervention: pentoxifylline no longer included, fertility enhancing drug
Wang 2010a	Ineligible based on intervention: fertility enhancing drug, protocol exclusion criteria. Group A L-carnitine + tamoxifen, Group B L-carnitine, Group C tamoxifen. No placebo or no treatment control
Williams 2020	Ineligible based on study population: not subfertile men
Wu 2012	Ineligible based on study design: probably not randomised, no mention of randomisation in the abstract and uneven numbers between the groups, attempted to contact authors with no reply

IVF: in vitro fertilisation; **RCT:** randomised controlled trial

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

DRKS00011616

Methods	Interventional (clinical trial) Design Allocation: randomised controlled trial Masking: blinded (patient/participant, investigator/therapist) Control: placebo Assignment: parallel Study design purpose: treatment
Participants	Males with minimum age of 18 years Inclusion criteria • Men with existing unfulfilled child wish • Unspecific (idiopathic) subfertility diagnosed by an already existing sperm analysis (may not be older than four weeks) and whilst observing a sexual abstinence period of at least 2 days to a maximum of 7 days; according to WHO reference values (2010, 5th Edition): • < 39 million total number of spermatozoa per ejaculate sample and/or • < 32 % progressive motile spermatozoa • Readiness to comply with at least 2 to a maximum of 7 days of sexual abstinence before creating a Spermogram • Consent to take a dietary food for three months Exclusion criteria

DRKS00011616 *(Continued)*

- Presumed or established organic causes of subfertility
- Azoospermia, aspermia, anejaculation
- Varicocele of the testis, assessment according to medical examination discretion
- Urogenital infections such as e.g. prostatitis, epididymitis, orchitis, sexually transmitted diseases
- Known relevant endocrine disorders, e.g. hypogonadotropic hypogonadism (assessment according to medical discretion)
- Operational interventions in the past:
- Orchidopexy in cryptorchid or hodentorsion, varicocele surgery, hodentrauma, pelvic, inguinal or scrotal surgical procedures
- Any surgical intervention during the last 6 months before the start of the study and planned interventions during the study
- Systemic disorders that could influence the outcome of the study, assessment by medical judgment (e.g. diabetes, renal failure, hepatic impairment malignancy, obesity)
- Pesticide exposure in the past and present
- Ingestion of substances or other forms of therapy that could influence the study result according to medical discretion, e.g.
- Medication, e.g. Anabolic agents, sulphasalazines, alpha-blockers, cimetidine and aldosterone antagonists, androgens, 6 months before study initiation and during the study
- Regular intake of dietary supplements/supplementary balanced diets in the last 6 months before the start of the study and during the study(with the exception of the study preparation)
- Applied therapy to improve sperm quality in the last 6 months before the start of the study and during the study
- Application of antioxidants in the last 6 months before study start and during the study
- Known intolerance / allergic reactions to the ingredients of the investigational medicinal product
- Significant changes in the patient's lifestyle, especially regarding medication intake, diet, smoking, alcohol last month study start and during the study
- Drug, alcohol and / or drug abuse
- Simultaneous participation in another clinical trial or participate in such an event within the last 30 days
- Signs that the participant is expected to fail test plan (e.g. lack of co-operation)
- Application of antioxidants in the last 6 months before study start and during the study
- Known intolerance / allergic reactions to the ingredients of the investigational medicinal product
- Significant changes in the patient's lifestyle, especially regarding medication intake, diet, smoking, alcohol last month Study start and during the study
- Drug, alcohol and / or drug abuse
- Simultaneous participation in another clinical trial or participate in such an event within the last 30 days
- Signs that the participant is expected to fail test plan (e.g. lack of co-operation)
- Simultaneous participation in another clinical trial or participate in such an event within the last 30 days
- Signs that the participant is expected to fail test plan (e.g. lack of co-operation)

Interventions	Drug: Taking AM019016 (verum), dietary food, 3 capsules once a day Ingredients: vitamin D, E, C, B12, B6, B2, Folic Acid, L-Carnithine, L-Arginine, Coenzyme Q10, Zinc, Selenium, β-carotene, Copper, Pigrafert (combination of pine bark, grape seed, green tea extract). Control: Taking AM019016 (placebo), 3 capsules once a day Ingredients placebo: maltodextrin, release agent magnesium salts of feed fatty acids and dye E171 and hydropropylmethylcellulose in the capsule shell. Free of gluten and lactose. Duration: 12 weeks
Outcomes	Primary

DRKS00011616 *(Continued)*

	Parameters for the assessment of the benefit by preparation and evaluation of spermograms according to the WHO criteria (2010, 5th edition) • change in progressive motility (visit 1 versus visit 2) • Change of sperm concentration (visit 1 versus visit 2); change of sperm morphology (visit 1 versus visit 2); change of sperm total (visit 1 versus visit 2) • Change in total motility (visit 1 versus visit 2) • Change of the ejaculate volume (visit 1 versus visit 2) • Occurrence of pregnancy during the study and about 3 months after visit 2 • Global evaluation of the benefit by the physician (to visit 2) on a scale with the four assessment points "very good", "good", "moderate" and "bad" Secondary Parameters for the assessment of tolerability: • Adverse events and serious adverse advents during the clinical trial • Global evaluation of the tolerability by the physician and subjects using a scale with the four assessment points "very good", "good", "moderate" and "bad" at final visit.
Notes	Secondary ID: S15(a)/2017 Email Baumgraβ 07.04.2021 to ask about current status.

Kuzmenko 2018

Methods	Randomised controlled trial Duration of study: unclear
Participants	Country: Russia Population: "men with pathozoospermia", N = 60 Mean age: Unclear (age ranfge 25-40 years) Inclusion criteria: unclear Exclusion criteria: unclear
Interventions	Speroton complex (L-carnitine + vitamin E + folic acid + selenium + zinc) (n = 30) versus No treatment (n = 30) Duration of treatment: unclear
Outcomes	Semen analysis, level of fructose and zinc, pregnancy
Notes	Full text not available. Contacted author Dr Kuzmenko (kuzmenkovv2003@mail.ru and kuzmenkoav09@yandex.ru) to request full text for more information on study population: pathozoospermia? No reply to date.

NCT00975117

Methods	Interventional (clinical trial) Design Allocation: randomised Masking: triple-blind (participant, caregiver, investigator) Placebo control Parallel assignment
Participants	Males, 19 years to 60 years Inclusion criteria • Male infertility unrelated to major testicular conditions • Must have at least one altered seminal parameter • Signed informed consent Exclusion criteria • Hydrocele, varicocele, orchitis, epididymitis, irradiation or chemotherapy • Previously treated and cured testicular condition • Non-transmissible chronic diseases • Use of antioxidant agents within 6 months • Use of vitamins within 6 months • Use of anti-inflammatory drugs within 6 months • Use of hormones prescribed by an andrologist within 6 months • Positive serology/HIV • Leukocytospermia
Interventions	Drug: Spermotrend (vitamins plus other antioxidants) twice a day Control: placebo twice a day Duration: 12 weeks
Outcomes	Primary • Parameters of seminal analysis at weeks 24 Secondary • Fertilisation achievement • Presence of mild or severe adverse effects
Notes	Email sent 08.02.2018 to miguel.aguilar@infomed.sld.cu Email sent 07.04.2021 to miguel.aguilar@infomed.sld.cu

NCT01407432

Methods	Interventional (clinical Trial). Phase 3 Design Allocation: randomised

NCT01407432 *(Continued)*

	Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor)
Participants	Males, 18 years to 60 years Inclusion criteria • Couple - male is from 18 to 60 years old • Couple - male presents with infertility indicating interest in *in vitro* fertilisation with or without intracytoplasmic sperm injection (IVF +/- ICSI) • Couple - male is 18 to 38 years old • Couple - male does not present particular factors of infertility • Couple - interest in IVF +/- ICSI • Couple with social insurance • both members of the couple having signed the consent Exclusion criteria • Aetiology of not genetic known male infertility: infertility of neoplastic origin, infertility of definitive obstructive origin • Presence of a factor of feminine infertility: a definitive infertility tubal, turned out ovarian incapacity (FSH > 9 and/or CFA <= 8) • Infertile men requiring fresh or frozen sperm • Men or women with HIV or hepatitis B or C • Men with epilepsy • Men receiving anti-folic treatment • Men presenting with a sensitivity to folic acid or one of the constituents of the drug • Couple of which one of the partners refuses to participate in the study
Interventions	Drug: folic acid 15 mg per day (tablets of 5 mg) Control: placebo of folic acid Duration: 3-4 months
Outcomes	Primary • The rates of pregnancy in IVF +/- ICSI and spontaneous pregnancy according to the arm of treatment Secondary • The rate of improvement of the sperm parameters with acid folic treatment • The rate of improvement of the nuclear quality of gametes with acid folic treatment • The rate of pregnancy of couple with infertile men treated by folic acid according to the methylene-tetrahydrofolate reductase (MTHFR) genotype • The difference between the MTHFR genotype of the patients on sperm parameters according to the arm of treatment
Notes	Email sent 08.02.18 to emmanuelle.mathieu@aphp.fr. Received an answer 09.02.18 that the trial recruiting phase is completed. Submitting the results within a few weeks. Email sent 07.04.21 to emmanuelle.mathieu@aphp.fr. Reply on 08.04.21 that the article is submitted.

NCT01828710

Methods	Interventional (clinical trial), phase 2/3 Design Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: screening
Participants	Male 25 years to 65 years Inclusion criteria • Undergoing IVF cycle, OAT Exclusion criteria • Not undergoing IVF cycle
Interventions	Sham arm (normospermic): 4000 mg/die of myo-inositol + 400 µg of folic acid (phase 2) Active arm (OAT): myo-inositol 4000 mg/die associated to 400 µg of folic acid (phase 3) Placebo arm (normospermic): 400 µg of folic acid Duration: three months
Outcomes	Primary • sperm concentration
Notes	Email sent 07.02.18 to Gulino (docferdi@hotmail.it) to ask if this study correlates with the same study population of study NCT01560065 (Gulino 2016) Email sent 07.04.2021 to docferdi@hotmail.it.

ICSI: intracytoplasmic sperm injection; **IVF:** in vitro fertilisation; **MTHFR:** methylene tetrahydrofolate reductas;**OAT:** oligoasthenoteratozoospermia; **WHO:** World \health \Organization

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

CTRI/2019/03/018303

Study name	Assessment of seminal plasma myeloperoxidase level (ROS) and the effect of vitamin C therapy on semen quality in infertile men
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: randomised, parallel group, placebo-controlled trial Masking: quadruple (participant, investigator, outcome assessor and date-entry operator) Target sample size: 258
Participants	Male patients aged 20-45 years with infertility.

CTRI/2019/03/018303 *(Continued)*

	Inclusion criteria: • Patients with bilateral testes • Patients reporting oxidative stress in whole semen (elevated myeloperoxidase) Exclusion criteria: • Patients on medications for infertility • Patients with known history of diabetes mellitus, hypertension, obesity, infection, ischaemic heart disease, metabolic syndrome and other chronic illness • Patients with history of alcohol > then 60 units/week and smoking • Patients who are allergic to vitamin C • Orchitis, tuberculosis and varicocele • Patients not willing to participate in the study
Interventions	Drug: vitamin C 500 mg, oral once daily Control: calcium supplements Duration: 3 months
Outcomes	Primary: • Myeloperoxidase level • Semen analysis Secondary: • Fertilisation rate • Embryo quality • Pregnancy rate • Live birth rate
Starting date	01-04-2019
Contact information	Radha Vembu, Designation Associate Professor Affiliation Sri Ramachandra Institute of Higher Education and Research Address No 74, II floor, Venkatasai flats, Rajagopalan street,SDK Amman Nagar, Valsaravakkam, Chennai 87 Sri Ramachandra Nagar, Porur, Chennai TAMIL NADU 600116 India Phone 9841141310 Email ganesh_radha@yahoo.in
Notes	Email sent 08-03-21 to Radha Vembu. Reply on 07-04-21: “We have certain issues in starting the trial. Hence, we don't have information to share.”

IRCT20120215009014N322

Study name	Effect of CO-Q 10 supplementation versus placebo on spermogram parameters and sexual function in infertile men: a double-blind randomized clinical trial
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: double-blind randomised clinical trial, phase II Masking: participant, care provider, investigator, outcome assessor Sample size: 70
Participants	Men with primary infertility, aged 18-40 years. Inclusion criteria: Abnormality in at least one of the sperm parameters (volume, concentration, number, motility, or morphology) and body mass index less than 30 Exclusion criteria: Chromosomal abnormalities, varicocele, cryptorchidism, chronic diseases such as diabetes, kidney disease, infectious diseases, genital tract infection, thyroid disorder, drug or alcohol use, taking spermatogenic drugs (methotrexate, nitrofurantoin, colchicine or chemotherapy), taking pituitary suppressive drugs (testosterone, GnRh analogs), taking anti-androgens (cimetidine or spironolactone), taking alpha-blockers, antidepressants, or phenothiazide, history of testis surgery
Interventions	Routine infertility treatment plus: Drug: coenzyme Q10 30 mg daily Control: placebo once daily Duration: 12 weeks
Outcomes	Primary: sperm volume, count, concentration, motility and morphology Secondary: None
Starting date	21-01-2020
Contact information	Taiebeh Gharakhani, Master Hamedan University of Medical Sciences Fatemieh Hospital, Pasdaran Ave., Hamadan, 6517838695 Phone: +98 81 3828 3939 Email: tabahar6@gmail.com Dr. Seyedeh Zahra Massomi, PhD, Fertility Health Specialist School of Nursing and Midwifery, Hamadan University of Medical Sciences, Shahid Fahmideh Ave. Hamadan, 6517838695 Phone: +98 81 3838 0572 Email: zahramid2001@yahoo.com

IRCT20120215009014N322 *(Continued)*

	Email: poorolajal@umsha.ac.ir
Notes	

IRCT20140622018187N9

Study name	The effect of vitamin C supplementation on quality of spermogram in infertile men with astheno-zoospermia with a balanced diet in Mother and Childhospital, Shiraz, 1392
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: randomised, double-blinded, placebo-controlled trial Masking: participant, care provider, investigator
Participants	Inclusion: • Infertile men who go to a infertility centre • Infertile men aged 25-45 years Exclusion: • Men have a special diet
Interventions	Drug: vitamin C tablets once daily Control: placebo Duration: one month
Outcomes	Primary: sperm count, shade, movement and volume Secondary: none
Starting date	21-03-2018
Contact information	Shiraz University of Medical Sciences Sedighe Forouhari, Ph.D, Supervisor, Reproductive Health College Of Nursing Midwifery, Shiraz, Fars, 71345-1978 Phone: +98 71 1647 4257 Email: forouharism@yahoo.com
Notes	According to www.irct.ir: recruitment complete.

IRCT20190406043177N1

Study name	The effect of alpha lipoic acid on sperm parameters, DNA integrity and oxidative stress in infertile men with increased level of sperm DNA damage

IRCT20190406043177N1 *(Continued)*

Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: triple-blind randomised clinical trial Masking: participant, care provider, investigator, outcome assessor, date analyser, data and safety monitoring board Sample size: 80
Participants	Inclusion criteria: • Infertile men with normal sperm parameters and high levels of DNA fragmentation (SCSA > 30%, TUNEL > 15%) • Infertile men with abnormal sperm parameters and high levels of DNA fragmentation (SCSA > 30%, TUNEL > 15%) • No age limit Exclusion criteria: • Varicocele • Leukocytospermia • Cancer- and chemotherapy, cytotoxic medicine usage
Interventions	Drug: Alpha lipoic acid (ALA) 300 mg twice daily Control: placebo 300 mg twice daily Duration: 3 months
Outcomes	Primary: DNA damage, sperm motility, sperm morphology, count, vitality, lipid peroxidation (MDA level), mitochondrial membrane potential, total antioxidant capacity, superoxide dismutase. glutathione peroxidase, reactive oxygen species, chromatin evaluation Secondary: fertilisation rate
Starting date	22-06-2018
Contact information	Prof. Mohammad Hossein Nasr Esfahani, Embryologist Royan Institute No.371, Allikhani Aleey, Mehr St., Salman Farsi Ave., Isfahan, Iran, 8158968433 Phone: +98 31 9501 5682 Email: mh.nasr-esfahani@royaninstitute.org
Notes	Email sent 08-03-2021. Reply from author on 23-03-2021 that the paper has been submitted to a journal but is not yet published.

IRCT20190714044209N1

Study name	Evaluating the therapeutic effect of theophylline and zinc sulphate vo-administration in infertile men
Methods	Interventional (clinical trial) Design Allocation: simple randomisation Intervention model: clinical trial with placebo-control group, parallel groups, double-blind, randomised Masking: participants, investigator, outcome assessors and data analysers Sample size: 120
Participants	Infertile men referred to the infertility treatment centre Inclusion criteria: • At least one year of unprotected intercourse • Natural fertility has not happened in their spouse • These men will all be married • These men will be between the ages of 20 and 50 • According to WHO criteria sperm parameters abnormalities should be observed in at least two spermiogram within 2 weeks Exclusion criteria: • Single men • Men with varicocele or any other specific disease • Men who have taken a particular drug for the past three months
Interventions	Drug: Group 2: theophylline 200 mg daily, Group 3: zinc sulphate 220 mg daily, Group 4: theophylline 200 mg daily + zinc sulphate 220 mg daily Control: placebo Duration: 3 months
Outcomes	**Primary:** spermiogram, hormone levels (LH, FSH, testosterone), malondialdehyde level, TNF-alpha and interleukin 10, DNA fragmentation (SDFA), sperm viability, total antioxidant level of semen (TAC), expression of caspase 3, BAX, BCL2 genes and -proteins, inflammatory factors, sperm maturation, sperm capacitation **Secondary:** None
Starting date	22-12-2019
Contact information	Dr. Alireza Noushad Kamran Rastak Fertility Clinic, Sina Hospital, Next to Imam Khomeini Stadium, Hepko Ave., Arak Markazi, 3818853558 Phone: +98 86 3340 5343

IRCT20190714044209N1 *(Continued)*

	Email: info@araksinahospital.ir Atena Sadat Azimi, PhD student Arak University, No. 6313, At the top of Azimi shop, Haqqani Street, Arak Markazi, 3815166315 Phone: +98 86 3277 7300 Email: a-azimi@phd.araku.ac.ir
Notes	Email sent to Atena Azimi 08-03-2021. Reply on 09-03-2021 that recruitment has been completed, no published paper available.

IRCT20200911048689N1

Study name	Effect of vitamin E on quality and quantity of sperm in infertile men after varicocelectomy
Methods	Interventional (Clinical trial) Design Allocation: randomised Interventional model: randomised, superiority, parallel group trial, blinded Masking: participants, outcome assessors and data analysers
Participants	Inclusion criteria: • Infertility due to palpable varicocele grade 2 and 3 • Age range between 18 to 50 years • Weight between 50 to 100 kg • Being married Exclusion criteria: • Absence of azoospermia • Diabetes mellitus • Hormonal diseases • Smoking and addiction • Routine use of multivitamins (one month before the study) • Active or chronic genitourinary infections • History of peptic ulcer • History of reaction, sensitivity or resistance to vitamin E • Use of prescription drugs (vitamin E capsules or placebo) • Signs of side effects of vitamin E • Testicular atrophy
Interventions	Drug: varicocelectomy and vitamin E 400 IU once daily Control: varicocelectomy and placebo Duration: 3 months
Outcomes	Primary: Variables in the spermiogram include semen volume, sperm count, and sperm motility

IRCT20200911048689N1 *(Continued)*

	Secondary: None
Starting date	22-09-2021
Contact information	Kasra Saeedian, medical student Mashhad University of Medical Sciences No. 34, Nazari Ave., Fajr Street., Motahari Street, Tehran, 1588746675 Phone: +98 21 8881 1033 Email: saeidiank931@mums.ac.ir
Notes	

NCT03104998

Study name	Neotililty trial: effect of coenzyme Q10 on semen parameters in men with idiopathic infertility
Methods	Interventional (clinical Trial) Design Intervention model: single-group assignment Masking: none (open-label)
Participants	Males, 20 years to 50 years Inclusion criteria • Signs the informed consent form • Patients will be recruited in the study if they will fulfilled the criteria of history of primary infertility of more than 2 years, abnormal sperm count and motility • Age between 20 and 50 years • No known medical or surgical condition which can result in infertility Exclusion criteria • Voluntary withdrawal • Poor compliance of visit/treatment • A history of cancer chemotherapy or radiotherapy • A history of genital disease such as cryptorchidism and varicocele; a history of genital surgery • Body mass index 30 kg/m or greater; any endocrinopathy • Y chromosome microdeletions or karyotype abnormalities • Leukocytospermia • Drug or substance abuse; tobacco use; • Use of anticonvulsants, androgens or antiandrogens • Significant liver (serum bilirubin greater than 2.0 mg/dL) • Renal function (serum creatinine greater than 2.0 mg/dL) impairment • Patients with severe oligozoospermia (less than 5 X 106/mL), azoospermia and testicular volume less than 12 mL will also be excluded from study
Interventions	Drug: coenzyme Q10 200 mg daily Control: placebo daily

NCT03104998 *(Continued)*

	Duration: 26 weeks
Outcomes	Primary • Measure the change in semen parameters after 26 weeks of coenzyme q10 Secondary • Adverse events
Starting date	August 2017
Contact information	Anum Siddiqui, PharmD / Masood Jawaid, MRCS,FCPS HillPark Hospital Karachi, Pakistan 9221-34315195 NCT03104998,%20PE/PK/Neotility/SP/2017-01,%20Neotililty%20Trial:%20Effect%20of%20Coenzyme%20Q10%20on%20Semen%20Parameters%20in%20Men%20With%20Idiopathic%20Infertility" type="EXTERNAL">anum.siddiqui@pharmevo.biz NCT03104998,%20PE/PK/Neotility/SP/2017-01,%20Neotililty%20Trial:%20Effect%20of%20Coenzyme%20Q10%20on%20Semen%20Parameters%20in%20Men%20With%20Idiopathic%20Infertility" type="EXTERNAL">Sonia_naqvi@hotmail.com
Notes	Email sent 07.04.2021 to Siddiqui and Jawaid asking for current status. Clinicaltrials.gov: withdrawn.

NCT03337360

Study name	The impact of a nutritional supplement (Impryl®) on male fertility (SUMMER)
Methods	Interventional (clinical Trial) Design Allocation: randomised Intervention model: multicentre, randomised double-blind placebo-controlled clinical trial/superiority study Masking: triple (participant, care provider, investigator)
Participants	Males, 18 years to 50 years Inclusion criteria • Couples with failure to conceive for at least 12 months and starting with EM OR • Couples starting with 1st cycle of IUI (with/without ovarian stimulation) OR • Couples starting with 1st/2nd/3rd cycle of IVF/ICSI Furthermore

NCT03337360 *(Continued)*

	• Male with age 18-50 years • Female partner with age 18-43 years • Willing and able to give informed consent Exclusion criteria • Planned or performed diagnostic testicular biopsy (TESE) or percutaneous epididymal sperm aspiration (PESA) • Use of donor-, cryopreserved- or electro-ejaculated semen • Ovulation induction (OI) without IUI • IVF for an absolute tubal factor • Embryo-transfers after cryopreservation • Embryo-transfer after pre-implantation genetic diagnosis • Known genetic abnormalities related to infertility • Known urological abnormality such as a varicocele or bilateral cryptorchism • Use of other vitamin supplements
Interventions	Drug: Impryl, one tablet daily Ingredients: food supplement with betaine, cystine, zinc, niacin, folic acid (di5MTHF-glucosamine), Vitamin B12 (cobalamin), Vitamin B6, Vitamin B2 (Riboflavin) Control: placebo, one tablet daily Duration: 6 months
Outcomes	Primary • Ongoing pregnancy rate ≥10-12 weeks of gestation Secondary • Overall pregnancy rate • The time between start of intervention and reaching ongoing pregnancy • The time between start of fertility treatment and reaching ongoing pregnancy • Change in semen parameters leading to change in treatment category • Number of miscarriages • Live birth rate • Adverse effects • Embryo fertilisation rate • Embryo-utilisation rate
Starting date	April 2018
Contact information	Wiep de Ligny, MD Radboud University Nijmegen, the Netherlands, 6500HB +31 (0) 651751244 NCT03337360,%20NL61414.091.17,%20SUMMER-study:%20the%20Impact%20of%20a%20Nutritional%20Supplement%20(Impryl%C2%AE)%20on%20Male%20Fertility">wiep.deligny@radboudumc.nl
Notes	02.06.2021: study is still recruiting, currently 470 patients included.

NCT03634644

Study name	Omega-3 PUFA for treatment of patients with idiopathic oligoasthenoteratospermia
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: double-blind, placebo-controlled and randomised exploratory clinical trial Masking: quadruple (participants, care providers, investigators and data analysers) Sample size: 30
Participants	Inclusion criteria: • Male aged 21 to 45 years • Clinical diagnosis of oligoasthenoteratospermia Exclusion criteria: • Leukocytospermia, prostatitis, genital trauma, testicular torsion, urinary tract infections, cryptorchidism, varicocele, diabetes, inguinal and genital surgery • Y chromosome microdeletion and chromosomal karyotype abnormality • Extreme oligospermia • Hepatobiliary diseases, kidney failure
Interventions	Drug: omega 3 fatty acid 1 g per capsule (EPA 400 mg + DHA 320 mg) Control: placebo capsule, mainly composed of corn oil Duration: 40 days
Outcomes	Primary: sperm concentration Secondary: progressive sperm ratio, DNA fragmentation index, gut microbiota composition
Starting date	08-11-2017
Contact information	Bing Yao Center for Reproductive Medicine, Jinling Hospital Nanjing, Jiangsu, China, 210000 86-25-80860174 yaobing@nju.edu.cn
Notes	

NCT04193358

Study name	Impact of a nutritional supplements' combination (FERTILIS) on male infertility: a monocentric double Bbind Rrndomized placebo controlled trial
Methods	Interventional (clinical trial)

NCT04193358 *(Continued)*

	Design Allocation: randomised Intervention model: comparative, interventional, prospective, monocentric, double-blind, randomised, placebo-controlled trial Masking: quadruple (participants, care providers, investigators and outcome assessors)
Participants	Inclusion criteria: • Male ≥ 20 years • Attending the Department of Obstetrics and Gynaecology of Farhat Hached University Hospital, Sousse, Tunisia, for consultation or semen analysis as part of infertility investigations • Diagnosis of oligozoospermia • Diagnosis of asthenozoospermia • Diagnosis of teratozoospermia • Diagnosis of idiopathic infertility • Couple is candidate for Intrauterine Insemination (IUI), In Vitro Fertilisation (IVF) and/or Intracytoplasmic Sperm Injection (ICSI). Exclusion criteria: none
Interventions	Drug: Fertilis Homme twice daily Ingredients: l-carnitine 220 mg, zinc 20 mg, selenium 0.03 mg, l-arginine 125 mg, l-glutathione 40 mg, folic acid 0.4 mg, coenzyme Q10 7.5 mg and vitamin E 60 mg Control: placebo (sugar pills) twice daily Duration: 3 months
Outcomes	Primary: sperm DNA fragmentation index Secondary: ejaculatory volume, sperm cell density, sperm quality (i.e. morphology, total motility and progressive motility), spontaneous pregnancy, pregnancy consecutive to assisted reproductive techniques, fertilization rate during IVF, embryo cleavage rate and embryo quality during ICSI, clinical pregnancy, live birth, adverse events
Starting date	17-02-2020
Contact information	Amina Radoui, MSc Tunisia Farhat Hached Hospital Sousse, Tunisia a.radoui@medis.com.tn
Notes	Email sent to Amina Radoui 08-03-2021. Reply on 07-04-2021: “The study is continuing inclusions of patients (currently at 97 inclusion) after putting it on hold during the first COVID-19 wave in Tunisia, March – June 2020. We haven’t produced any preliminary results as insufficient monitoring & follow-up data is available.”

NCT04256278

Study name	Administration of antioxidants to infertile men and spermqQuality
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: randomised, quadruple-blinded, placebo-controlled clinical trial Masking: participant, care provider, investigator, outcome assessor

Participants	Inclusion criteria:
	• Men aged 18 to 50 years
	• Infertility defined as follows:
	  ○ Failure to obtain a pregnancy after at least twelve months of regular sexual intercourse without the use of contraceptives or six months if the woman is > 35 years old AND
	  ○ At least one previous abnormal spermiogram, with at least one pathological parameter (concentration, motility, morphology), according to the WHO 2010 criteria
	• No treatment for infertility in the last 3 months
	• Normal hormone profile (TSH, FSH, LH, total testosterone, prolactin)
	• Negative culture for mycoplasma or ureaplasma
	• Physiological scrotal ultrasound
	Exclusion criteria:
	• Genetic cause of infertility
	• History of cryptorchidism
	• History of orchectomy
	• History of testicular cancer
	• History of severe heart, liver or kidney disease
	• History of endocrine disease (primary or secondary hypogonadism, hyperprolactinaemia, thyroid, pituitary or adrenal disease)
	• History of systemic disease or treatment in the last three months
	• BMI > 30 kg/m^2
	• Participation in another study and the possibility of the patient not being available for follow-up

Interventions	Drug: Spermotrend Ingredients: vitamin C 30 mg, vitamin B6 1 mg, folic acid 100 mcg, vitamin B12 0.5 mcg, vitamin E 5 mg, zinc 7.5 mg, selenium 13.2 mcg, l-cysteine Control: placebo Duration: 3 months
Outcomes	Primary: sperm motility (A, B, C and D), sperm concentration, vitality, morphology Secondary: ROS (8OHdG), DNA fragmentation index
Starting date	30-03-2020
Contact information	Stratis Kolibianakis, Professor stratis.kolibianakis@gmail.com Pinelopi Ioannidou, MD pinioannidou@hotmail.com

NCT04256278 *(Continued)*

	Aristotle University Of Thessaloniki, Andrology lab Zeginiadou Armatura, Greece
Notes	

NCT04509583

Study name	The role of micro nutrient supplement in improvement of the sperm DNA fragmentation
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: randomised controlled trial Masking: triple (participant, care provider, investigator)
Participants	Male from infertile couples treated at the Center of Reproductive Endocrinology and Infertility, Hue University Hospital, Vietnam, aged 18-60 years. Inclusion criteria: • DNA fragmentation ≥ 30% Exclusion criteria: • Men with acute systemic diseases • Acute urinary tract infection • Hepatic function disorders • Malignant diseases • Retrograde ejaculation • Azoospermia
Interventions	Drug: PROfortil twice daily + Vitamin E 400 IU once daily Ingredients: l-carnitine 440 mg + l-arginine 250 mg, coenzyme Q10 15 mg, vitamin E 120 mg, zinc 40 mg, folic acid 800 mcg, glutathione 80 mg, selenium 60 mcg Control: Vitamin E 400 IU once daily Duration: 3 months
Outcomes	Primary: • change of sperm DNA Fragmentation Index Secondary: • The blastocyst quality in IVF/ICSI cycles • The pregnancy rate in IVF/ICSI cycles
Starting date	18-09-219
Contact information	Minh Tam Le, A.Prof 0084989228779

NCT04509583 *(Continued)*

	leminhtam@huemed-univ.edu.vn Hue University Vietnam
Notes	

PACTR201802003076341

Study name	Effects of different antioxidants on sperm parameters in infertile males
Methods	Interventional (clinical trial) Design Allocation: randomised Intervention model: randomised controlled trial Masking: outcome assessors Sample size: 105
Participants	Inclusion criteria: • Male factor primary infertility • Male aged 20-40 years Exclusion criteria: • Azoospermia • Testicular atrophy • Hepatitis C • Drug addicts
Interventions	Drug: vitamin C 1000 mg and zinc 20 mg once daily Control: acetyl-cysteine 200 mg and selenium 100 mg once daily, vitamin E 1000 mg and folic acid 400 mcg once daily Duration: 12 weeks
Outcomes	Primary: sperm motility, concentration and morphology Secondary: none
Starting date	15-02-2016
Contact information	Mohamed Elsamra, Professor of Obstetrics and Gynaecology Faculty of Medicine, University of Alexandria 175 Horyia Street, Ibrahimia, Alexandria, 21524, Egypt melsamra@yahoo.com; 002-01111113015 Elsayedamr Basma, Patient Information Manager 30 Garden City Smouha, Alexandria, 21615, Egypt elsayedamr@yahoo.com; 00201223106023

PACTR201802003076341 *(Continued)*

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Notes

ART: assisted reproductive technique; **BMI:** body mass index; **DHA:** docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **FSH:** follicle-stimulating hormone; **GnRH:** gonadotropin releasing hormone; **ICSI:** intracytoplasmic sperm injection;**DHA:** docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **IUI:** intrauterine insemination; **IVF:** in vitro fertilisation; **LH:** luteinizing hormone; **MDA:** malondialdehyde; **OAT:**oligoasthenoteratozoospermia; **PUFA:** polyunsaturated fatty acids; **ROS:** reactive oxygen species; **SCSA:** sperm chromatin structure analysis; **TAC:** total antioxidant capacity; **TUNEL:** Terminal deoxynucleotidyl transferase dUTP nick end labeling; **WHO:** World Health Organization.

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth; type of antioxidant	12	1283	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [1.07, 1.91]
1.1.1 Astaxanthin + Vitamin E	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [0.34, 7.69]
1.1.2 Carnitines	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.24, 4.25]
1.1.3 Coenzyme Q10	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.53, 8.82]
1.1.4 Vitamin D + Calcium	1	330	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.59, 1.80]
1.1.5 Vitamin E	2	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.51 [2.36, 30.70]
1.1.6 Zinc	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.74 [1.02, 13.74]
1.1.7 Combined antioxidants	5	557	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.86, 1.91]
1.2 Live birth; IVF/ICSI	5	372	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.01, 2.61]
1.3 Clinical pregnancy; type of antioxidant	20	1706	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [1.45, 2.47]
1.3.1 Astaxanthin + Vitamin E	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.35, 4.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Carnitines	2	125	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.30, 4.59]
1.3.3 Coenzyme Q10	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.53, 8.82]
1.3.4 Folic acid	1	53	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.3.5 Magnesium	1	26	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.73 [0.17, 445.08]
1.3.6 N-acetylcysteine (NAC)	2	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.00 [0.71, 5.63]
1.3.7 Vitamin E	2	117	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.71 [1.98, 22.69]
1.3.8 Zinc	2	153	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.43 [1.39, 14.14]
1.3.9 Zinc + Folic acid	1	53	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.86 [0.15, 99.84]
1.3.10 Combined antioxidants	10	983	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [1.22, 2.28]
1.4 Clinical pregnancy; IVF/ICSI	6	452	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [1.15, 2.61]
1.5 Adverse events	21		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.5.1 Miscarriage	6	664	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.75, 2.83]
1.5.2 Ectopic pregnancy	2	260	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.16, 16.01]
1.5.3 Stillbirth	1	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
1.5.4 Gastrointestinal	16	1355	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [1.46, 4.99]
1.5.5 Euphoria	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.16, 9.01]
1.5.6 Headache	1	171	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [0.95, 5.67]
1.5.7 Upper respiratory infection	1	171	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.25, 4.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.8 Nasofaryngitis	1	171	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.17, 1.92]
1.6 Sperm DNA fragmentation at 3 months or less; type of antioxidant	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 Astaxanthin + Vitamin E	1	72	Mean Difference (IV, Fixed, 95% CI)	1.40 [-6.64, 9.44]
1.6.2 Folic acid	1	38	Mean Difference (IV, Fixed, 95% CI)	-5.80 [-13.40, 1.80]
1.6.3 Folic acid + Zinc	1	39	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-9.36, 6.96]
1.6.4 N-acetylcysteine (NAC)	1	35	Mean Difference (IV, Fixed, 95% CI)	3.90 [-0.42, 8.22]
1.6.5 PUFAs	3	137	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-4.00, 1.68]
1.6.6 Vitamin C + Vitamin E	1	64	Mean Difference (IV, Fixed, 95% CI)	-13.80 [-17.50, -10.10]
1.6.7 Zinc	1	42	Mean Difference (IV, Fixed, 95% CI)	1.30 [-8.62, 11.22]
1.6.8 Combined antioxidants	5	569	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-2.00, 0.96]
1.7 Sperm DNA fragmentation at 6 months; type of antioxidant	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 Combined antioxidants	3	320	Mean Difference (IV, Fixed, 95% CI)	-4.57 [-6.49, -2.66]
1.7.2 Zinc + Folic acid	1	853	Mean Difference (IV, Fixed, 95% CI)	3.00 [0.02, 5.98]
1.8 Sperm DNA fragmentation (data not suitable for meta-analysis)	1		Other data	No numeric data
1.8.1 Folic acid	1		Other data	No numeric data
1.9 Total sperm motility at 3 months or less; type of antioxidant	25		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.9.1 Astaxanthin + Vitamin E	1	72	Mean Difference (IV, Fixed, 95% CI)	-5.20 [-11.56, 1.16]
1.9.2 Carnitines	5	244	Mean Difference (IV, Fixed, 95% CI)	31.28 [31.19, 31.37]
1.9.3 Carotenoids	1	36	Mean Difference (IV, Fixed, 95% CI)	3.50 [-6.95, 13.95]
1.9.4 Coenzyme Q10	1	47	Mean Difference (IV, Fixed, 95% CI)	3.61 [-6.13, 13.35]
1.9.5 Folic acid	2	89	Mean Difference (IV, Fixed, 95% CI)	4.56 [-5.63, 14.74]
1.9.6 Magnesium	1	20	Mean Difference (IV, Fixed, 95% CI)	14.50 [-6.01, 35.01]
1.9.7 N-acetylcysteine (NAC)	1	35	Mean Difference (IV, Fixed, 95% CI)	14.60 [0.32, 28.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.8 PUFAs	3	105	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-9.89, 5.09]
1.9.9 Selenium	1	34	Mean Difference (IV, Fixed, 95% CI)	14.90 [1.14, 28.66]
1.9.10 Vitamin C + Vitamin E	1	64	Mean Difference (IV, Fixed, 95% CI)	2.90 [-7.76, 13.56]
1.9.11 Vitamin E	1	45	Mean Difference (IV, Fixed, 95% CI)	18.90 [4.90, 32.90]
1.9.12 Zinc	3	118	Mean Difference (IV, Fixed, 95% CI)	12.85 [5.40, 20.29]
1.9.13 Zinc + Folic acid	2	93	Mean Difference (IV, Fixed, 95% CI)	5.26 [-3.64, 14.16]
1.9.14 Zinc + Vitamin E	1	20	Mean Difference (IV, Fixed, 95% CI)	26.00 [12.85, 39.15]
1.9.15 Zinc + Vitamin E + Vitamin C	1	22	Mean Difference (IV, Fixed, 95% CI)	26.00 [12.62, 39.38]
1.9.16 Combined antioxidants	7	684	Mean Difference (IV, Fixed, 95% CI)	12.71 [11.33, 14.08]
1.10 Total sperm motility at 3 months or less (data not suitable for meta analysis)	2		Other data	No numeric data
1.10.1 Vitamin E	1		Other data	No numeric data
1.10.2 Combined antioxidants	1		Other data	No numeric data
1.11 Total sperm motility at 6 months; type of antioxidant	17		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 Carnitines	3	136	Mean Difference (IV, Fixed, 95% CI)	10.09 [5.99, 14.19]
1.11.2 Coenzyme Q10	3	479	Mean Difference (IV, Fixed, 95% CI)	7.28 [6.85, 7.72]
1.11.3 Folic acid	2	98	Mean Difference (IV, Fixed, 95% CI)	0.16 [-6.96, 7.29]
1.11.4 N-acetylcysteine (NAC)	1	211	Mean Difference (IV, Fixed, 95% CI)	1.90 [1.20, 2.60]
1.11.5 Selenium	1	211	Mean Difference (IV, Fixed, 95% CI)	3.20 [2.50, 3.90]
1.11.6 Selenium + N-acetylcysteine (NAC)	1	210	Mean Difference (IV, Fixed, 95% CI)	6.30 [5.60, 7.00]
1.11.7 Vitamin D + Calcium	1	260	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-9.57, 1.57]
1.11.8 Vitamin E	2	132	Mean Difference (IV, Fixed, 95% CI)	11.60 [6.18, 17.02]
1.11.9 Zinc	2	105	Mean Difference (IV, Fixed, 95% CI)	0.00 [-6.95, 6.95]
1.11.10 Zinc + Folic acid	3	956	Mean Difference (IV, Fixed, 95% CI)	0.24 [-2.54, 3.02]

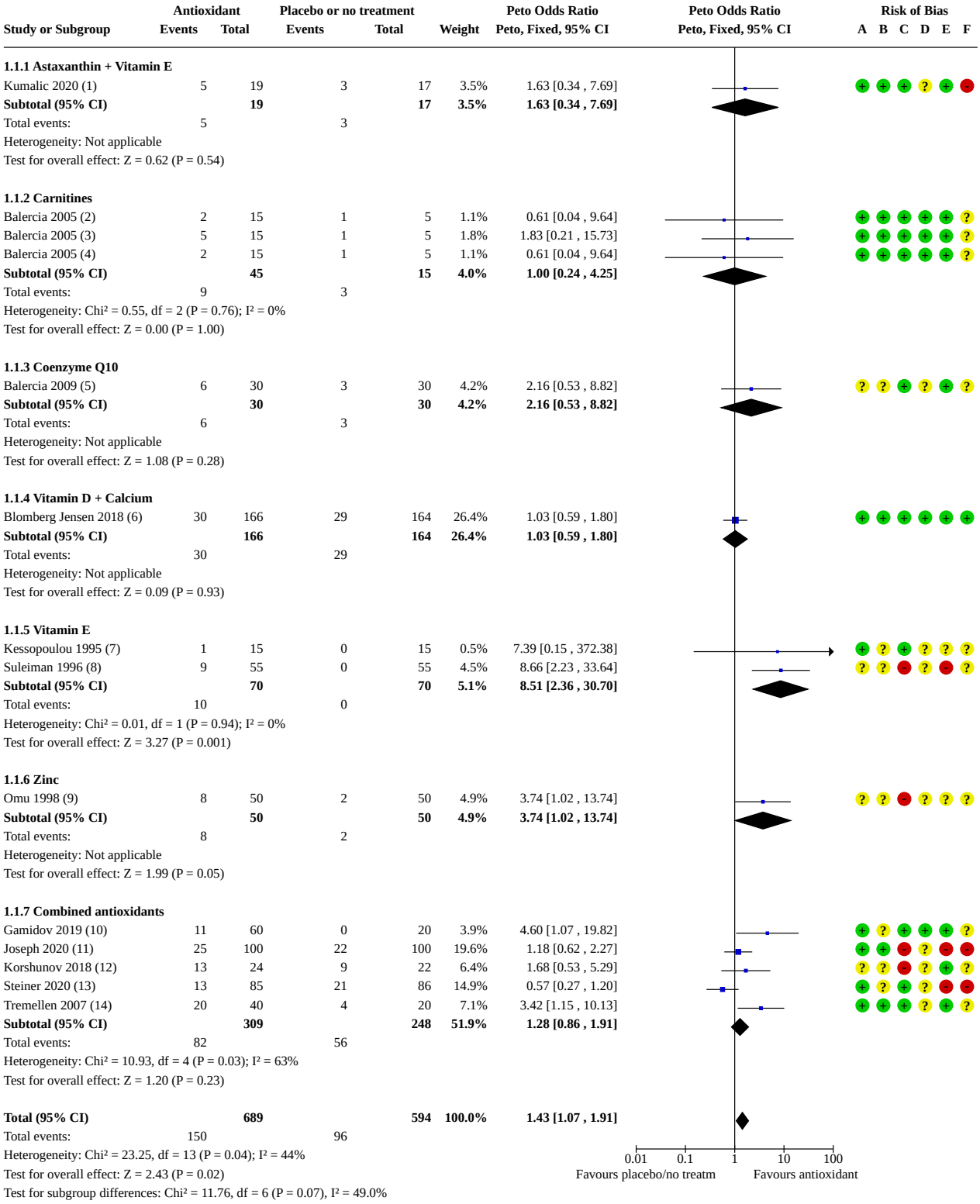
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.11 Combined antioxidants	4	394	Mean Difference (IV, Fixed, 95% CI)	6.76 [4.77, 8.75]
1.12 Total sperm motility at 9 months or more; type of antioxidant	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 Carnitines	1	59	Mean Difference (IV, Fixed, 95% CI)	8.54 [3.01, 14.07]
1.12.2 Coenzyme Q10	3	479	Mean Difference (IV, Fixed, 95% CI)	3.33 [2.91, 3.76]
1.12.3 Vitamin E	1	45	Mean Difference (IV, Fixed, 95% CI)	2.20 [-8.48, 12.88]
1.13 Total sperm motility over time	36		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.13.1 Total sperm motility at 3 months or less	25	1638	Mean Difference (IV, Fixed, 95% CI)	31.17 [31.07, 31.26]
1.13.2 Total sperm motility at 6 months	17	2880	Mean Difference (IV, Fixed, 95% CI)	5.77 [5.45, 6.10]
1.13.3 Total sperm motility at 9 months or more	5	583	Mean Difference (IV, Fixed, 95% CI)	3.36 [2.94, 3.78]
1.14 Progressive sperm motility at 3 months or less; type of antioxidant	28		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.14.1 Astaxanthin + Vitamin E	1	72	Mean Difference (IV, Fixed, 95% CI)	-5.10 [-11.46, 1.26]
1.14.2 Carnitines	4	285	Mean Difference (IV, Fixed, 95% CI)	20.92 [20.52, 21.32]
1.14.3 Carotenoids	1	36	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-7.27, 6.87]
1.14.4 Coenzyme Q10	1	47	Mean Difference (IV, Fixed, 95% CI)	4.60 [-3.54, 12.74]
1.14.5 Folic acid	2	81	Mean Difference (IV, Fixed, 95% CI)	5.08 [-4.00, 14.16]
1.14.6 N-acetylcysteine (NAC)	1	60	Mean Difference (IV, Fixed, 95% CI)	3.80 [-1.03, 8.63]
1.14.7 PUFAs	4	181	Mean Difference (IV, Fixed, 95% CI)	1.53 [0.32, 2.74]
1.14.8 Vitamin C	2	145	Mean Difference (IV, Fixed, 95% CI)	10.95 [4.10, 17.80]
1.14.9 Vitamin C + Vitamin E	1	31	Mean Difference (IV, Fixed, 95% CI)	0.20 [-9.77, 10.17]
1.14.10 Vitamin D	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-7.65, 5.97]
1.14.11 Zinc	2	157	Mean Difference (IV, Fixed, 95% CI)	1.14 [-3.37, 5.64]
1.14.12 Zinc + Folic acid	1	54	Mean Difference (IV, Fixed, 95% CI)	3.80 [-13.66, 21.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14.13 Combined antioxidants	9	993	Mean Difference (IV, Fixed, 95% CI)	11.16 [9.91, 12.41]
1.15 Progressive sperm motility at 6 months; type of antioxidant	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.15.1 Carnitines	2	145	Mean Difference (IV, Fixed, 95% CI)	11.66 [8.68, 14.64]
1.15.2 Coenzyme Q10	1	60	Mean Difference (IV, Fixed, 95% CI)	5.00 [2.13, 7.87]
1.15.3 Folic acid	2	81	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-10.21, 6.67]
1.15.4 PUFAs	1	227	Mean Difference (IV, Fixed, 95% CI)	8.80 [8.11, 9.49]
1.15.5 Vitamin D + Calcium	1	260	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-9.59, 1.59]
1.15.6 Zinc	1	57	Mean Difference (IV, Fixed, 95% CI)	2.00 [-13.56, 17.56]
1.15.7 Zinc + Folic acid	1	54	Mean Difference (IV, Fixed, 95% CI)	2.70 [-14.58, 19.98]
1.15.8 Combined antioxidants	5	470	Mean Difference (IV, Fixed, 95% CI)	4.01 [2.05, 5.96]
1.16 Progressive sperm motility at 6 months (data not suitable for meta analysis)	1		Other data	No numeric data
1.16.1 Coenzyme Q10	1		Other data	No numeric data
1.16.2 Glutathione	1		Other data	No numeric data
1.17 Progressive sperm motility at 9 months or more; type of antioxidant	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.17.1 Carnitines	1	59	Mean Difference (IV, Fixed, 95% CI)	7.77 [2.68, 12.87]
1.17.2 Coenzyme Q10	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.68, 0.88]
1.18 Progressive sperm motility over time	32		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.18.1 Progressive sperm motility at 3 months or less	27	2054	Mean Difference (IV, Fixed, 95% CI)	17.98 [17.62, 18.34]
1.18.2 Progressive sperm motility at 6 months	12	1304	Mean Difference (IV, Fixed, 95% CI)	8.05 [7.43, 8.66]
1.18.3 Progressive sperm motility at 9 months or more	2	119	Mean Difference (IV, Fixed, 95% CI)	0.04 [-1.64, 1.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.19 Sperm concentration at 3 months or less; type of antioxidant	36		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.19.1 Astaxathin + Vitamin E	1	72	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-6.79, 4.79]
1.19.2 Carnitines	5	333	Mean Difference (IV, Fixed, 95% CI)	8.71 [8.09, 9.34]
1.19.3 Carotenoids	1	36	Mean Difference (IV, Fixed, 95% CI)	6.30 [0.62, 11.98]
1.19.4 Coenzyme Q10	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-12.37, 12.17]
1.19.5 Folic acid	3	119	Mean Difference (IV, Fixed, 95% CI)	3.72 [-4.01, 11.44]
1.19.6 Magnesium	1	20	Mean Difference (IV, Fixed, 95% CI)	5.20 [-2.61, 13.01]
1.19.7 N-acetylcysteine (NAC)	2	95	Mean Difference (IV, Fixed, 95% CI)	4.59 [-0.27, 9.46]
1.19.8 PUFAs	5	209	Mean Difference (IV, Fixed, 95% CI)	3.42 [1.69, 5.15]
1.19.9 Selenium	1	34	Mean Difference (IV, Fixed, 95% CI)	21.20 [-4.90, 47.30]
1.19.10 Vitamin C	1	115	Mean Difference (IV, Fixed, 95% CI)	9.70 [0.09, 19.31]
1.19.11 Vitamin C + Vitamin E	2	95	Mean Difference (IV, Fixed, 95% CI)	1.31 [-6.58, 9.20]
1.19.12 Vitamin D	1	62	Mean Difference (IV, Fixed, 95% CI)	-2.12 [-8.85, 4.61]
1.19.13 Vitamin E	1	45	Mean Difference (IV, Fixed, 95% CI)	18.90 [3.92, 33.88]
1.19.14 Zinc	3	199	Mean Difference (IV, Fixed, 95% CI)	6.74 [2.81, 10.68]
1.19.15 Zinc + Folic acid	2	93	Mean Difference (IV, Fixed, 95% CI)	0.48 [-6.79, 7.75]
1.19.16 Combined antioxidants	11	1165	Mean Difference (IV, Fixed, 95% CI)	0.53 [-0.33, 1.40]
1.20 Sperm concentration at 3 months or less (data not suitable for meta analysis)	2		Other data	No numeric data
1.20.1 Carnitines	1		Other data	No numeric data
1.20.2 Vitamin E	1		Other data	No numeric data
1.21 Sperm concentration at 6 months; type of antioxidant	20		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.21.1 Carnitines	3	201	Mean Difference (IV, Fixed, 95% CI)	7.42 [4.97, 9.87]
1.21.2 Coenzyme Q10	3	479	Mean Difference (IV, Fixed, 95% CI)	8.80 [7.95, 9.64]
1.21.3 Folic acid	3	128	Mean Difference (IV, Fixed, 95% CI)	17.39 [11.09, 23.69]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21.4 N-acetylcysteine (NAC)	1	211	Mean Difference (IV, Fixed, 95% CI)	3.30 [1.80, 4.80]
1.21.5 PUFAs	1	227	Mean Difference (IV, Fixed, 95% CI)	12.50 [11.39, 13.61]
1.21.6 Selenium	1	211	Mean Difference (IV, Fixed, 95% CI)	4.10 [2.45, 5.75]
1.21.7 Selenium + N-acetylcysteine (NAC)	1	210	Mean Difference (IV, Fixed, 95% CI)	8.60 [6.89, 10.31]
1.21.8 Vitamin D + Calcium	1	269	Mean Difference (IV, Fixed, 95% CI)	-2.50 [-8.18, 3.18]
1.21.9 Vitamin E	1	45	Mean Difference (IV, Fixed, 95% CI)	5.90 [-10.83, 22.63]
1.21.10 Zinc	2	105	Mean Difference (IV, Fixed, 95% CI)	5.51 [-4.00, 15.01]
1.21.11 Zinc + Folic acid	3	956	Mean Difference (IV, Fixed, 95% CI)	1.44 [-6.70, 9.58]
1.21.12 Combined antioxidants	6	534	Mean Difference (IV, Fixed, 95% CI)	3.16 [2.28, 4.05]
1.22 Sperm concentration at 6 months (data not suitable for meta analysis)	1		Other data	No numeric data
1.22.1 Glutathione	1		Other data	No numeric data
1.22.2 Coenzyme Q10	1		Other data	No numeric data
1.23 Sperm concentration at 9 months or more; type of antioxidant	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.23.1 Carnitines	1	59	Mean Difference (IV, Fixed, 95% CI)	4.17 [-1.71, 10.06]
1.23.2 Coenzyme Q10	3	479	Mean Difference (IV, Fixed, 95% CI)	3.93 [3.19, 4.67]
1.23.3 Vitamin E	1	45	Mean Difference (IV, Fixed, 95% CI)	11.40 [-2.56, 25.36]
1.24 Sperm concentration over time	46		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.24.1 Sperm concentration at 3 months or less	35	2535	Mean Difference (IV, Fixed, 95% CI)	5.49 [5.02, 5.96]
1.24.2 Sperm concentration 6 months	19	2995	Mean Difference (IV, Fixed, 95% CI)	7.21 [6.73, 7.70]
1.24.3 Sperm concentration at 9 months or more	5	583	Mean Difference (IV, Fixed, 95% CI)	3.95 [3.22, 4.69]

Analysis 1.1. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 1: Live birth; type of antioxidant



Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.

(2) L-acetyl carnitine 3000 mg. Natural conception. Additional data from author received.

Analysis 1.1. (Continued)

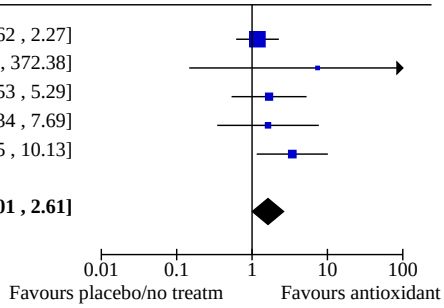
(1) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.
(2) L-acetyl carnitine 3000 mg. Natural conception. Additional data from author received.
(3) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Natural conception. Additional data from author received.
(4) L-carnitine 3000 mg. Natural conception. Additional data from author received.
(5) Coenzyme Q10 200 mg. Natural conception. Additional data from author received.
(6) Vitamin D 1400IU + Calcium 500 mg. Natural conception for 11/ 59 pregnancies, no significant difference between groups.
(7) Vitamin E 600 mg. IVF.
(8) Vitamin E 300 mg. Natural conception. Unable to use ITT as it was unknown from which group the 23 were lost from.
(9) Zinc 500 mg. Natural conception.
(10) SpermActin Forte. From e-mail: natural conception.
(11) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(12) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(13) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D. Natural conception and IUI with ovulation induction with Clomid.
(14) Menevit. IVF: 3 sets of twin pregnancies in the combined antioxidants group and nil in the control group. Each twin pregnancy was counted as one pregnancy event.

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

Analysis 1.2. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 2: Live birth; IVF/ICSI

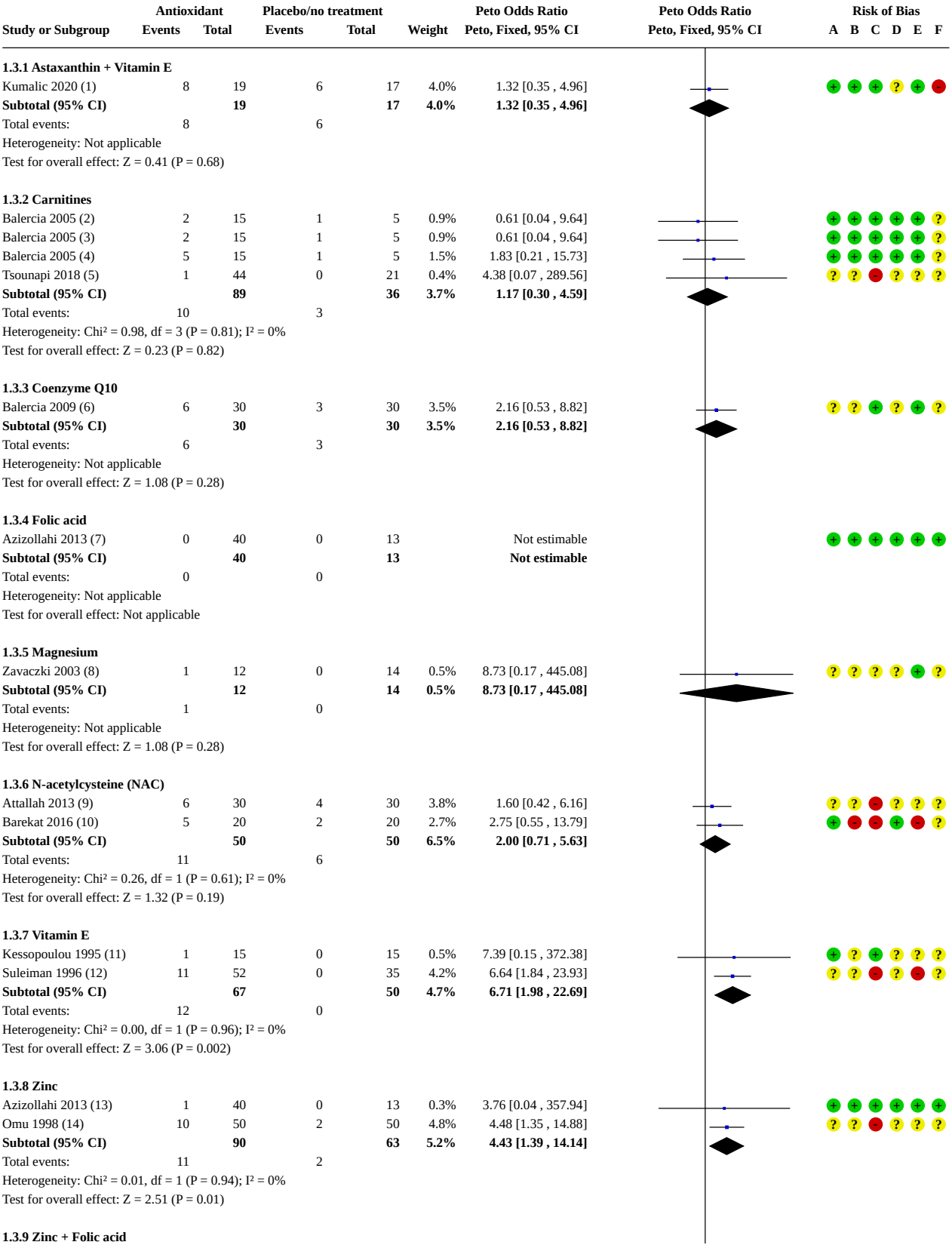
Study or Subgroup	Antioxidant Events	Antioxidant Total	Placebo/no treatm Events	Placebo/no treatm Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Joseph 2020 (1)	25	100	22	100	53.0%	1.18 [0.62 , 2.27]
Kessopoulou 1995 (2)	1	15	0	15	1.5%	7.39 [0.15 , 372.38]
Korshunov 2018 (3)	13	24	9	22	17.2%	1.68 [0.53 , 5.29]
Kumalic 2020 (4)	5	19	3	17	9.3%	1.63 [0.34 , 7.69]
Tremellen 2007 (5)	20	40	4	20	19.1%	3.42 [1.15 , 10.13]
Total (95% CI)		**198**		**174**	**100.0%**	**1.63 [1.01 , 2.61]**
Total events:	64		38			

Heterogeneity: Chi² = 3.30, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable

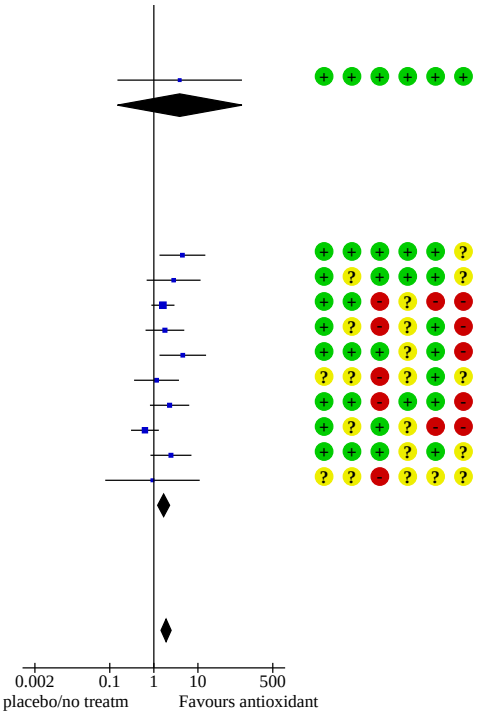


Footnotes
(1) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(2) Vitamin E 600 mg.
(3) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(4) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.
(5) Combined antioxidants (Menevit). 3 sets of twin pregnancies in the combined antioxidants group: each twin was counted as one pregnancy event.

Analysis 1.3. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 3: Clinical pregnancy; type of antioxidant



Analysis 1.3. (Continued)



1.3.9 Zinc + Folic acid						
Azizollahi 2013 (15)	2	40	0	13	0.7%	3.86 [0.15 , 99.84]
Subtotal (95% CI)		**40**		**13**	**0.7%**	**3.86 [0.15 , 99.84]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.3.10 Combined antioxidants						
Busetto 2018 (16)	10	52	2	52	4.9%	4.45 [1.34 , 14.73]
Gamidov 2019 (17)	11	60	1	20	3.5%	2.81 [0.69 , 11.49]
Joseph 2020 (18)	35	100	25	100	19.2%	1.61 [0.88 , 2.94]
Kizilay 2019 (19)	18	64	5	29	6.8%	1.78 [0.65 , 4.90]
Kopets 2020 (20)	10	42	2	41	4.7%	4.54 [1.34 , 15.31]
Korshunov 2018 (21)	15	24	13	22	5.1%	1.15 [0.36 , 3.72]
Popova 2019 (22)	27	60	5	20	6.6%	2.28 [0.82 , 6.36]
Steiner 2020 (23)	15	85	22	86	13.2%	0.63 [0.30 , 1.30]
Tremellen 2007 (24)	21	40	6	20	6.1%	2.44 [0.84 , 7.13]
Tsounapi 2018 (25)	2	45	1	21	1.1%	0.93 [0.08 , 10.98]
Subtotal (95% CI)		**572**		**411**	**71.2%**	**1.67 [1.22 , 2.28]**
Total events:	164		82			
Heterogeneity: Chi² = 14.14, df = 9 (P = 0.12); I² = 36%						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)		**1009**		**697**	**100.0%**	**1.89 [1.45 , 2.47]**
Total events:	225		102			
Heterogeneity: Chi² = 23.79, df = 23 (P = 0.42); I² = 3%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
Test for subgroup differences: Chi² = 8.41, df = 8 (P = 0.39), I² = 4.9%						

Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.
(2) L-acetyl carnitine 3000 mg. Natural conception.
(3) L-carnitine 3000 mg. Natural conception.
(4) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Natural conception.
(5) L-carnitine 1000 mg. Appear to be spontaneous. Trial with 5 arms, 1 event in control group used in "Combined antioxidants" subgroup.
(6) Coenzyme Q10 200 mg. Natural conception.
(7) Folic acid 5 mg. Natural conception. After varicocelectomy. Additional data from authors received on pregnancy and dropouts.
(8) Magnesium 3000 mg. Natural conception.
(9) N-acetylcysteine (NAC) 600 mg. IUI.
(10) N-acetylcysteine (NAC) 200 mg. Natural conception. After varicocelectomy
(11) Vitamin E 600 mg. IVF.
(12) Vitamin E 300 mg. Natural conception.
(13) Zinc 66 mg. Natural conception. After varicocelectomy. Additional data from authors received on pregnancy and dropouts.
(14) Zinc 500 mg. Natural conception.
(15) Zinc 66 mg + Folic acid 5 mg. Natural conception. After varicocelectomy. Additional data from authors received on pregnancy and dropouts.
(16) Proxeed plus. Spontaneous. Also 1 spontaneous abortion. Varicocele patients
(17) SpermActin Forte. Spontaneous. Clarification in e-mail, see included studies table.
(18) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(19) L-carnitine 1 g + acetyl-L-carnitine 0,5 g + fructose 1 g + citric acid 50 mg + vitamin C 90 mg + zinc 10 mg + folic acid 200 mcg + selenium 50 mcg + coenzyme Q10 20 mg +
(20) Verum TDS (l-carnitine/ l-acetyl-carnitine 1990 mg + l-arginine 250 mg + glutathione 100 mg + coenzyme Q10 40 mg + zinc 7.5 mg + vitamin B9 234 mg + vitamin B12 2 mcg
(21) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(22) Androdoz. IVF/ICSI.
(23) Vitamin C 500 mg + vitamin E 400 mg + selenium 0.20 mg + l-carnitine 1000 mg + zinc 20 mg + folic acid 1000 mg + lycopene 10 mg + vitamin D 2,000 IU. Natural conceptic
(24) Menevit. Additional data from author received: IVF: 3 sets of twin pregnancies in the combined antioxidants group, each twin was counted as one pregnancy event.
(25) Profertil. Appear to be spontaneous.

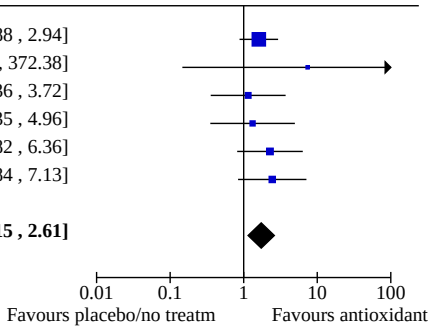
Risk of bias legend

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

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

Study or Subgroup	Antioxidant Events	Antioxidant Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Joseph 2020 (1)	35	100	25	100	46.3%	1.61 [0.88 , 2.94]
Kessopoulou 1995 (2)	1	15	0	15	1.1%	7.39 [0.15 , 372.38]
Korshunov 2018 (3)	15	24	13	22	12.3%	1.15 [0.36 , 3.72]
Kumalic 2020 (4)	8	19	6	17	9.6%	1.32 [0.35 , 4.96]
Popova 2019 (5)	27	60	5	20	16.0%	2.28 [0.82 , 6.36]
Tremellen 2007 (6)	21	40	6	20	14.7%	2.44 [0.84 , 7.13]
Total (95% CI)		**258**		**194**	**100.0%**	**1.73 [1.15 , 2.61]**
Total events:	107		55			

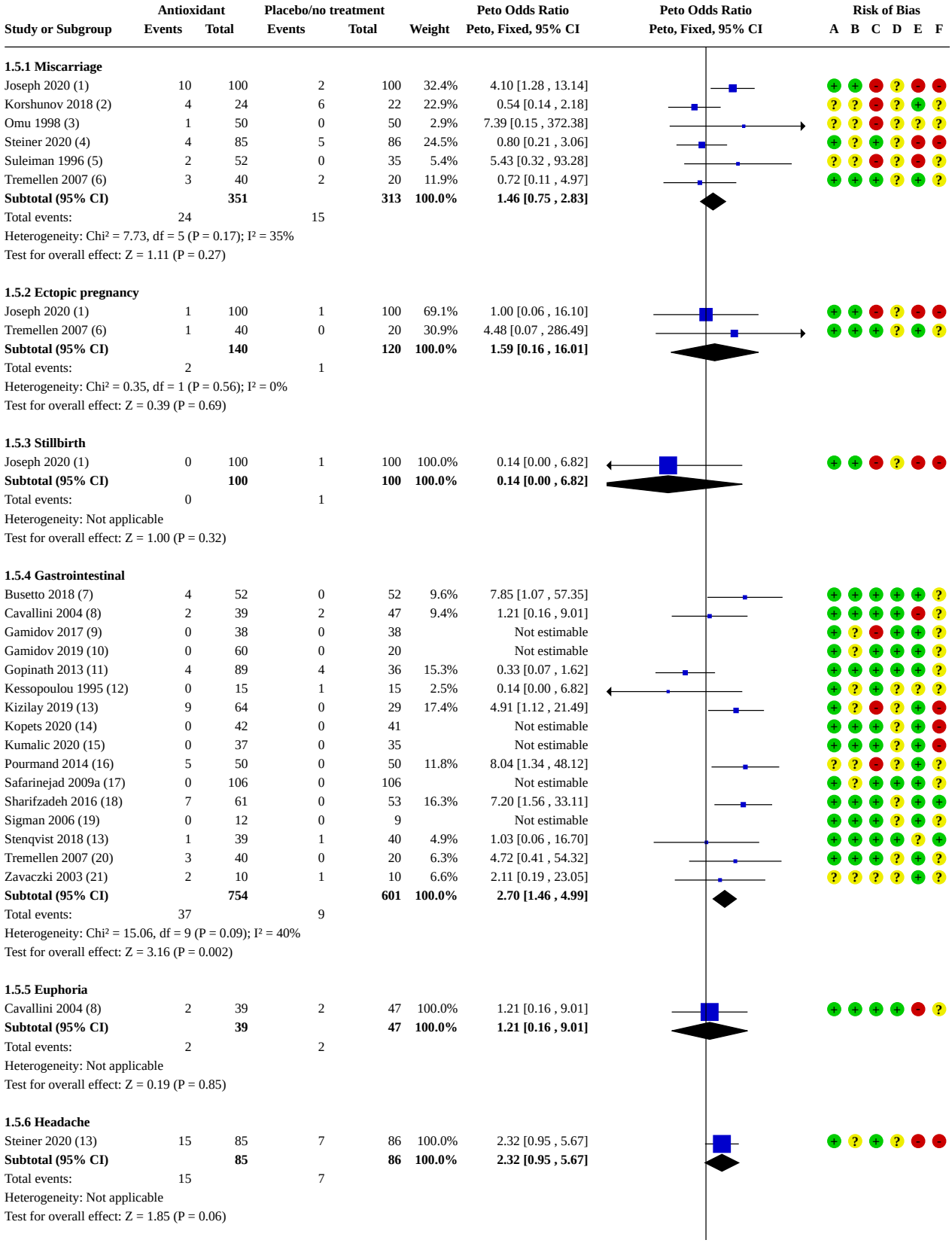
Heterogeneity: Chi² = 1.89, df = 5 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)
Test for subgroup differences: Not applicable



Footnotes

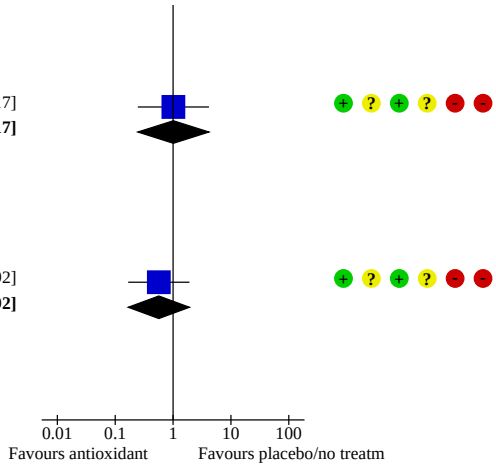
(1) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(2) Vitamin E 600 mg.
(3) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(4) Astaxanthin 16 mg + Vitamin E 40 mg. ICSI.
(5) Combined antioxidants (Androdoz).
(6) Combined antioxidants (Menevit). IVF: 3 sets of twin pregnancies in the combined antioxidants group and nil in the control group. Each twin pregnancy was

Analysis 1.5. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 5: Adverse events



Analysis 1.5. (Continued)

Test for overall effect: Z = 1.85 (P = 0.06)						
1.5.7 Upper respiratory infection						
Steiner 2020 (22)	4	85	4	86	100.0%	1.01 [0.25 , 4.17]
Subtotal (95% CI)		**85**		**86**	**100.0%**	**1.01 [0.25 , 4.17]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
1.5.8 Nasofaryngitis						
Steiner 2020 (13)	4	85	7	86	100.0%	0.57 [0.17 , 1.92]
Subtotal (95% CI)		**85**		**86**	**100.0%**	**0.57 [0.17 , 1.92]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Chi² = 8.19, df = 7 (P = 0.32), I² = 14.5%						



Footnotes

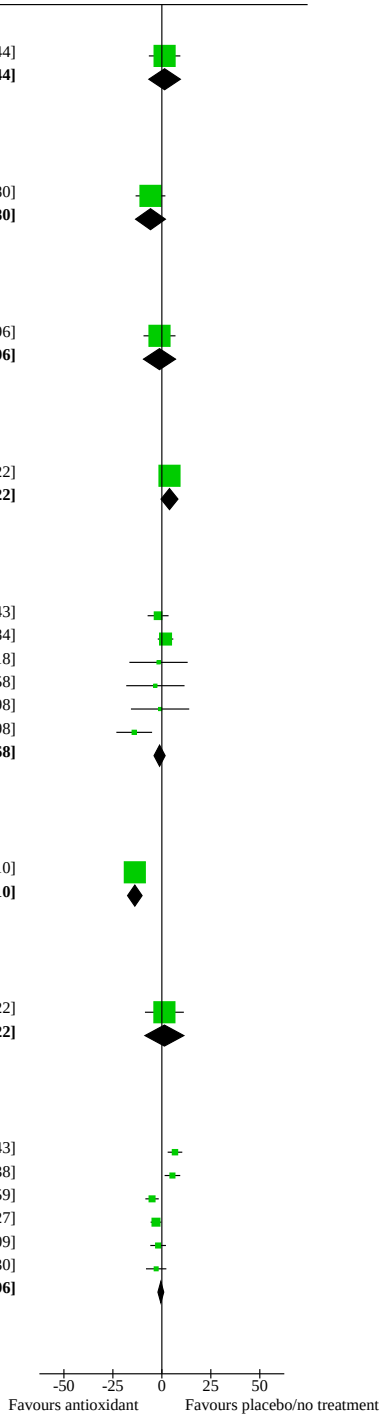
(1) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg. ICSI.
(2) Vitamin E 400 mg + Vitamin C 1000 mg + selenium 50 mcg + L-carnitine 1000 mg. TESA/ICSI.
(3) Zinc 500 mg versus no treatment. Natural conception.
(4) Combined antioxidants versus placebo. Natural conception and IUI.
(5) Vitamin E 300 mg versus placebo. Natural conception.
(6) Combined antioxidants (Menevit) versus placebo. IVF.
(7) Combined antioxidants (Proxeed Plus) versus placebo.
(8) L-carnitine 1 x 2000 mg/day + acetyl-L-carnitine 500 x 2 mg/day + glycerine suppository versus placebo. After varicocelectomy.
(9) Combined antioxidant (SpermActin-forte) versus no treatment.
(10) Combined antioxidants (SpermActin Forte) versus placebo.
(11) 1 or 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg) versus placebo.
(12) Vitamin E 600 mg versus placebo.
(13) Combined antioxidants versus placebo.
(14) Combined antioxidant (Verum TDS) versus placebo TDS
(15) Astaxanthin 16 mg + Vitamin E 40 mg versus placebo.
(16) L-carnitine 750 mg versus no treatment.
(17) Coenzyme Q10 300 mg versus placebo.
(18) Zinc solution 0.5% 10 ml versus placebo solution 10 ml.
(19) L-carnitine 2000 mg + L-acetylcarnitine 1000 mg versus placebo.
(20) Combined antioxidants (Menevit) versus placebo.
(21) Magnesium 3000 mg versus placebo.
(22) Combined antioxidants versus placebo. Upper respiratory infections.

Risk of bias legend

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

Analysis 1.6. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 6: Sperm DNA fragmentation at 3 months or less; type of antioxidant

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 Astaxanthin + Vitamin E								
Kumalic 2020 (1)	51.2	17.9	37	49.8	16.9	35	100.0%	1.40 [-6.64 , 9.44]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**1.40 [-6.64 , 9.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
1.6.2 Folic acid								
Raigani 2014 (2)	33.1	8.2	20	38.9	14.5	18	100.0%	-5.80 [-13.40 , 1.80]
Subtotal (95% CI)			**20**			**18**	**100.0%**	**-5.80 [-13.40 , 1.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.50 (P = 0.13)								
1.6.3 Folic acid + Zinc								
Raigani 2014 (3)	37.7	10.9	21	38.9	14.5	18	100.0%	-1.20 [-9.36 , 6.96]
Subtotal (95% CI)			**21**			**18**	**100.0%**	**-1.20 [-9.36 , 6.96]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
1.6.4 N-acetylcysteine (NAC)								
Barekat 2016 (4)	89.8	5.4222	15	85.9	7.6026	20	100.0%	3.90 [-0.42 , 8.22]
Subtotal (95% CI)			**15**			**20**	**100.0%**	**3.90 [-0.42 , 8.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.77 (P = 0.08)								
1.6.5 PUFAs								
Abbasi 2020 (5)	16.45	6	9	18.37	6.15	11	28.2%	-1.92 [-7.27 , 3.43]
Abbasi 2020 (6)	12.26	4.62	10	10.38	4.64	11	51.2%	1.88 [-2.08 , 5.84]
Gonzalez-Ravina 2018 (7)	7.8	9.8	15	9.5	16	5	3.6%	-1.70 [-16.58 , 13.18]
Gonzalez-Ravina 2018 (8)	6.2	9.8	15	9.5	16	5	3.6%	-3.30 [-18.18 , 11.58]
Gonzalez-Ravina 2018 (9)	8.6	9.8	15	9.5	16	5	3.6%	-0.90 [-15.78 , 13.98]
Martinez-Soto 2010 (10)	11	9.8	21	25.1	16	15	9.7%	-14.10 [-23.22 , -4.98]
Subtotal (95% CI)			**85**			**52**	**100.0%**	**-1.16 [-4.00 , 1.68]**
Heterogeneity: Chi² = 10.16, df = 5 (P = 0.07); I² = 51%								
Test for overall effect: Z = 0.80 (P = 0.42)								
1.6.6 Vitamin C + Vitamin E								
Greco 2005 (11)	9.1	7.2	32	22.9	7.9	32	100.0%	-13.80 [-17.50 , -10.10]
Subtotal (95% CI)			**32**			**32**	**100.0%**	**-13.80 [-17.50 , -10.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.30 (P < 0.00001)								
1.6.7 Zinc								
Raigani 2014 (12)	40.2	18.3	24	38.9	14.5	18	100.0%	1.30 [-8.62 , 11.22]
Subtotal (95% CI)			**24**			**18**	**100.0%**	**1.30 [-8.62 , 11.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
1.6.8 Combined antioxidants								
Gamidov 2017 (13)	24.9	6.7	38	18.2	6.8	19	15.8%	6.70 [2.97 , 10.43]
Gamidov 2017 (14)	23.6	8	38	18.2	6.8	19	13.9%	5.40 [1.42 , 9.38]
Gamidov 2019 (15)	18	5.1	60	23	7.2	20	18.9%	-5.00 [-8.41 , -1.59]
Micic 2019 (16)	35	13.9	119	38	3.8	46	29.5%	-3.00 [-5.73 , -0.27]
Steiner 2020 (17)	21.4	10.5	65	23.3	13.1	70	13.8%	-1.90 [-5.89 , 2.09]
Stenqvist 2018 (18)	31.2	10.4	37	34.1	12.5	38	8.1%	-2.90 [-8.10 , 2.30]
Subtotal (95% CI)			**357**			**212**	**100.0%**	**-0.52 [-2.00 , 0.96]**
Heterogeneity: Chi² = 34.00, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 0.69 (P = 0.49)								
Test for subgroup differences: Chi² = 52.10, df = 7 (P < 0.00001), I² = 86.6%								



Footnotes

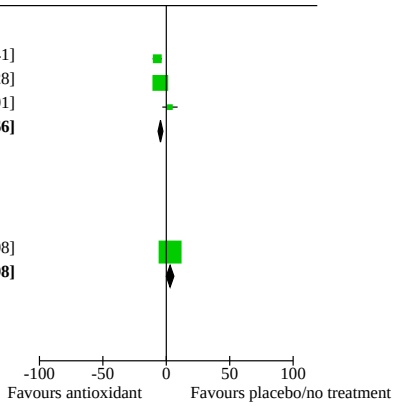
(1) TUNEL assay. Astaxanthin 16 mg + Vitamin E 40 mg.
(2) Toluidine blue (TB) staining. Folic acid 5 mg.
(3) Toluidine blue (TB) staining. Folic acid 5 mg + Zinc 220 mg.
(4) TUNEL assay. N-acetylcysteine (NAC) 200 mg. Post varicocelectomy.
(5) SCSA assay. Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(6) TUNEL assay. Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(7) TUNEL assay. Docosahexaenoic acid (DHA) 1 g

Analysis 1.6. (Continued)

(5) SCSA assay. Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(6) TUNEL assay. Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(7) TUNEL assay. Docosahexaenoic acid (DHA) 1 g.
(8) TUNEL assay. Docosahexaenoic acid (DHA) 2 g.
(9) TUNEL assay. Docosahexaenoic acid (DHA) 0.5 g.
(10) TUNEL assay. Brudy Plus (DHA 1000 mg + eicosapentaenoic acid (EPA) 135 mg). At 10 weeks.
(11) TUNEL assay. Vitamin C 1000 mg + Vitamin E 1000 mg. At 2 months.
(12) Toluidine blue (TB) staining. Zinc 220 mg.
(13) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(14) SpermActin Forte. After varicocelectomy.
(15) TUNEL assay. SpermActin Forte.
(16) Sperm chromatin dispersion test (Halosperm). Proxeed plus.
(17) Sperm chromatin structure analysis (SCSA) test. Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(18) Sperm chromatin structure analysis (SCSA) test. Androferti.

Analysis 1.7. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 7: Sperm DNA fragmentation at 6 months; type of antioxidant

	Antioxidant			Placebo/no treatment				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
1.7.1 Combined antioxidants									
Gamidov 2019 (1)	15.6	5.5	60	22.7	7.8	20	27.0%	-7.10 [-10.79 , -3.41]	
Micic 2019 (2)	32.3	12	119	37	3.8	46	62.8%	-4.70 [-7.12 , -2.28]	
Stenqvist 2018 (3)	34	12	36	31.1	14.5	39	10.2%	2.90 [-3.11 , 8.91]	
Subtotal (95% CI)			**215**			**105**	**100.0%**	**-4.57 [-6.49 , -2.66]**	
Heterogeneity: Chi² = 7.76, df = 2 (P = 0.02); I² = 74%									
Test for overall effect: Z = 4.67 (P < 0.00001)									
1.7.2 Zinc + Folic acid									
Schisterman 2020 (4)	33	24	425	30	20.3	428	100.0%	3.00 [0.02 , 5.98]	
Subtotal (95% CI)			**425**			**428**	**100.0%**	**3.00 [0.02 , 5.98]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.97 (P = 0.05)									
Test for subgroup differences: Chi² = 17.51, df = 1 (P < 0.0001), I² = 94.3%									



Footnotes
(1) TUNEL assay. Spermactin Forte.
(2) Sperm chromatin dispersion test (Halosperm). Proxeed Plus.
(3) Sperm chromatin structure analysis (SCSA) test. Androferti.
(4) Comet assay. Zinc 30 mg + Folic acid 5 mg.

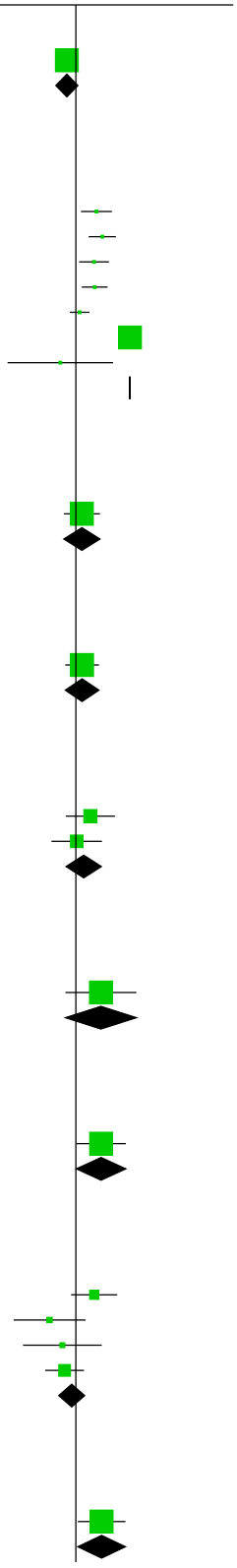
Analysis 1.8. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 8: Sperm DNA fragmentation (data not suitable for meta-analysis)

Sperm DNA fragmentation (data not suitable for meta-analysis)

Study	Intervention	Control	P-value
Folic acid			
Boonyarangkul 2015	**Folic acid** DNA tail length, COMET assay 3 month: Mean = 4.04 (n = 15) SE = 0.94 6 month: Mean = 6.01 SE = 1.49	**Placebo** DNA tail length, COMET assay 3 month**:** Mean = 10.08 (n = 15) SE = 3.39 6 month: Mean = 8.69 SE = 4.28	Not provided

Analysis 1.9. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 9: Total sperm motility at 3 months or less; type of antioxidant

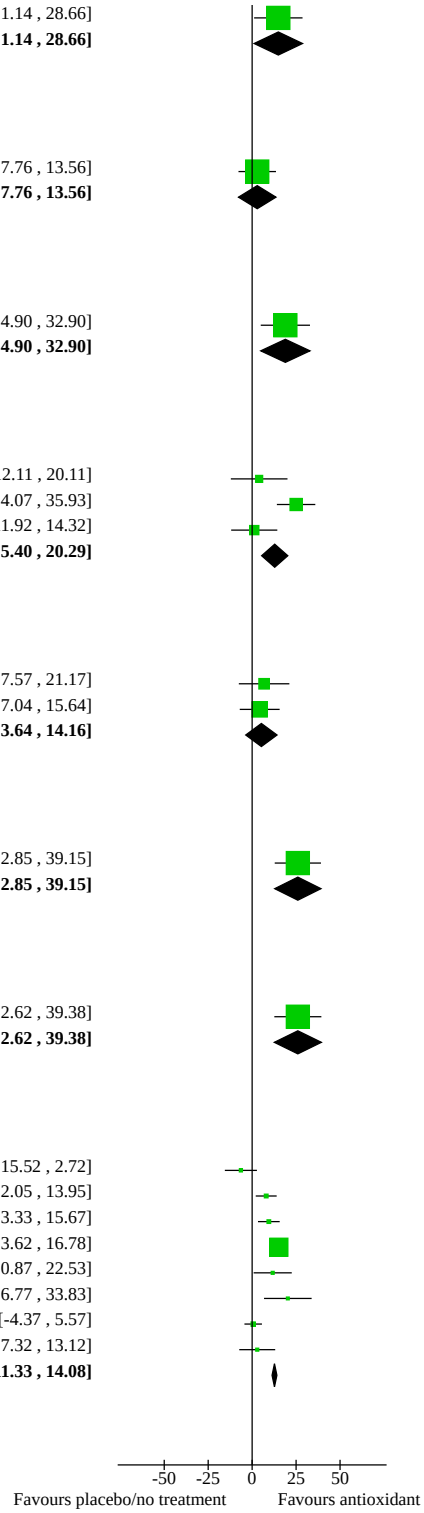
Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Astaxanthin + Vitamin E								
Kumalic 2020 (1)	37.9	14.7	37	43.1	12.8	35	100.0%	-5.20 [-11.56 , 1.16]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**-5.20 [-11.56 , 1.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.60 (P = 0.11)								
1.9.2 Carnitines								
Balercia 2005 (2)	56.5	11.6	15	44.6	7.7	5	0.0%	11.90 [2.96 , 20.84]
Balercia 2005 (3)	59.9	8	15	44.6	7.7	5	0.0%	15.30 [7.43 , 23.17]
Balercia 2005 (4)	55.1	10.2	14	44.6	7.7	5	0.0%	10.50 [1.89 , 19.11]
Dimitriadis 2010 (5)	35.6	15.5	26	24.7	10.8	22	0.0%	10.90 [3.43 , 18.37]
Lenzi 2003 (6)	11	15.5	43	8.8	10.8	43	0.0%	2.20 [-3.45 , 7.85]
Peivandi 2010 (7)	48.3	0.16	15	17	0.09	15	99.9%	31.30 [31.21 , 31.39]
Sigman 2006 (8)	28.6	38.1	12	37.6	33	9	0.0%	-9.00 [-39.49 , 21.49]
Subtotal (95% CI)			**140**			**104**	**100.0%**	**31.28 [31.19 , 31.37]**
Heterogeneity: Chi² = 193.59, df = 6 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 660.23 (P < 0.00001)								
1.9.3 Carotenoids								
Nouri 2019 (9)	30.7	16.8	17	27.2	15	19	100.0%	3.50 [-6.95 , 13.95]
Subtotal (95% CI)			**17**			**19**	**100.0%**	**3.50 [-6.95 , 13.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
1.9.4 Coenzyme Q10								
Nadjarzadeh 2011 (10)	41.91	15.6	23	38.3	18.4	24	100.0%	3.61 [-6.13 , 13.35]
Subtotal (95% CI)			**23**			**24**	**100.0%**	**3.61 [-6.13 , 13.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								
1.9.5 Folic acid								
Azizollahi 2013 (11)	53.3	15.3	26	44.9	33	25	51.4%	8.40 [-5.81 , 22.61]
Raigani 2014 (12)	33.3	27.9	20	32.8	17.3	18	48.6%	0.50 [-14.11 , 15.11]
Subtotal (95% CI)			**46**			**43**	**100.0%**	**4.56 [-5.63 , 14.74]**
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.88 (P = 0.38)								
1.9.6 Magnesium								
Zavaczki 2003 (13)	33.5	29.8	10	19	14.4	10	100.0%	14.50 [-6.01 , 35.01]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**14.50 [-6.01 , 35.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.39 (P = 0.17)								
1.9.7 N-acetylcysteine (NAC)								
Barekat 2016 (14)	58.2	20.9	15	43.6	21.9	20	100.0%	14.60 [0.32 , 28.88]
Subtotal (95% CI)			**15**			**20**	**100.0%**	**14.60 [0.32 , 28.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.00 (P = 0.05)								
1.9.8 PUFAs								
Abbasi 2020 (15)	50.34	22.67	19	39.76	20.64	22	31.5%	10.58 [-2.77 , 23.93]
Conquer 2000 (16)	32	16.1	10	47.2	18.6	4	13.0%	-15.20 [-35.98 , 5.58]
Conquer 2000 (17)	39.4	24.3	9	47.2	18.6	5	10.8%	-7.80 [-30.56 , 14.96]
Martinez-Soto 2010 (18)	41.5	18.7	21	48	15.5	15	44.7%	-6.50 [-17.70 , 4.70]
Subtotal (95% CI)			**59**			**46**	**100.0%**	**-2.40 [-9.89 , 5.09]**
Heterogeneity: Chi² = 5.82, df = 3 (P = 0.12); I² = 48%								
Test for overall effect: Z = 0.63 (P = 0.53)								
1.9.9 Selenium								
Scott 1998 (19)	30.2	22.8	16	15.3	17.4	18	100.0%	14.90 [1.14 , 28.66]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**14.90 [1.14 , 28.66]**



Analysis 1.9. (Continued)

Scott 1998 (19)	30.2	22.8	16	15.3	17.4	18	100.0%	14.90 [1.14 , 28.66]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**14.90 [1.14 , 28.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.12 (P = 0.03)								
1.9.10 Vitamin C + Vitamin E								
Greco 2005 (20)	41.6	22	32	38.7	21.5	32	100.0%	2.90 [-7.76 , 13.56]
Subtotal (95% CI)			**32**			**32**	**100.0%**	**2.90 [-7.76 , 13.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.59)								
1.9.11 Vitamin E								
Ener 2016 (21)	61.4	18.3	22	42.5	28.7	23	100.0%	18.90 [4.90 , 32.90]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**18.90 [4.90 , 32.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.65 (P = 0.008)								
1.9.12 Zinc								
Azizollahi 2013 (22)	48.9	27.7	32	44.9	33	25	21.4%	4.00 [-12.11 , 20.11]
Omu 2008 (23)	49	12	11	24	12	8	46.4%	25.00 [14.07 , 35.93]
Raigani 2014 (24)	34	26	24	32.8	17.3	18	32.2%	1.20 [-11.92 , 14.32]
Subtotal (95% CI)			**67**			**51**	**100.0%**	**12.85 [5.40 , 20.29]**
Heterogeneity: Chi² = 8.94, df = 2 (P = 0.01); I² = 78%								
Test for overall effect: Z = 3.38 (P = 0.0007)								
1.9.13 Zinc + Folic acid								
Azizollahi 2013 (25)	51.7	17.2	29	44.9	33	25	38.4%	6.80 [-7.57 , 21.17]
Raigani 2014 (26)	37.1	18.8	21	32.8	17.3	18	61.6%	4.30 [-7.04 , 15.64]
Subtotal (95% CI)			**50**			**43**	**100.0%**	**5.26 [-3.64 , 14.16]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%								
Test for overall effect: Z = 1.16 (P = 0.25)								
1.9.14 Zinc + Vitamin E								
Omu 2008 (27)	50	18	12	24	12	8	100.0%	26.00 [12.85 , 39.15]
Subtotal (95% CI)			**12**			**8**	**100.0%**	**26.00 [12.85 , 39.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.88 (P = 0.0001)								
1.9.15 Zinc + Vitamin E + Vitamin C								
Omu 2008 (28)	50	20	14	24	12	8	100.0%	26.00 [12.62 , 39.38]
Subtotal (95% CI)			**14**			**8**	**100.0%**	**26.00 [12.62 , 39.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.81 (P = 0.0001)								
1.9.16 Combined antioxidants								
Bahmyari 2021 (29)	30.3	19.3	30	36.7	17.2	32	2.3%	-6.40 [-15.52 , 2.72]
Gopinath 2013 (30)	50.1	11.3	43	42.1	10.6	18	5.3%	8.00 [2.05 , 13.95]
Gopinath 2013 (31)	51.6	13	46	42.1	10.6	18	5.0%	9.50 [3.33 , 15.67]
Morgante 2010 (32)	40.3	6.4	90	25.1	4.2	90	75.4%	15.20 [13.62 , 16.78]
Scott 1998 (33)	27	20.3	30	15.3	17.4	18	1.6%	11.70 [0.87 , 22.53]
Sivkov 2011 (34)	38.3	20.3	15	18	17.4	15	1.0%	20.30 [6.77 , 33.83]
Steiner 2020 (35)	42.8	16.4	82	42.2	16.1	82	7.6%	0.60 [-4.37 , 5.57]
Stenqvist 2018 (36)	62.8	18.1	37	59.9	26.4	38	1.8%	2.90 [-7.32 , 13.12]
Subtotal (95% CI)			**373**			**311**	**100.0%**	**12.71 [11.33 , 14.08]**
Heterogeneity: Chi² = 57.38, df = 7 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 18.14 (P < 0.00001)								

Test for subgroup differences: Chi² = 1086.87, df = 15 (P < 0.00001), I² = 98.6%



Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg.
(2) L-acetyl carnitine 3000 mg.
(3) L-carnitine 3000 mg.
(4) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(5) L-carnitine 1000 mg.

Analysis 1.9. (Continued)

(4) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(5) L-carnitine 1000 mg.
(6) L-carnitine 2000 mg. Only mean, no SD given.
(7) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(8) L-carnitine 2000 mg + L-acetylcarnitine 1000 mg.
(9) Lycopene 25 mg.
(10) Coenzyme Q10 200 mg.
(11) Folic acid 5 mg. After varicocelectomy.
(12) Folic acid 5 mg. At 16 weeks.
(13) Magnesium 3000 mg.
(14) N-acetylcysteine (NAC) 200 mg. After varicocelectomy.
(15) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(16) Docosahexaenoic acid (DHA) 800 mg.
(17) Docosahexaenoic acid (DHA) 400 mg.
(18) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(19) Selenium 100 µg.
(20) Vitamin C 1000 mg + Vitamin E 1000 mg. At 2 months.
(21) Vitamin E 600 mg. Varicocele patients.
(22) Zinc 66 mg. After varicocelectomy.
(23) Zinc 500 mg.
(24) Zinc 220 mg. At 16 weeks.
(25) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(26) Zinc 220 mg + Folic acid 5 mg. At 16 weeks.
(27) Zinc 400 mg + Vitamin E 20 mg.
(28) Zinc 400 mg + Vitamin E 20 mg + Vitamin C 10 mg.
(29) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(30) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(31) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(32) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(33) Selenium 100 µg + Vitamin A 1 mg + Vitamin C 10 mg + Vitamin E 15 mg.
(34) Selznic (selenium + zinc + vitamins).
(35) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(36) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

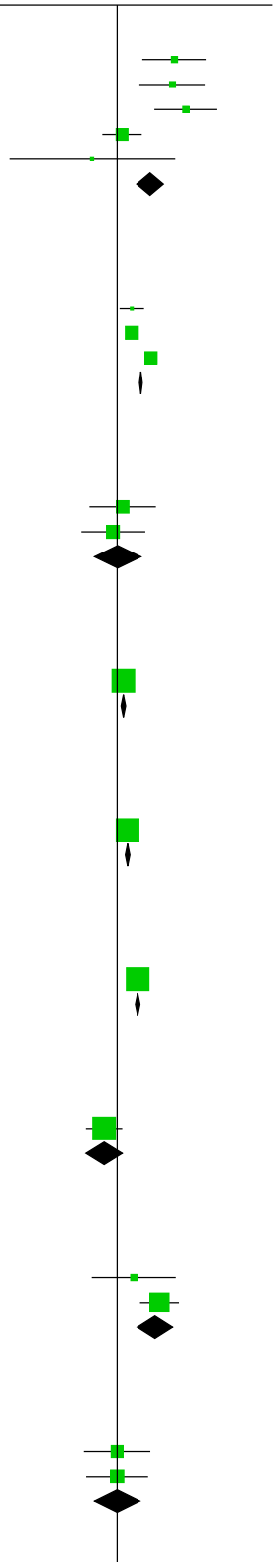
Analysis 1.10. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 10: Total sperm motility at 3 months or less (data not suitable for meta analysis)

Total sperm motility at 3 months or less (data not suitable for meta analysis)

Study	Intervention	Control	P value
Vitamin E			
Kessopoulou 1995	**Vitamin E** Median difference = 7 (n = 15) Min/max difference = -27 - 34	**Placebo** Median difference = 7 (n = 15) Min/max difference = -33 - 36	Not provided
Combined antioxidants			
Galatioto 2008	**N-acetylcysteine (NAC) 600 mg + vitamins-minerals** % of motile sperm (Class A WHO) = 58% (n = 20)	**No treatment** % of motile sperm (Class A WHO) = 51% (n = 22)	P = 0.847

Analysis 1.11. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 11: Total sperm motility at 6 months; type of antioxidant

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.11.1 Carnitines								
Balercia 2005 (1)	61	9	14	43.4	9.9	5	17.3%	17.60 [7.72 , 27.48]
Balercia 2005 (2)	60.4	10.5	15	43.4	9.9	5	16.3%	17.00 [6.82 , 27.18]
Balercia 2005 (3)	64.5	8.41	15	43.4	9.9	5	18.0%	21.10 [11.43 , 30.77]
Lenzi 2004 (4)	31.1	13.5	30	29.6	9.5	26	45.9%	1.50 [-4.56 , 7.56]
Sigman 2006 (5)	32.3	24.2	12	40	33	9	2.6%	-7.70 [-33.24 , 17.84]
Subtotal (95% CI)			**86**			**50**	**100.0%**	**10.09 [5.99 , 14.19]**
Heterogeneity: Chi² = 18.57, df = 4 (P = 0.0010); I² = 78%								
Test for overall effect: Z = 4.82 (P < 0.00001)								
1.11.2 Coenzyme Q10								
Balercia 2009 (6)	39.4	6.8	30	34.9	8	30	1.3%	4.50 [0.74 , 8.26]
Safarinejad 2009a (7)	27.6	2.2	98	23.1	2.1	96	51.5%	4.50 [3.89 , 5.11]
Safarinejad 2012 (6)	35.8	2.7	112	25.4	2.1	113	47.2%	10.40 [9.77 , 11.03]
Subtotal (95% CI)			**240**			**239**	**100.0%**	**7.28 [6.85 , 7.72]**
Heterogeneity: Chi² = 176.67, df = 2 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 32.87 (P < 0.00001)								
1.11.3 Folic acid								
Azizollahi 2013 (8)	51.5	10.2	26	49.8	24	25	48.8%	1.70 [-8.49 , 11.89]
Wong 2002 (9)	35	15.7	22	36.3	19.1	25	51.2%	-1.30 [-11.25 , 8.65]
Subtotal (95% CI)			**48**			**50**	**100.0%**	**0.16 [-6.96 , 7.29]**
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
1.11.4 N-acetylcysteine (NAC)								
Safarinejad 2009 (10)	24.8	2.9	105	22.9	2.2	106	100.0%	1.90 [1.20 , 2.60]
Subtotal (95% CI)			**105**			**106**	**100.0%**	**1.90 [1.20 , 2.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.36 (P < 0.00001)								
1.11.5 Selenium								
Safarinejad 2009 (11)	26.1	2.9	105	22.9	2.2	106	100.0%	3.20 [2.50 , 3.90]
Subtotal (95% CI)			**105**			**106**	**100.0%**	**3.20 [2.50 , 3.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.02 (P < 0.00001)								
1.11.6 Selenium + N-acetylcysteine (NAC)								
Safarinejad 2009 (12)	29.2	2.9	104	22.9	2.2	106	100.0%	6.30 [5.60 , 7.00]
Subtotal (95% CI)			**104**			**106**	**100.0%**	**6.30 [5.60 , 7.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 17.71 (P < 0.00001)								
1.11.7 Vitamin D + Calcium								
Blomberg Jensen 2018 (13)	41	22.7	129	45	23.1	131	100.0%	-4.00 [-9.57 , 1.57]
Subtotal (95% CI)			**129**			**131**	**100.0%**	**-4.00 [-9.57 , 1.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.41 (P = 0.16)								
1.11.8 Vitamin E								
Ener 2016 (14)	60.1	16.1	22	55	26.9	23	17.7%	5.10 [-7.79 , 17.99]
Suleiman 1996 (15)	48.9	15.5	52	35.9	12.8	35	82.3%	13.00 [7.02 , 18.98]
Subtotal (95% CI)			**74**			**58**	**100.0%**	**11.60 [6.18 , 17.02]**
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.28); I² = 16%								
Test for overall effect: Z = 4.19 (P < 0.0001)								
1.11.9 Zinc								
Azizollahi 2013 (16)	49.8	11.3	32	49.8	24	25	46.5%	0.00 [-10.19 , 10.19]
Wong 2002 (17)	36.3	14.3	23	36.3	19.1	25	53.5%	0.00 [-9.50 , 9.50]
Subtotal (95% CI)			**55**			**50**	**100.0%**	**0.00 [-6.95 , 6.95]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								



Analysis 1.11. (Continued)

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

1.11.10 Zinc + Folic acid

Azizollahi 2013 (18)	52.4	17.8	29	49.8	24	25	5.9%	2.60 [-8.82 , 14.02]
Schisterman 2020 (19)	45.2	23	425	45.1	21.6	428	86.4%	0.10 [-2.89 , 3.09]
Wong 2002 (20)	36.3	16.7	24	36.3	19.1	25	7.7%	0.00 [-10.03 , 10.03]
Subtotal (95% CI)			**478**			**478**	**100.0%**	**0.24 [-2.54 , 3.02]**

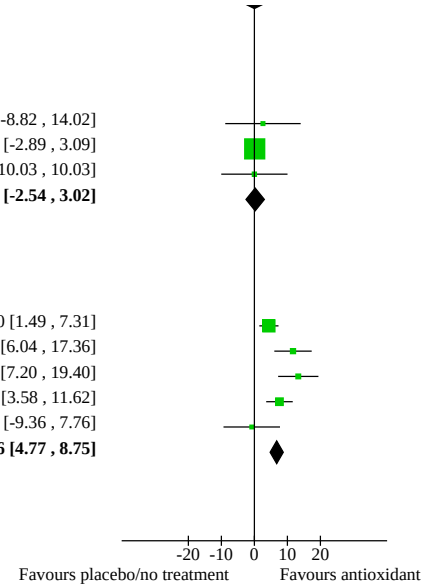
Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)

1.11.11 Combined antioxidants

Busetto 2018 (21)	39	8	52	34.6	7.1	52	47.0%	4.40 [1.49 , 7.31]
Gopinath 2013 (22)	55.8	11.9	43	44.1	9.53	18	12.4%	11.70 [6.04 , 17.36]
Gopinath 2013 (23)	57.4	14.6	46	44.1	9.53	18	10.7%	13.30 [7.20 , 19.40]
Kizilay 2019 (24)	38.8	10.4	62	31.2	8.3	28	24.6%	7.60 [3.58 , 11.62]
Stenqvist 2018 (25)	59.2	17.8	36	60	20	39	5.4%	-0.80 [-9.36 , 7.76]
Subtotal (95% CI)			**239**			**155**	**100.0%**	**6.76 [4.77 , 8.75]**

Heterogeneity: Chi² = 13.04, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 6.65 (P < 0.00001)

Test for subgroup differences: Chi² = 254.81, df = 10 (P < 0.00001), I² = 96.1%

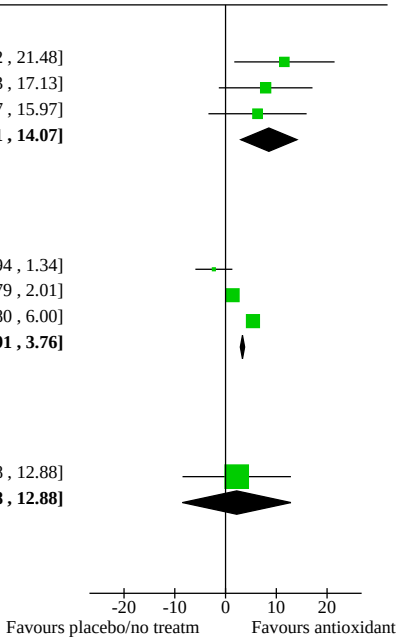


Footnotes

(1) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(2) L-acetyl carnitine 3000 mg.
(3) L-carnitine 3000 mg.
(4) L-carnitine 2000 mg + L-acetyl-carnitine 1000 mg.
(5) L-carnitine 2000 mg + L-acetylcarnitine 1000 mg.
(6) Coenzyme Q10 200 mg.
(7) Coenzyme Q10 300 mg.
(8) Folic acid 5 mg. After varicocelectomy.
(9) Folic acid 5 mg. At 26 weeks.
(10) N-acetylcysteine (NAC) 600 mg. 26 weeks.
(11) Selenium 200 µg. 26 weeks
(12) Selenium 200 µg + N-acetylcysteine (NAC) 600 mg. 26 weeks.
(13) Vitamin D 1400IU + Calcium 500 mg. At 5 months.
(14) Vitamin E 600 mg. Varicocele patients.
(15) Vitamin E 300 mg.
(16) Zinc 66 mg. After varicocelectomy.
(17) Zinc 66 mg. At 26 weeks.
(18) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(19) Zinc 30 mg + Folic acid 5 mg.
(20) Zinc 66 mg + Folic acid 5 mg. At 26 weeks.
(21) Proxeed Plus. Varicocele patients.
(22) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(23) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(24) L-carnitine + acetyl-L-carnitine + fructose + citric acid + vitamin C + zinc + folic acid + seleniumn+ coenzyme Q10 + vitamin B12. After varicocelectomy.
(25) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

Analysis 1.12. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 12: Total sperm motility at 9 months or more; type of antioxidant

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 Carnitines								
Balercia 2005 (1)	54.3	9	15	42.7	10	5	31.4%	11.60 [1.72 , 21.48]
Balercia 2005 (2)	50.6	5.7	15	42.7	10	5	35.9%	7.90 [-1.33 , 17.13]
Balercia 2005 (3)	49	7.8	14	42.7	10	5	32.7%	6.30 [-3.37 , 15.97]
Subtotal (95% CI)			**44**			**15**	**100.0%**	**8.54 [3.01 , 14.07]**
Heterogeneity: Chi² = 0.59, df = 2 (P = 0.74); I² = 0%								
Test for overall effect: Z = 3.02 (P = 0.002)								
1.12.2 Coenzyme Q10								
Balercia 2009 (4)	33	6.3	30	35.3	8	30	1.4%	-2.30 [-5.94 , 1.34]
Safarinejad 2009a (5)	24.2	2.1	98	22.8	2.2	96	49.0%	1.40 [0.79 , 2.01]
Safarinejad 2012 (4)	31.2	2.4	112	25.8	2.2	113	49.6%	5.40 [4.80 , 6.00]
Subtotal (95% CI)			**240**			**239**	**100.0%**	**3.33 [2.91 , 3.76]**
Heterogeneity: Chi² = 93.67, df = 2 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 15.42 (P < 0.00001)								
1.12.3 Vitamin E								
Ener 2016 (6)	59.3	16.2	22	57.1	20.2	23	100.0%	2.20 [-8.48 , 12.88]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**2.20 [-8.48 , 12.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
Test for subgroup differences: Chi² = 3.42, df = 2 (P = 0.18), I² = 41.6%								



Footnotes

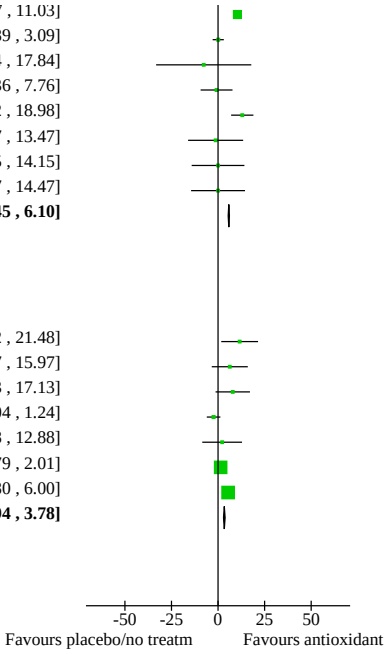
(1) L-carnitine 3000 mg.
(2) L-acetyl carnitine 3000 mg.
(3) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(4) Coenzyme Q10 200 mg.
(5) Coenzyme Q10 300 mg.
(6) Vitamin E 600 mg. Varicocele patients. At 12 months.

Analysis 1.13. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 13: Total sperm motility over time

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.13.1 Total sperm motility at 3 months or less								
Abbasi 2020 (1)	36.4	24.5	19	38.4	26.8	22	0.0%	-2.00 [-17.71 , 13.71]
Attallah 2013 (2)	22.5	11	30	18.7	7.8	30	0.0%	3.80 [-1.03 , 8.63]
Azizollahi 2013 (3)	53.3	15.3	26	44.9	33	9	0.0%	8.40 [-13.95 , 30.75]
Azizollahi 2013 (4)	48.9	27.7	32	44.9	33	8	0.0%	4.00 [-20.80 , 28.80]
Azizollahi 2013 (5)	51.7	17.2	29	44.9	33	8	0.0%	6.80 [-16.91 , 30.51]
Bahmyari 2021 (6)	30.3	19.3	30	36.7	17.2	32	0.0%	-6.40 [-15.52 , 2.72]
Balercia 2005 (7)	59.93	8.04	15	44.6	7.7	5	0.0%	15.33 [7.45 , 23.21]
Balercia 2005 (8)	55.1	10.2	14	44.6	7.7	5	0.0%	10.50 [1.89 , 19.11]
Balercia 2005 (9)	56.5	11.6	15	44.6	7.7	5	0.0%	11.90 [2.96 , 20.84]
Barekat 2016 (10)	58.2	20.9	15	43.6	21.9	20	0.0%	14.60 [0.32 , 28.88]
Conquer 2000 (11)	32	16.1	10	47.2	18.6	4	0.0%	-15.20 [-35.98 , 5.58]
Conquer 2000 (12)	39.4	24.3	9	47.2	18.6	5	0.0%	-7.80 [-30.56 , 14.96]
Dimitriadis 2010 (13)	35.6	15.5	26	24.7	10.8	22	0.0%	10.90 [3.43 , 18.37]
Ener 2016 (14)	61.4	18.3	22	42.5	28.7	23	0.0%	18.90 [4.90 , 32.90]
Gopinath 2013 (15)	51.6	13	46	42.1	10.6	18	0.0%	9.50 [3.33 , 15.67]
Gopinath 2013 (16)	50.1	11.3	43	42.1	10.6	18	0.0%	8.00 [2.05 , 13.95]
Greco 2005 (17)	41.6	22	32	38.7	21.5	32	0.0%	2.90 [-7.76 , 13.56]
Kumalic 2020 (18)	37.9	41.7	37	43.1	12.8	35	0.0%	-5.20 [-19.29 , 8.89]
Lenzi 2003 (19)	11	15.5	43	8.8	10.8	43	0.0%	2.20 [-3.45 , 7.85]
Martinez-Soto 2010 (20)	41.5	18.7	21	48	15.5	15	0.0%	-6.50 [-17.70 , 4.70]
Morgante 2010 (21)	40.3	6.4	90	25.1	4.2	90	0.3%	15.20 [13.62 , 16.78]
Nadjarzadeh 2011 (22)	41.9	15.6	23	38.3	18.4	24	0.0%	3.60 [-6.14 , 13.34]
Nouri 2019 (23)	30.7	16.8	17	27.2	15	19	0.0%	3.50 [-6.95 , 13.95]
Omu 2008 (24)	50	20	14	24	12	2	0.0%	26.00 [6.34 , 45.66]
Omu 2008 (25)	49	12	11	24	12	3	0.0%	25.00 [9.68 , 40.32]
Omu 2008 (26)	50	18	12	24	12	3	0.0%	26.00 [9.03 , 42.97]
Peivandi 2010 (27)	48.3	0.16	15	17	0.09	15	99.4%	31.30 [31.21 , 31.39]
Raigani 2014 (28)	33.3	27.9	20	32.8	17.3	6	0.0%	0.50 [-17.97 , 18.97]
Raigani 2014 (29)	37.1	18.8	21	32.8	17.3	6	0.0%	4.30 [-11.71 , 20.31]
Raigani 2014 (30)	34	26	24	32.8	17.3	6	0.0%	1.20 [-16.12 , 18.52]
Scott 1998 (31)	30.2	22.8	16	15.3	12.3	9	0.0%	14.90 [1.14 , 28.66]
Scott 1998 (32)	27	20.3	30	15.3	12.3	9	0.0%	11.70 [0.87 , 22.53]
Sigman 2006 (33)	28.6	38.1	12	37.6	33	9	0.0%	-9.00 [-39.49 , 21.49]
Steiner 2020 (34)	42.8	16.4	82	42.2	16.1	82	0.0%	0.60 [-4.37 , 5.57]
Stenqvist 2018 (35)	62.8	18.1	37	59.9	26.4	38	0.0%	2.90 [-7.32 , 13.12]
Zavaczki 2003 (36)	33.5	29.8	10	19	14.4	10	0.0%	14.50 [-6.01 , 35.01]
Subtotal (95% CI)			**948**			**690**	**100.0%**	**31.17 [31.07 , 31.26]**
Heterogeneity: Chi² = 1336.17, df = 35 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 659.69 (P < 0.00001)								
1.13.2 Total sperm motility at 6 months								
Azizollahi 2013 (3)	51.5	10.2	26	49.8	14.4	9	0.1%	1.70 [-8.49 , 11.89]
Azizollahi 2013 (5)	52.4	17.8	29	49.8	13.6	8	0.1%	2.60 [-8.84 , 14.04]
Azizollahi 2013 (4)	49.8	11.3	32	49.8	13.6	8	0.1%	0.00 [-10.21 , 10.21]
Balercia 2005 (9)	60.4	10.5	15	43.4	9.9	5	0.1%	17.00 [6.82 , 27.18]
Balercia 2005 (8)	61.1	9.1	14	43.4	9.9	5	0.1%	17.70 [7.80 , 27.60]
Balercia 2005 (7)	64.5	8.4	15	43.4	9.9	5	0.1%	21.10 [11.44 , 30.76]
Balercia 2009 (37)	39.4	6.8	30	34.9	8	30	0.8%	4.50 [0.74 , 8.26]
Blomberg Jensen 2018 (38)	41	22.7	129	45	23.1	131	0.3%	-4.00 [-9.57 , 1.57]
Busetto 2018 (39)	31.7	8.2	52	32.6	9.2	52	0.9%	-0.90 [-4.25 , 2.45]
Ener 2016 (40)	60.1	16.1	22	55	26.9	23	0.1%	5.10 [-7.79 , 17.99]
Gopinath 2013 (15)	57.4	14.6	46	44.1	9.5	18	0.3%	13.30 [7.21 , 19.39]
Gopinath 2013 (16)	55.8	11.9	43	44.1	9.5	18	0.3%	11.70 [6.05 , 17.35]
Kizilay 2019 (41)	38.8	10.4	62	31.2	8.3	28	0.7%	7.60 [3.58 , 11.62]
Lenzi 2004 (42)	31.1	13.5	30	29.6	9.5	26	0.3%	1.50 [-4.56 , 7.56]
Safarinejad 2009 (43)	29.2	2.9	104	22.9	2.2	35	12.6%	6.30 [5.38 , 7.22]
Safarinejad 2009 (44)	26.1	2.9	105	22.9	2.2	36	12.9%	3.20 [2.29 , 4.11]
Safarinejad 2009 (45)	24.8	2.9	105	22.9	2.2	35	12.7%	1.90 [0.98 , 2.82]
Safarinejad 2009a (46)	27.6	2.2	98	23.1	2.1	96	29.1%	4.50 [3.89 , 5.11]
Safarinejad 2012 (37)	35.8	2.7	112	25.4	2.1	113	26.6%	10.40 [9.77 , 11.03]
Schisterman 2020 (47)	45.2	23	425	45.1	21.6	428	1.2%	0.10 [-2.89 , 3.09]
Sigman 2006 (33)	22.2	24.2	12	40	22	9	0.0%	-7.70 [-22.24 , 17.84]

Analysis 1.13. (Continued)

Safarinejad 2012 (37)	35.8	2.7	112	25.4	2.1	113	26.6%	10.40 [9.77 , 11.03]
Schisterman 2020 (47)	45.2	23	425	45.1	21.6	428	1.2%	0.10 [-2.89 , 3.09]
Sigman 2006 (33)	32.3	24.2	12	40	33	9	0.0%	-7.70 [-33.24 , 17.84]
Stenqvist 2018 (48)	59.2	17.8	36	60	20	39	0.1%	-0.80 [-9.36 , 7.76]
Suleiman 1996 (49)	48.9	15.5	52	35.9	12.8	35	0.3%	13.00 [7.02 , 18.98]
Wong 2002 (50)	35	15.7	22	36.3	19.1	8	0.0%	-1.30 [-16.07 , 13.47]
Wong 2002 (51)	36.3	16.7	24	36.3	19.1	9	0.1%	0.00 [-14.15 , 14.15]
Wong 2002 (52)	36.3	14.3	23	36.3	19.1	8	0.1%	0.00 [-14.47 , 14.47]
Subtotal (95% CI)			**1663**			**1217**	**100.0%**	**5.77 [5.45 , 6.10]**
Heterogeneity: Chi² = 410.71, df = 25 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 34.69 (P < 0.00001)								
1.13.3 Total sperm motility at 9 months or more								
Balercia 2005 (7)	54.3	9	15	42.7	10	5	0.2%	11.60 [1.72 , 21.48]
Balercia 2005 (8)	49	7.8	14	42.7	10	5	0.2%	6.30 [-3.37 , 15.97]
Balercia 2005 (9)	50.6	5.7	15	42.7	10	5	0.2%	7.90 [-1.33 , 17.13]
Balercia 2009 (37)	32.9	6.3	30	35.3	8	30	1.3%	-2.40 [-6.04 , 1.24]
Ener 2016 (53)	59.3	16.2	22	57.1	20.2	23	0.2%	2.20 [-8.48 , 12.88]
Safarinejad 2009a (46)	24.2	2.1	98	22.8	2.2	96	48.7%	1.40 [0.79 , 2.01]
Safarinejad 2012 (37)	31.2	2.4	112	25.8	2.2	113	49.3%	5.40 [4.80 , 6.00]
Subtotal (95% CI)			**306**			**277**	**100.0%**	**3.36 [2.94 , 3.78]**
Heterogeneity: Chi² = 98.01, df = 6 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 15.60 (P < 0.00001)								



Footnotes

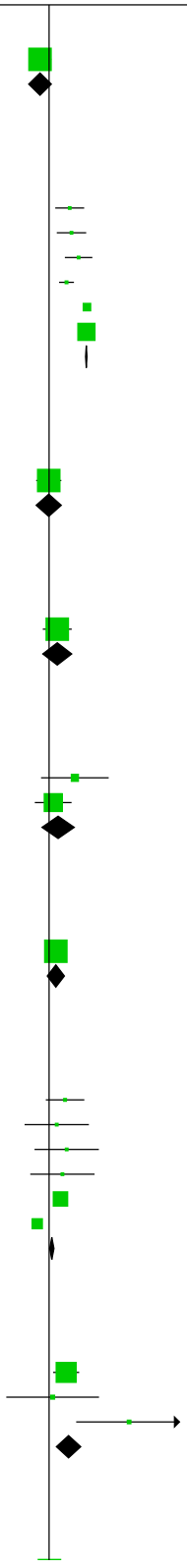
(1) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(2) N-acetylcysteine (NAC) 600 mg.
(3) Folic acid 5 mg. After varicocelectomy.
(4) Zinc 66 mg. After varicocelectomy.
(5) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(6) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(7) L-carnitine 3000 mg.
(8) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(9) L-acetyl carnitine 3000 mg.
(10) N-acetylcysteine (NAC) 200 mg. After varicocelectomy.
(11) Docosahexaenoic acid (DHA) 800 mg.
(12) Docosahexaenoic acid (DHA) 400 mg.
(13) L-carnitine 1000 mg.
(14) Vitamin E 600 mg. Varicocele patients.
(15) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(16) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(17) Vitamin C 1000 mg + Vitamin E 1000 mg.
(18) Astaxanthin 16 mg + Vitamin E 40 mg.
(19) L-carnitine 2000 mg. Only mean, no SD given.
(20) Docosahexaenoic acid (DHA) 1000 mg.
(21) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(22) Coenzyme Q10 (CoQ10) 200 mg.
(23) Lycopene 25 mg.
(24) Zinc 400 mg + Vitamin E 20 mg + Vitamin C 10 mg.
(25) Zinc 500 mg.
(26) Zinc 400 mg + Vitamin E 20 mg.
(27) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(28) Folic acid 5 mg. 16 weeks.
(29) Zinc 220 mg + Folic acid 5 mg. 16 weeks.
(30) Zinc 220 mg. 16 weeks.
(31) Selenium 100 µg.
(32) Selenium 100 µg + Vitamin A 1 mg + Vitamin C 10 mg + Vitamin E 15 mg.
(33) L-carnitine 2000 mg + L-acetylcarnitine 1000 mg.
(34) Vitamin C + vitamin E + selenium + l-carnitine+ zinc + folic acid + lycopene + vitamin D.
(35) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).
(36) Magnesium 3000 mg.
(37) Coenzyme Q10 200 mg.
(38) Vitamin D 1400IU + Calcium 500 mg. At 5 months.
(39) Proxeed Plus (l-carnitine, fumarate, acetyl-l-carnitine, fructose, CoQ10, vitamin C, zinc, folic acid and vitamin B12). Varicocele patients.
(40) Vitamin E 600 mg. After varicocelectomy.

Analysis 1.13. (Continued)

(39) Proxeed Plus (l-carnitine, fumarate, acetyl-l-carnitine, fructose, CoQ10, vitamin C, zinc, folic acid and vitamin B12). Varicocele patients.
(40) Vitamin E 600 mg. After varicocelectomy.
(41) L-carnitine 1 g + acetyl-L-carnitine 0,5 g + fructose 1 g + citric acid 50 mg + vitamin C 90 mg + zinc 10 mg + folic acid 200 mcg + selenium 50 mcg + coenzyme Q10 20 mg +
(42) L-carnitine 2000 mg + L-acetyl-carnitine 1000 mg.
(43) Selenium 200 µg + N-acetylcysteine (NAC) 600 mg. 26 weeks.
(44) Selenium 200 µg. 26 weeks
(45) N-acetylcysteine (NAC) 600 mg. 26 weeks.
(46) Coenzyme Q10 300 mg.
(47) Zinc 30 mg + Folic acid 5 mg.
(48) Androferti (vitamin C 30 mg + vitamin E 5 mg + vitamin B12 0.5 mcg + l-carnitine 750 mg + coenzyme Q10 10 mg + folic acid 100 mcg + zinc 5 mg + selenium 25 mcg).
(49) Vitamin E 300 mg.
(50) Folic acid 5 mg. 26 weeks.
(51) Zinc 66 mg + Folic acid 5 mg. 26 weeks.
(52) Zinc 66 mg. 26 weeks.
(53) 12 months. Vitamin E 600 mg. Varicocele patients.

Analysis 1.14. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 14: Progressive sperm motility at 3 months or less; type of antioxidant

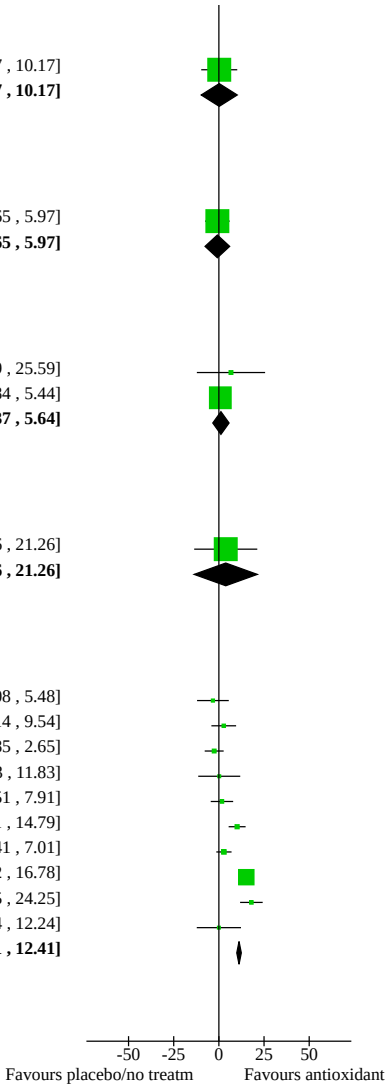
Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 Astaxanthin + Vitamin E								
Kumalic 2020 (1)	33	14.7	37	38.1	12.8	35	100.0%	-5.10 [-11.46 , 1.26]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**-5.10 [-11.46 , 1.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.57 (P = 0.12)								
1.14.2 Carnitines								
Balercia 2005 (2)	33.9	8.4	14	22.3	7.8	5	0.2%	11.60 [3.47 , 19.73]
Balercia 2005 (3)	34.9	9.2	15	22.3	7.8	5	0.2%	12.60 [4.33 , 20.87]
Balercia 2005 (4)	38.9	7.1	15	22.3	7.8	5	0.3%	16.60 [8.88 , 24.32]
Cavallini 2004 (5)	22	10.2	39	12.2	9.4	47	0.9%	9.80 [5.62 , 13.98]
Mehni 2014 (6)	24.6	1.5	51	3.3	2.7	59	24.8%	21.30 [20.50 , 22.10]
Peivandi 2010 (7)	30	0.2	15	9	0.9	15	73.5%	21.00 [20.53 , 21.47]
Subtotal (95% CI)			**149**			**136**	**100.0%**	**20.92 [20.52 , 21.32]**
Heterogeneity: Chi² = 38.30, df = 5 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 102.50 (P < 0.00001)								
1.14.3 Carotenoids								
Nouri 2019 (8)	15	8.9	17	15.2	12.6	19	100.0%	-0.20 [-7.27 , 6.87]
Subtotal (95% CI)			**17**			**19**	**100.0%**	**-0.20 [-7.27 , 6.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.96)								
1.14.4 Coenzyme Q10								
Nadjarzadeh 2011	28.9	14.8	23	24.3	13.6	24	100.0%	4.60 [-3.54 , 12.74]
Subtotal (95% CI)			**23**			**24**	**100.0%**	**4.60 [-3.54 , 12.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
1.14.5 Folic acid								
Azizollahi 2013 (9)	48.6	32.6	26	34.1	36.5	25	22.8%	14.50 [-4.52 , 33.52]
Boonyarangkul 2015 (10)	20.4	15.4	15	18.1	13.4	15	77.2%	2.30 [-8.03 , 12.63]
Subtotal (95% CI)			**41**			**40**	**100.0%**	**5.08 [-4.00 , 14.16]**
Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%								
Test for overall effect: Z = 1.10 (P = 0.27)								
1.14.6 N-acetylcysteine (NAC)								
Attallah 2013 (11)	22.5	11	30	18.7	7.8	30	100.0%	3.80 [-1.03 , 8.63]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**3.80 [-1.03 , 8.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.54 (P = 0.12)								
1.14.7 PUFAs								
Abbasi 2020 (12)	35.75	17.26	19	26.76	18.06	22	1.3%	8.99 [-1.84 , 19.82]
Gonzalez-Ravina 2018 (13)	36	17.26	15	31.7	18.06	5	0.4%	4.30 [-13.78 , 22.38]
Gonzalez-Ravina 2018 (14)	41.6	17.26	15	31.7	18.06	5	0.4%	9.90 [-8.18 , 27.98]
Gonzalez-Ravina 2018 (15)	39.2	17.26	15	31.7	18.06	5	0.4%	7.50 [-10.58 , 25.58]
Haghighian 2015 (16)	33.5	2.9	23	27.1	2.4	21	59.6%	6.40 [4.83 , 7.97]
Martinez-Soto 2010 (17)	37.8	3.2	21	44.4	2.8	15	37.8%	-6.60 [-8.57 , -4.63]
Subtotal (95% CI)			**108**			**73**	**100.0%**	**1.53 [0.32 , 2.74]**
Heterogeneity: Chi² = 105.64, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.48 (P = 0.01)								
1.14.8 Vitamin C								
Cyrus 2015 (18)	54.5	18.3	46	44.9	21.4	69	87.8%	9.60 [2.29 , 16.91]
Dawson 1990 (19)	51	22.1	10	49	25.3	5	6.9%	2.00 [-24.07 , 28.07]
Dawson 1990 (20)	94	32	10	49	25.3	5	5.3%	45.00 [15.25 , 74.75]
Subtotal (95% CI)			**66**			**79**	**100.0%**	**10.95 [4.10 , 17.80]**
Heterogeneity: Chi² = 5.62, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 3.13 (P = 0.002)								
1.14.9 Vitamin C + Vitamin E								



Analysis 1.14. (Continued)

1.14.9 Vitamin C + Vitamin E								
Rolf 1999 (21)	34.1	11.8	15	33.9	16.3	16	100.0%	0.20 [-9.77 , 10.17]
Subtotal (95% CI)			**15**			**16**	**100.0%**	**0.20 [-9.77 , 10.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.04 (P = 0.97)								
1.14.10 Vitamin D								
Amini 2020 (22)	14	15.76	30	14.84	11.01	32	100.0%	-0.84 [-7.65 , 5.97]
Subtotal (95% CI)			**30**			**32**	**100.0%**	**-0.84 [-7.65 , 5.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
1.14.11 Zinc								
Azizollahi 2013 (23)	40.8	35.6	32	34.1	36.5	25	5.7%	6.70 [-12.19 , 25.59]
Sharifzadeh 2016 (24)	25.5	11.1	51	24.7	12.5	49	94.3%	0.80 [-3.84 , 5.44]
Subtotal (95% CI)			**83**			**74**	**100.0%**	**1.14 [-3.37 , 5.64]**
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.49 (P = 0.62)								
1.14.12 Zinc + Folic acid								
Azizollahi 2013 (25)	37.9	27.5	29	34.1	36.5	25	100.0%	3.80 [-13.66 , 21.26]
Subtotal (95% CI)			**29**			**25**	**100.0%**	**3.80 [-13.66 , 21.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.14.13 Combined antioxidants								
Bahmyari 2021 (26)	18	16	30	21.3	19.2	32	2.0%	-3.30 [-12.08 , 5.48]
Gamidov 2017 (27)	36.5	16.2	38	33.8	10	19	3.4%	2.70 [-4.14 , 9.54]
Gamidov 2017 (28)	31.2	8.5	38	33.8	10	19	5.7%	-2.60 [-7.85 , 2.65]
Gamidov 2019 (29)	34.6	19.2	60	34.4	24.1	20	1.2%	0.20 [-11.43 , 11.83]
Joseph 2020 (30)	33	18.9	75	31.3	20.4	79	4.1%	1.70 [-4.51 , 7.91]
Kopets 2020 (31)	34.1	11.5	42	24	10.3	41	7.1%	10.10 [5.41 , 14.79]
Micic 2019 (32)	27	20.3	119	24.2	7.3	46	8.8%	2.80 [-1.41 , 7.01]
Morgante 2010 (33)	40.3	6.4	90	25.1	4.2	90	62.7%	15.20 [13.62 , 16.78]
Popova 2019 (34)	38.6	14.1	60	20.6	11.7	20	4.0%	18.00 [11.75 , 24.25]
Stenqvist 2018 (35)	39.2	25.1	37	39.2	28.9	38	1.0%	0.00 [-12.24 , 12.24]
Subtotal (95% CI)			**589**			**404**	**100.0%**	**11.16 [9.91 , 12.41]**
Heterogeneity: Chi² = 103.26, df = 9 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 17.47 (P < 0.00001)								

Test for subgroup differences: Chi² = 1258.83, df = 12 (P < 0.00001), I² = 99.0%



Footnotes

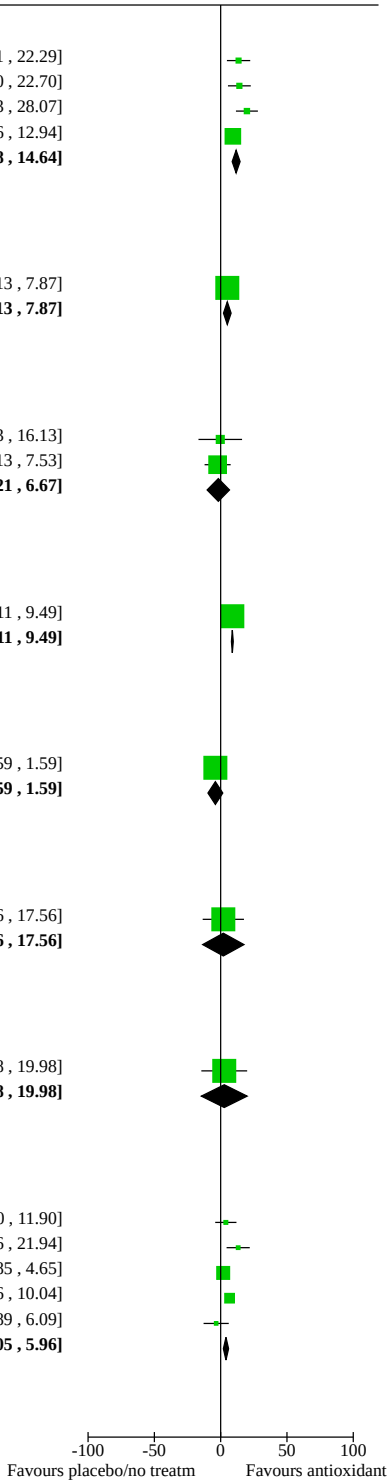
(1) Astaxanthin 16 mg + Vitamin E 40 mg.
(2) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(3) L-acetyl carnitine 3000 mg.
(4) L-carnitine 3000 mg.
(5) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Only WHO class A motile sperm.
(6) L-carnitine 1000 mg.
(7) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(8) Lycopene 25 mg.
(9) Folic acid 5 mg. After varicocelectomy.
(10) Folic acid 5 mg.
(11) N-acetylcysteine (NAC) 600 mg.
(12) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(13) Docosahexaenoic acid (DHA) 1 g.
(14) Docosahexaenoic acid (DHA) 2 g.
(15) Docosahexaenoic acid (DHA) 0.5 g.
(16) Alpha-lipoic acid (ALA) 600 mg.
(17) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(18) Vitamin C 500 mg. After varicocelectomy.
(19) Vitamin C 200 mg.
(20) Vitamin C 1000 mg.
(21) Vitamin C 1000 mg + Vitamin E 800 mg. At 2 months.
(22) Vitamin D3 50.000IU/week for 8 weeks, followed by 50.000IU/month for 1 month

Analysis 1.14. (Continued)

(20) Vitamin C 1000 mg.
(21) Vitamin C 1000 mg + Vitamin E 800 mg. At 2 months.
(22) Vitamin D3 50,000IU/week for 8 weeks, followed by 50,000IU/month for 1 month
(23) Zinc 66 mg. After varicocelectomy.
(24) Zinc 10 ml solution of 0.5%.
(25) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(26) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(27) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(28) SpermActin Forte (acetyl-L-carnitine + L-carnitine + alpha-lipoic acid). After varicocelectomy.
(29) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(30) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.
(31) 1 dose TDS (l-carnitine/ l-acetyl-carnitine + l-arginine + glutathione + coenzyme Q10 + zinc + vitamin B9 + vitamin B12 + selenium).
(32) Proxeed plus (l-carnitine + acetyl-l-carinitine + fumarate + fructose + critic acid + zinc + coenzyme Q10 + selenium + vitamin C + folic acid + vitamin B12).
(33) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(34) Androdoz (l-arginine + l-carnitine + l-carnosine + coenzyme Q10 + glycyrrhizic acid).
(35) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

Analysis 1.15. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 15: Progressive sperm motility at 6 months; type of antioxidant

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.15.1 Carnitines								
Balercia 2005 (1)	37.5	9.2	15	24	8.5	5	11.5%	13.50 [4.71 , 22.29]
Balercia 2005 (2)	38.1	8.2	14	24	8.5	5	12.0%	14.10 [5.50 , 22.70]
Balercia 2005 (3)	43.8	7.1	15	24	8.5	5	13.0%	19.80 [11.53 , 28.07]
Cavallini 2004 (4)	22.8	9.9	39	13.6	7.3	47	63.5%	9.20 [5.46 , 12.94]
Subtotal (95% CI)			**83**			**62**	**100.0%**	**11.66 [8.68 , 14.64]**
Heterogeneity: Chi² = 5.86, df = 3 (P = 0.12); I² = 49%								
Test for overall effect: Z = 7.67 (P < 0.00001)								
1.15.2 Coenzyme Q10								
Balercia 2009 (5)	15.1	7.3	30	10.1	3.3	30	100.0%	5.00 [2.13 , 7.87]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**5.00 [2.13 , 7.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.42 (P = 0.0006)								
1.15.3 Folic acid								
Azizollahi 2013 (6)	40	25	26	40.3	34	25	26.4%	-0.30 [-16.73 , 16.13]
Boonyarangkul 2015 (7)	15	10.1	15	17.3	16.6	15	73.6%	-2.30 [-12.13 , 7.53]
Subtotal (95% CI)			**41**			**40**	**100.0%**	**-1.77 [-10.21 , 6.67]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.15.4 PUFAs								
Safarinejad 2011b (8)	27.4	2.6	113	18.6	2.7	114	100.0%	8.80 [8.11 , 9.49]
Subtotal (95% CI)			**113**			**114**	**100.0%**	**8.80 [8.11 , 9.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 25.01 (P < 0.00001)								
1.15.5 Vitamin D + Calcium								
Blomberg Jensen 2018 (9)	31	23	129	35	23	131	100.0%	-4.00 [-9.59 , 1.59]
Subtotal (95% CI)			**129**			**131**	**100.0%**	**-4.00 [-9.59 , 1.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.40 (P = 0.16)								
1.15.6 Zinc								
Azizollahi 2013 (10)	42.3	23.2	32	40.3	34	25	100.0%	2.00 [-13.56 , 17.56]
Subtotal (95% CI)			**32**			**25**	**100.0%**	**2.00 [-13.56 , 17.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
1.15.7 Zinc + Folic acid								
Azizollahi 2013 (11)	43	30.2	29	40.3	34	25	100.0%	2.70 [-14.58 , 19.98]
Subtotal (95% CI)			**29**			**25**	**100.0%**	**2.70 [-14.58 , 19.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
1.15.8 Combined antioxidants								
Ardestani 2019 (12)	50.3	15.1	30	46.4	16.5	30	6.0%	3.90 [-4.10 , 11.90]
Gamidov 2019 (13)	41.3	11	60	28.1	18.9	20	5.0%	13.20 [4.46 , 21.94]
Kizilay 2019 (14)	26.1	7.6	62	24.2	5.4	28	50.5%	1.90 [-0.85 , 4.65]
Micic 2019 (15)	30.7	15.8	119	24	6.1	46	34.3%	6.70 [3.36 , 10.04]
Stenqvist 2018 (16)	36.9	17.8	36	40.3	23.9	39	4.2%	-3.40 [-12.89 , 6.09]
Subtotal (95% CI)			**307**			**163**	**100.0%**	**4.01 [2.05 , 5.96]**
Heterogeneity: Chi² = 11.34, df = 4 (P = 0.02); I² = 65%								
Test for overall effect: Z = 4.01 (P < 0.0001)								
Test for subgroup differences: Chi² = 54.94, df = 7 (P < 0.00001), I² = 87.3%								



Footnotes

(1) L-acetyl carnitine 3000 mg.
(2) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(3) L-carnitine 3000 mg.

Analysis 1.15. (Continued)

(2) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(3) L-carnitine 3000 mg.
(4) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Only WHO class A motile sperm.
(5) Coenzyme Q10 200 mg.
(6) Folic acid 5 mg. After varicocelectomy.
(7) Folic acid 5 mg.
(8) DHA 0.72 g + EPA 1.12 g. At 8 months.
(9) Vitamin D 1400IU + Calcium 500 mg. At 5 months.
(10) Zinc 66 mg. After varicocelectomy.
(11) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(12) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU. After varicocelectomy.
(13) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(14) L-carnitine 1 g + acetyl-L-carnitine 0,5 g + fructose 1 g + citric acid 50 mg + vitamin C 90 mg + zinc 10 mg + folic acid 200 mcg + selenium 50 mcg + coenzyme Q10 20 mg
(15) Proxeed plus (l-carnitine 1 g + acetyl-l-carinitine 0.5 g + fumarate 0.725 g + fructose 1 g + critic acid 50 mg + zinc 10 mg + coenzyme Q10 20 mg + selenium 50 mcg + vitam
(16) Androferti (vitamin C 30 mg + vitamin E 5 mg + vitamin B12 0.5 mcg + l-carnitine 750 mg + coenzyme Q10 10 mg + folic acid 100 mcg + zinc 5 mg + selenium 25 mcg).

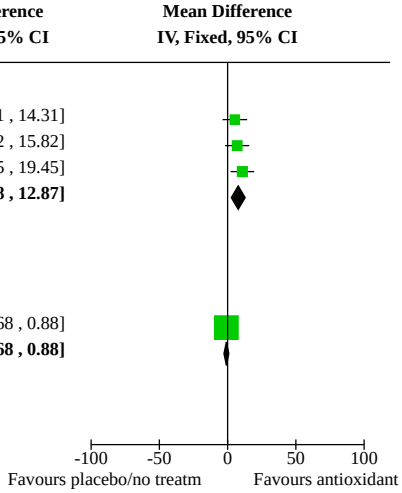
Analysis 1.16. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 16: Progressive sperm motility at 6 months (data not suitable for meta analysis)

Progressive sperm motility at 6 months (data not suitable for meta analysis)

Study	Intervention	Control	P value
Coenzyme Q10			
Saeed Alkumait 2020	**Coenzyme Q10 200 mg** % improvement = 36 (n = 50)	**Placebo** % improvement = 4 (n = 50)	0.01
Glutathione			
Saeed Alkumait 2020	**Glutathione 250 mg** % improvement = 38 (n = 51)	**Placebo** % improvement = 4 (n = 50)	0.01

Analysis 1.17. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 17: Progressive sperm motility at 9 months or more; type of antioxidant

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.17.1 Carnitines								
Balercia 2005 (1)	28.5	8.3	14	23.2	9	5	32.0%	5.30 [-3.71 , 14.31]
Balercia 2005 (2)	30.2	7.8	15	23.2	9	5	33.3%	7.00 [-1.82 , 15.82]
Balercia 2005 (3)	34	7	15	23.2	9	5	34.7%	10.80 [2.15 , 19.45]
Subtotal (95% CI)			**44**			**15**	**100.0%**	**7.77 [2.68 , 12.87]**
Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%								
Test for overall effect: Z = 2.99 (P = 0.003)								
1.17.2 Coenzyme Q10								
Balercia 2009 (4)	10.1	3.2	30	11	3.8	30	100.0%	-0.90 [-2.68 , 0.88]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.90 [-2.68 , 0.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.99 (P = 0.32)								
Test for subgroup differences: Chi² = 9.93, df = 1 (P = 0.002), I² = 89.9%								



Footnotes
(1) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(2) L-acetyl carnitine 3000 mg.
(3) L-carnitine 3000 mg.
(4) Coenzyme Q10 200 mg.

Analysis 1.18. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 18: Progressive sperm motility over time

Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.18.1 Progressive sperm motility at 3 months or less								
Abbasi 2020 (1)	23.7	15	19	24.9	19.2	22	0.1%	-1.20 [-11.68 , 9.28]
Amini 2020 (2)	14	15.8	30	14.8	11	32	0.3%	-0.80 [-7.62 , 6.02]
Attallah 2013 (3)	22.5	11	30	18.7	7.8	30	0.6%	3.80 [-1.03 , 8.63]
Azizollahi 2013 (4)	37.9	27.5	29	34.1	20.6	8	0.0%	3.80 [-13.63 , 21.23]
Azizollahi 2013 (5)	48.6	32.6	26	34.1	21.9	9	0.0%	14.50 [-4.52 , 33.52]
Azizollahi 2013 (6)	40.8	35.6	32	34.1	20.6	8	0.0%	6.70 [-12.17 , 25.57]
Bahmyari 2021 (7)	18	16	30	21.3	19.2	32	0.2%	-3.30 [-12.08 , 5.48]
Balercia 2005 (8)	33.9	8.4	14	22.3	7.8	5	0.2%	11.60 [3.47 , 19.73]
Balercia 2005 (9)	34.9	9.2	15	22.3	7.8	5	0.2%	12.60 [4.33 , 20.87]
Balercia 2005 (10)	38.9	7.1	15	22.3	7.8	5	0.2%	16.60 [8.88 , 24.32]
Boonyarangkul 2015 (11)	20.4	15.4	15	18.1	13.4	15	0.1%	2.30 [-8.03 , 12.63]
Cavallini 2004 (12)	22	10.2	39	12.2	9.4	47	0.7%	9.80 [5.62 , 13.98]
Cyrus 2015 (13)	54.5	18.3	46	44.9	21.4	69	0.2%	9.60 [2.29 , 16.91]
Dawson 1990 (14)	51	22.1	10	49	25.3	5	0.0%	2.00 [-24.07 , 28.07]
Dawson 1990 (15)	94	32	10	49	25.3	5	0.0%	45.00 [15.25 , 74.75]
Gamidov 2017 (16)	31.2	8.5	38	33.8	10	19	0.5%	-2.60 [-7.85 , 2.65]
Gamidov 2017 (17)	36.5	16.2	38	33.8	10	19	0.3%	2.70 [-4.14 , 9.54]
Gamidov 2019 (18)	34.6	19.2	60	34.4	24.1	20	0.1%	0.20 [-11.43 , 11.83]
Gonzalez-Ravina 2018 (19)	41.6	17.26	15	31.7	18.06	5	0.0%	9.90 [-8.18 , 27.98]
Gonzalez-Ravina 2018 (20)	39.2	17.26	15	31.7	18.06	5	0.0%	7.50 [-10.58 , 25.58]
Gonzalez-Ravina 2018 (21)	36	17.26	15	31.7	18.06	5	0.0%	4.30 [-13.78 , 22.38]
Haghighian 2015 (22)	33.5	2.9	23	27.1	2.4	21	5.3%	6.40 [4.83 , 7.97]
Joseph 2020 (23)	33	18.9	75	31.3	20.4	79	0.3%	1.70 [-4.51 , 7.91]
Kopets 2020 (24)	34.1	11.5	42	24	10.3	41	0.6%	10.10 [5.41 , 14.79]
Kumalic 2020 (25)	33	14.7	37	38.1	12.8	35	0.3%	-5.10 [-11.46 , 1.26]
Martinez-Soto 2010 (26)	37.8	3.2	21	44.4	2.8	15	3.3%	-6.60 [-8.57 , -4.63]
Mehni 2014 (27)	24.6	1.5	51	3.3	2.7	59	20.0%	21.30 [20.50 , 22.10]
Micic 2019 (28)	27	20.3	119	24.2	7.3	46	0.7%	2.80 [-1.41 , 7.01]
Morgante 2010 (29)	40.3	6.4	90	25.1	4.2	90	5.2%	15.20 [13.62 , 16.78]
Nadjarzadeh 2011 (30)	28.9	14.8	23	24.3	13.6	24	0.2%	4.60 [-3.54 , 12.74]
Nouri 2019 (31)	15	8.9	17	15.2	12.6	19	0.3%	-0.20 [-7.27 , 6.87]
Peivandi 2010 (32)	30	0.2	15	9	0.9	15	59.3%	21.00 [20.53 , 21.47]
Popova 2019 (33)	38.6	14.1	60	20.6	11.7	20	0.3%	18.00 [11.75 , 24.25]
Rolf 1999 (34)	34.1	11.8	15	33.9	16.3	16	0.1%	0.20 [-9.77 , 10.17]
Stenqvist 2018 (35)	39.2	25.1	37	39.2	28.9	38	0.1%	0.00 [-12.24 , 12.24]
Subtotal (95% CI)			**1166**			**888**	**100.0%**	**17.98 [17.62 , 18.34]**
Heterogeneity: Chi² = 1470.83, df = 34 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 98.06 (P < 0.00001)								
1.18.2 Progressive sperm motility at 6 months								
Ardestani 2019 (36)	50.3	15.1	30	46.4	16.5	30	0.6%	3.90 [-4.10 , 11.90]
Azizollahi 2013 (5)	40	25	26	40.3	20.4	9	0.1%	-0.30 [-16.73 , 16.13]
Azizollahi 2013 (4)	43	30.2	29	40.3	19.2	8	0.1%	2.70 [-14.56 , 19.96]
Azizollahi 2013 (6)	42.3	23.2	32	40.3	19.2	8	0.2%	2.00 [-13.54 , 17.54]
Balercia 2005 (8)	38.1	8.2	14	24	8.5	5	0.5%	14.10 [5.50 , 22.70]
Balercia 2005 (9)	37.5	9.2	15	24	8.5	5	0.5%	13.50 [4.71 , 22.29]
Balercia 2005 (10)	43.8	7.1	15	24	8.5	5	0.6%	19.80 [11.53 , 28.07]
Balercia 2009 (30)	15.1	7.3	30	10.1	3.3	30	4.6%	5.00 [2.13 , 7.87]
Blomberg Jensen 2018 (37)	31	23	129	35	23	131	1.2%	-4.00 [-9.59 , 1.59]
Boonyarangkul 2015 (11)	15	10.1	15	17.3	16.6	15	0.4%	-2.30 [-12.13 , 7.53]
Cavallini 2004 (12)	22.8	9.9	39	13.6	7.3	47	2.7%	9.20 [5.46 , 12.94]
Gamidov 2019 (18)	41.3	11	60	28.1	18.9	20	0.5%	13.20 [4.46 , 21.94]
Kizilay 2019 (38)	26.1	7.6	62	24.2	5.4	28	5.0%	1.90 [-0.85 , 4.65]
Micic 2019 (28)	30.7	15.8	119	24	6.1	46	3.4%	6.70 [3.36 , 10.04]
Safarinejad 2011b (39)	27.4	2.6	113	18.6	2.7	114	79.3%	8.80 [8.11 , 9.49]
Stenqvist 2018 (35)	36.9	17.8	36	40.3	23.9	39	0.4%	-3.40 [-12.89 , 6.09]
Subtotal (95% CI)			**764**			**540**	**100.0%**	**8.05 [7.43 , 8.66]**
Heterogeneity: Chi² = 72.18, df = 15 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 25.68 (P < 0.00001)								
1.18.3 Progressive sperm motility at 9 months or more								
Balercia 2005 (10)	34	7	15	23.2	9	5	3.8%	10.80 [2.15 , 19.45]
Balercia 2005 (9)	30.2	7.8	15	23.2	9	5	3.6%	7.00 [-1.82 , 15.82]
Balercia 2005 (8)	28.5	8.3	14	23.2	9	5	3.5%	5.30 [-3.71 , 14.31]
Balercia 2009 (30)	10.1	3.2	30	11	3.8	30	89.1%	-0.90 [-2.68 , 0.88]

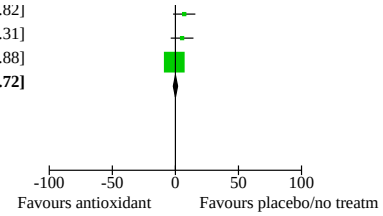
Analysis 1.18. (Continued)

Balercia 2005 (9)	30.2	7.8	15	23.2	9	5	3.6%	7.00 [-1.82 , 15.82]
Balercia 2005 (8)	28.5	8.3	14	23.2	9	5	3.5%	5.30 [-3.71 , 14.31]
Balercia 2009 (30)	10.1	3.2	30	11	3.8	30	89.1%	-0.90 [-2.68 , 0.88]
Subtotal (95% CI)			**74**			**45**	**100.0%**	**0.04 [-1.64 , 1.72]**

Heterogeneity: Chi² = 10.72, df = 3 (P = 0.01); I² = 72%

Test for overall effect: Z = 0.05 (P = 0.96)

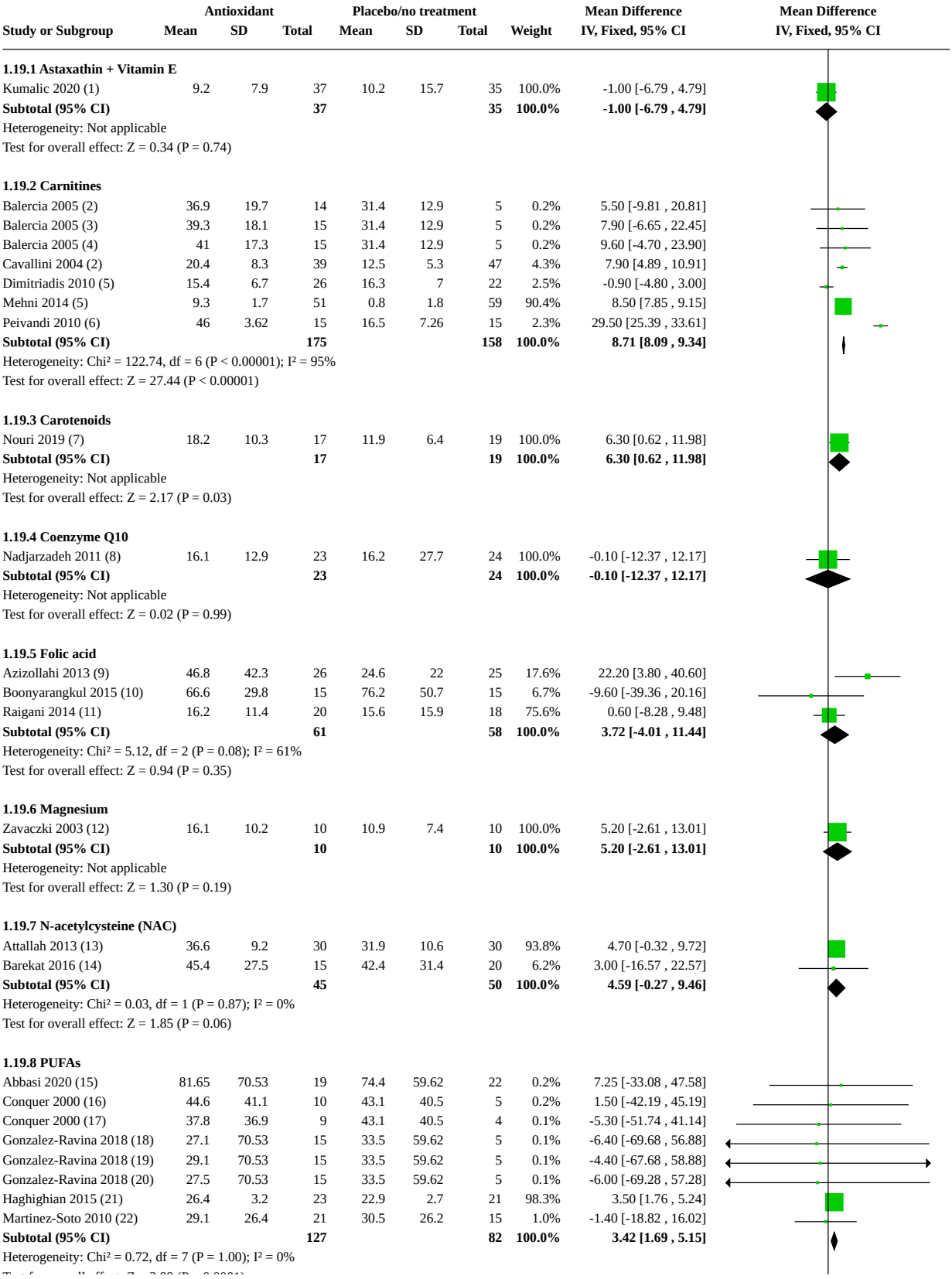
Test for subgroup differences: Chi² = 1061.41, df = 2 (P < 0.00001), I² = 99.8%



Footnotes

(1) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(2) Vitamin D3 50,000 IU.
(3) N-acetylcysteine (NAC) 600 mg.
(4) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(5) Folic acid 5 mg. After varicocelectomy.
(6) Zinc 66 mg. After varicocelectomy.
(7) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(8) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(9) L-acetyl carnitine 3000 mg.
(10) L-carnitine 3000 mg.
(11) Folic acid 5 mg.
(12) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg. Only WHO class A motile sperm.
(13) Vitamin C 500 mg. After varicocelectomy.
(14) Vitamin C 200 mg.
(15) Vitamin C 1000 mg.
(16) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg). After varicocelectomy.
(17) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(18) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(19) Docosahexaenoic acid (DHA) 2 g.
(20) Docosahexaenoic acid (DHA) 0.5 g.
(21) Docosahexaenoic acid (DHA) 1 g.
(22) Alpha-lipoic acid (ALA) 600 mg.
(23) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.
(24) L-carnitine/ l-acetyl-carnitine + l-arginine + glutathione + coenzyme Q10 + zinc + vitamin B9 + vitamin B12 + selenium. At 2 months.
(25) Astaxanthin 16 mg + Vitamin E 40 mg.
(26) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(27) L-carnitine 1000mg.
(28) Proxeed plus (l-carnitine + acetyl-l-carinitine + fumarate + fructose + critic acid + zinc + coenzyme Q10 + selenium + vitamin C + folic acid + vitamin B12).
(29) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(30) Coenzyme Q10 200 mg.
(31) Lycopene 25 mg.
(32) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(33) Androdoz (l-arginine 720 mg + l-carnitine 240 mg + l-carnosine 92 mg + coenzyme Q10 10 mg + glycyrrhizic acid 6 mg).
(34) Vitamin C 1000 mg + Vitamin E 800 mg. At 2 months.
(35) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).
(36) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU. After varicocelectomy.
(37) Vitamin D 1400IU + Calcium 500 mg. At 5 months.
(38) L-carnitine + acetyl-L-carnitine + fructose + citric acid + vitamin C + zinc + folic acid + selenium + coenzyme Q10 + vitamin B12. After varicocelectomy.
(39) DHA 0.72 g + EPA 1.12 g. At 8 months.

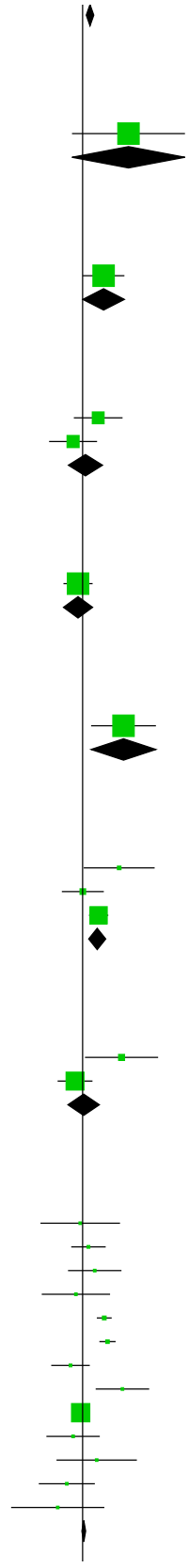
Analysis 1.19. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 19: Sperm concentration at 3 months or less; type of antioxidant



Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.19.1 Astaxathin + Vitamin E								
Kumalic 2020 (1)	9.2	7.9	37	10.2	15.7	35	100.0%	-1.00 [-6.79 , 4.79]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**-1.00 [-6.79 , 4.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.74)								
1.19.2 Carnitines								
Balercia 2005 (2)	36.9	19.7	14	31.4	12.9	5	0.2%	5.50 [-9.81 , 20.81]
Balercia 2005 (3)	39.3	18.1	15	31.4	12.9	5	0.2%	7.90 [-6.65 , 22.45]
Balercia 2005 (4)	41	17.3	15	31.4	12.9	5	0.2%	9.60 [-4.70 , 23.90]
Cavallini 2004 (2)	20.4	8.3	39	12.5	5.3	47	4.3%	7.90 [4.89 , 10.91]
Dimitriadis 2010 (5)	15.4	6.7	26	16.3	7	22	2.5%	-0.90 [-4.80 , 3.00]
Mehni 2014 (5)	9.3	1.7	51	0.8	1.8	59	90.4%	8.50 [7.85 , 9.15]
Peivandi 2010 (6)	46	3.62	15	16.5	7.26	15	2.3%	29.50 [25.39 , 33.61]
Subtotal (95% CI)			**175**			**158**	**100.0%**	**8.71 [8.09 , 9.34]**
Heterogeneity: Chi² = 122.74, df = 6 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 27.44 (P < 0.00001)								
1.19.3 Carotenoids								
Nouri 2019 (7)	18.2	10.3	17	11.9	6.4	19	100.0%	6.30 [0.62 , 11.98]
Subtotal (95% CI)			**17**			**19**	**100.0%**	**6.30 [0.62 , 11.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.17 (P = 0.03)								
1.19.4 Coenzyme Q10								
Nadjarzadeh 2011 (8)	16.1	12.9	23	16.2	27.7	24	100.0%	-0.10 [-12.37 , 12.17]
Subtotal (95% CI)			**23**			**24**	**100.0%**	**-0.10 [-12.37 , 12.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.99)								
1.19.5 Folic acid								
Azizollahi 2013 (9)	46.8	42.3	26	24.6	22	25	17.6%	22.20 [3.80 , 40.60]
Boonyarangkul 2015 (10)	66.6	29.8	15	76.2	50.7	15	6.7%	-9.60 [-39.36 , 20.16]
Raigani 2014 (11)	16.2	11.4	20	15.6	15.9	18	75.6%	0.60 [-8.28 , 9.48]
Subtotal (95% CI)			**61**			**58**	**100.0%**	**3.72 [-4.01 , 11.44]**
Heterogeneity: Chi² = 5.12, df = 2 (P = 0.08); I² = 61%								
Test for overall effect: Z = 0.94 (P = 0.35)								
1.19.6 Magnesium								
Zavaczki 2003 (12)	16.1	10.2	10	10.9	7.4	10	100.0%	5.20 [-2.61 , 13.01]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**5.20 [-2.61 , 13.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.19.7 N-acetylcysteine (NAC)								
Attallah 2013 (13)	36.6	9.2	30	31.9	10.6	30	93.8%	4.70 [-0.32 , 9.72]
Barekat 2016 (14)	45.4	27.5	15	42.4	31.4	20	6.2%	3.00 [-16.57 , 22.57]
Subtotal (95% CI)			**45**			**50**	**100.0%**	**4.59 [-0.27 , 9.46]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%								
Test for overall effect: Z = 1.85 (P = 0.06)								
1.19.8 PUFAs								
Abbasi 2020 (15)	81.65	70.53	19	74.4	59.62	22	0.2%	7.25 [-33.08 , 47.58]
Conquer 2000 (16)	44.6	41.1	10	43.1	40.5	5	0.2%	1.50 [-42.19 , 45.19]
Conquer 2000 (17)	37.8	36.9	9	43.1	40.5	4	0.1%	-5.30 [-51.74 , 41.14]
Gonzalez-Ravina 2018 (18)	27.1	70.53	15	33.5	59.62	5	0.1%	-6.40 [-69.68 , 56.88]
Gonzalez-Ravina 2018 (19)	29.1	70.53	15	33.5	59.62	5	0.1%	-4.40 [-67.68 , 58.88]
Gonzalez-Ravina 2018 (20)	27.5	70.53	15	33.5	59.62	5	0.1%	-6.00 [-69.28 , 57.28]
Haghighian 2015 (21)	26.4	3.2	23	22.9	2.7	21	98.3%	3.50 [1.76 , 5.24]
Martinez-Soto 2010 (22)	29.1	26.4	21	30.5	26.2	15	1.0%	-1.40 [-18.82 , 16.02]
Subtotal (95% CI)			**127**			**82**	**100.0%**	**3.42 [1.69 , 5.15]**
Heterogeneity: Chi² = 0.72, df = 7 (P = 1.00); I² = 0%								

Analysis 1.19. (Continued)

Subtotal (95% CI)			**127**			**82**	**100.0%**	**3.42 [1.69 , 5.15]**
Heterogeneity: Chi² = 0.72, df = 7 (P = 1.00); I² = 0%								
Test for overall effect: Z = 3.88 (P = 0.0001)								
1.19.9 Selenium								
Scott 1998 (23)	48.7	35.2	16	27.5	42.4	18	100.0%	21.20 [-4.90 , 47.30]
Subtotal (95% CI)			**16**			**18**	**100.0%**	**21.20 [-4.90 , 47.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.59 (P = 0.11)								
1.19.10 Vitamin C								
Cyrus 2015 (24)	58.4	24.3	46	48.7	27.8	69	100.0%	9.70 [0.09 , 19.31]
Subtotal (95% CI)			**46**			**69**	**100.0%**	**9.70 [0.09 , 19.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.98 (P = 0.05)								
1.19.11 Vitamin C + Vitamin E								
Greco 2005 (25)	27.5	24.6	32	20.3	21.2	32	49.2%	7.20 [-4.05 , 18.45]
Rolf 1999 (26)	20.6	13.5	15	25	17.8	16	50.8%	-4.40 [-15.48 , 6.68]
Subtotal (95% CI)			**47**			**48**	**100.0%**	**1.31 [-6.58 , 9.20]**
Heterogeneity: Chi² = 2.07, df = 1 (P = 0.15); I² = 52%								
Test for overall effect: Z = 0.33 (P = 0.74)								
1.19.12 Vitamin D								
Amini 2020 (27)	88.28	13.64	30	90.4	13.37	32	100.0%	-2.12 [-8.85 , 4.61]
Subtotal (95% CI)			**30**			**32**	**100.0%**	**-2.12 [-8.85 , 4.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.54)								
1.19.13 Vitamin E								
Ener 2016 (28)	49.5	27.9	22	30.6	23	23	100.0%	18.90 [3.92 , 33.88]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**18.90 [3.92 , 33.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.47 (P = 0.01)								
1.19.14 Zinc								
Azizollahi 2013 (29)	41.5	40.2	32	24.6	22	25	5.8%	16.90 [0.52 , 33.28]
Raigani 2014 (30)	15.7	15.8	24	15.6	15.9	18	16.5%	0.10 [-9.59 , 9.79]
Sharifzadeh 2016 (31)	17.2	13.5	51	9.8	8.9	49	77.7%	7.40 [2.93 , 11.87]
Subtotal (95% CI)			**107**			**92**	**100.0%**	**6.74 [2.81 , 10.68]**
Heterogeneity: Chi² = 3.37, df = 2 (P = 0.19); I² = 41%								
Test for overall effect: Z = 3.36 (P = 0.0008)								
1.19.15 Zinc + Folic acid								
Azizollahi 2013 (32)	42.6	39.9	29	24.6	22	25	18.5%	18.00 [1.11 , 34.89]
Raigani 2014 (33)	12.1	7.7	21	15.6	15.9	18	81.5%	-3.50 [-11.55 , 4.55]
Subtotal (95% CI)			**50**			**43**	**100.0%**	**0.48 [-6.79 , 7.75]**
Heterogeneity: Chi² = 5.07, df = 1 (P = 0.02); I² = 80%								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.19.16 Combined antioxidants								
Bahmyari 2021 (34)	54.7	32.1	30	55.8	41.4	32	0.2%	-1.10 [-19.48 , 17.28]
Gamidov 2017 (35)	22.7	18.9	38	20	11.6	19	1.2%	2.70 [-5.26 , 10.66]
Gamidov 2017 (36)	25.6	35.2	38	20	11.6	19	0.5%	5.60 [-6.75 , 17.95]
Gamidov 2019 (37)	36.3	35.3	60	39.4	29.7	20	0.3%	-3.10 [-18.89 , 12.69]
Gopinath 2013 (38)	24.9	7	43	14.9	5.9	18	6.4%	10.00 [6.56 , 13.44]
Gopinath 2013 (39)	26.4	8.9	46	14.9	5.9	18	5.4%	11.50 [7.75 , 15.25]
Joseph 2020 (40)	21.4	21.8	75	27	33.6	79	1.0%	-5.60 [-14.50 , 3.30]
Kopets 2020 (41)	62.2	33.6	42	43.8	23	41	0.5%	18.40 [6.04 , 30.76]
Morgante 2010 (42)	18.2	3.5	90	19.1	3	90	83.2%	-0.90 [-1.85 , 0.05]
Popova 2019 (43)	39.3	27.6	60	43.7	23.2	20	0.5%	-4.40 [-16.74 , 7.94]
Scott 1998 (44)	34	34.5	30	27.5	30	18	0.2%	6.50 [-12.06 , 25.06]
Steiner 2020 (45)	30.2	37	82	37.5	47	82	0.5%	-7.30 [-20.25 , 5.65]
Stenqvist 2018 (46)	33.1	38.6	37	44.6	55.3	38	0.2%	-11.50 [-33.04 , 10.04]
Subtotal (95% CI)			**671**			**494**	**100.0%**	**0.53 [-0.33 , 1.40]**
Heterogeneity: Chi² = 85.39, df = 12 (P < 0.00001); I² = 86%								

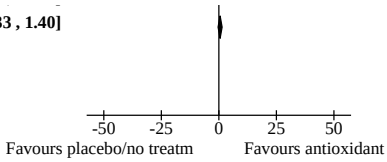


Analysis 1.19. (Continued)

Subtotal (95% CI)	**671**	**494**	**100.0%**	**0.53 [-0.33 , 1.40]**	

Heterogeneity: Chi² = 85.39, df = 12 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.21 (P = 0.23)

Test for subgroup differences: Chi² = 252.54, df = 15 (P < 0.00001), I² = 94.1%



Footnotes

(1) Astaxanthin 16 mg + Vitamin E 40 mg.
(2) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(3) L-acetyl carnitine 3000 mg.
(4) L-carnitine 3000 mg.
(5) L-carnitine 1000 mg.
(6) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(7) Lycopene 25 mg.
(8) Coenzyme Q10 200 mg.
(9) Folic acid 5 mg. After varicocelectomy.
(10) Folic acid 5 mg.
(11) Folic acid 5 mg. At 16 weeks.
(12) Magnesium 3000 mg.
(13) N-acetylcysteine (NAC) 600 mg
(14) N-acetylcysteine (NAC) 200 mg. After varicocelectomy.
(15) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(16) Docosahexaenoic acid (DHA) 800 mg.
(17) Docosahexaenoic acid (DHA) 400 mg.
(18) Docosahexaenoic acid (DHA) 1 g.
(19) Docosahexaenoic acid (DHA) 2 g.
(20) Docosahexaenoic acid (DHA) 0.5 g.
(21) Alpha-lipoic acid (ALA) 600 mg.
(22) Docosahexaenoic acid (DHA) 1000 mg. At 10 weeks.
(23) Selenium 100 µg.
(24) Vitamin C 500 mg. After varicocelectomy.
(25) Vitamin C 1000 mg + Vitamin E 1000 mg. 2 months.
(26) Vitamin C 1000 mg + Vitamin E 800 mg. 2 months.
(27) Vitamin D3 50,000IU/week for 8 weeks, followed by 50,000IU/month for 1 month
(28) Vitamin E 600 mg. After varicocelectomy.
(29) Zinc 66 mg. After varicocelectomy.
(30) Zinc 220 mg. At 16 weeks.
(31) Zinc 10 ml solution of 0.5%.
(32) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(33) Zinc 220 mg + Folic acid 5 mg. At 16 weeks.
(34) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(35) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(36) SpermActin Forte (acetyl-L-carnitine + L-carnitine fumarate + alpha-lipoic acid). After varicocelectomy.
(37) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(38) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(39) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(40) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.
(41) 1 dose TDS (l-carnitine/ l-acetyl-carnitine + l-arginine + glutathione + coenzyme Q10 + zinc + vitamin B9 + vitamin B12 + selenium)
(42) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(43) Androdoz (l-arginine 720 mg + l-carnitine 240 mg + l-carnosine 92 mg + coenzyme Q10 10 mg + glycyrrhizic acid 6 mg)
(44) Selenium 100 µg + Vitamin A 1 mg + Vitamin C 10 mg + Vitamin E 15 mg.
(45) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(46) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

Analysis 1.20. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 20: Sperm concentration at 3 months or less (data not suitable for meta analysis)

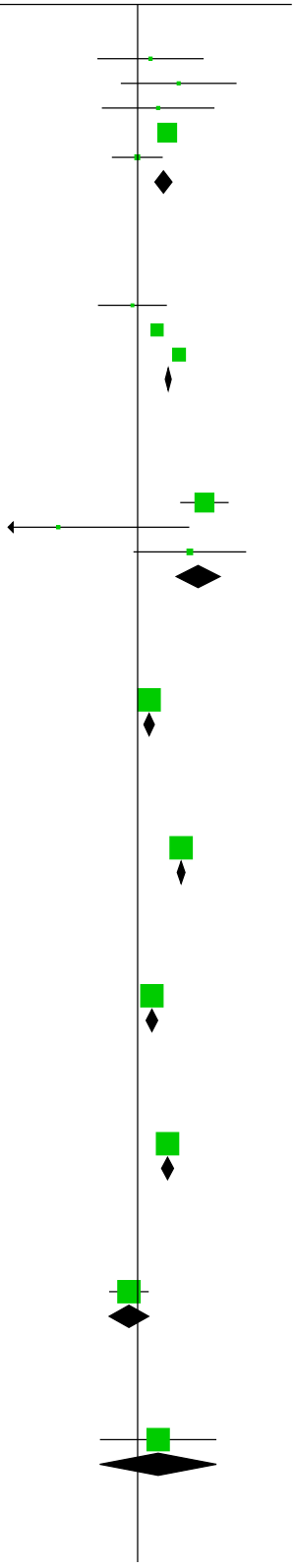
Sperm concentration at 3 months or less (data not suitable for meta analysis)

Study	Intervention	Control	P value
Carnitines			
Lenzi 2003	**L-carnitine** Mean = 9 (1st phase data) (n = 43) No SD given	**Placebo** Mean = 5.3 (n = 43) No SD given	P = 0.03
Vitamin E			

Kessopoulou 1995	**Vitamin E** Median difference = -15 (n = 15) Min/max difference = -58 - 59	**Placebo** Median difference = 0 (n = 15) Min/max difference = -37 - 160	Not provided

Analysis 1.21. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 21: Sperm concentration at 6 months; type of antioxidant

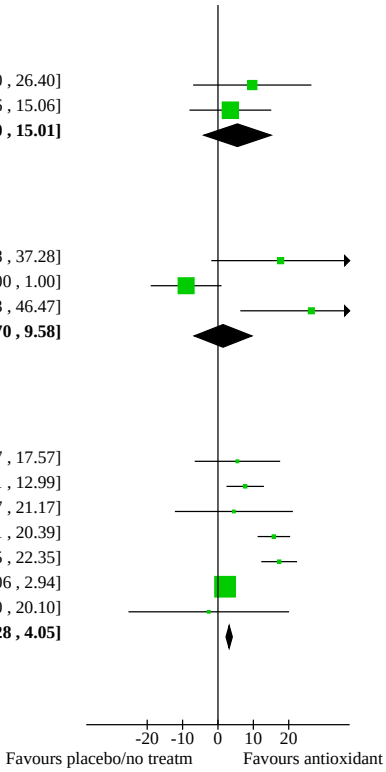
Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.21.1 Carnitines								
Balercia 2005 (1)	37.4	16.4	14	33.7	14.4	5	2.6%	3.70 [-11.57 , 18.97]
Balercia 2005 (2)	45.5	21.4	15	33.7	14.4	5	2.2%	11.80 [-4.83 , 28.43]
Balercia 2005 (3)	39.6	20	15	33.7	14.4	5	2.3%	5.90 [-10.28 , 22.08]
Cavallini 2004 (1)	20.2	7.5	39	11.7	4.7	47	81.7%	8.50 [5.79 , 11.21]
Lenzi 2004 (4)	22.1	9.1	30	22.2	17	26	11.3%	-0.10 [-7.40 , 7.20]
Subtotal (95% CI)			**113**			**88**	**100.0%**	**7.42 [4.97 , 9.87]**
Heterogeneity: Chi² = 5.21, df = 4 (P = 0.27); I² = 23%								
Test for overall effect: Z = 5.94 (P < 0.00001)								
1.21.2 Coenzyme Q10								
Balercia 2009 (5)	44.9	19.3	30	46.4	19.8	30	0.7%	-1.50 [-11.39 , 8.39]
Safarinejad 2009a (6)	26.4	4.4	98	20.8	4.3	96	47.7%	5.60 [4.38 , 6.82]
Safarinejad 2012 (5)	28.7	4.6	112	16.8	4.4	113	51.6%	11.90 [10.72 , 13.08]
Subtotal (95% CI)			**240**			**239**	**100.0%**	**8.80 [7.95 , 9.64]**
Heterogeneity: Chi² = 57.08, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 20.41 (P < 0.00001)								
1.21.3 Folic acid								
Azizollahi 2013 (7)	49.1	16.8	26	29.9	6.6	25	82.1%	19.20 [12.24 , 26.16]
Boonyarangkul 2015 (8)	53.3	22.8	15	76.1	70.8	15	2.8%	-22.80 [-60.44 , 14.84]
Wong 2002 (9)	39.7	33.8	22	24.7	20.2	25	15.1%	15.00 [-1.19 , 31.19]
Subtotal (95% CI)			**63**			**65**	**100.0%**	**17.39 [11.09 , 23.69]**
Heterogeneity: Chi² = 4.72, df = 2 (P = 0.09); I² = 58%								
Test for overall effect: Z = 5.41 (P < 0.00001)								
1.21.4 N-acetylcysteine (NAC)								
Safarinejad 2009 (10)	26.8	5.3	105	23.5	5.8	106	100.0%	3.30 [1.80 , 4.80]
Subtotal (95% CI)			**105**			**106**	**100.0%**	**3.30 [1.80 , 4.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.31 (P < 0.0001)								
1.21.5 PUFAs								
Safarinejad 2011b (11)	28.7	4.4	113	16.2	4.1	114	100.0%	12.50 [11.39 , 13.61]
Subtotal (95% CI)			**113**			**114**	**100.0%**	**12.50 [11.39 , 13.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 22.14 (P < 0.00001)								
1.21.6 Selenium								
Safarinejad 2009 (12)	27.6	6.4	105	23.5	5.8	106	100.0%	4.10 [2.45 , 5.75]
Subtotal (95% CI)			**105**			**106**	**100.0%**	**4.10 [2.45 , 5.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.87 (P < 0.00001)								
1.21.7 Selenium + N-acetylcysteine (NAC)								
Safarinejad 2009 (13)	32.1	6.8	104	23.5	5.8	106	100.0%	8.60 [6.89 , 10.31]
Subtotal (95% CI)			**104**			**106**	**100.0%**	**8.60 [6.89 , 10.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.85 (P < 0.00001)								
1.21.8 Vitamin D + Calcium								
Blomberg Jensen 2018 (14)	16.2	21.7	133	18.7	25.7	136	100.0%	-2.50 [-8.18 , 3.18]
Subtotal (95% CI)			**133**			**136**	**100.0%**	**-2.50 [-8.18 , 3.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
1.21.9 Vitamin E								
Ener 2016 (15)	53.9	22	22	48	34.2	23	100.0%	5.90 [-10.83 , 22.63]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**5.90 [-10.83 , 22.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.69 (P = 0.49)								
1.21.10 Zinc								



Analysis 1.21. (Continued)

Test for overall effect: Z = 0.69 (P = 0.49)

1.21.10 Zinc								
Azizollahi 2013 (16)	39.6	30.5	32	29.9	33	25	32.4%	9.70 [-7.00 , 26.40]
Wong 2002 (17)	28.2	20.6	23	24.7	20.2	25	67.6%	3.50 [-8.06 , 15.06]
Subtotal (95% CI)			**55**			**50**	**100.0%**	**5.51 [-4.00 , 15.01]**
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 1.14 (P = 0.26)								
1.21.11 Zinc + Folic acid								
Azizollahi 2013 (18)	47.6	40.4	29	29.9	33	25	17.3%	17.70 [-1.88 , 37.28]
Schisterman 2020 (19)	54.4	70.1	425	63.4	78.7	428	66.3%	-9.00 [-19.00 , 1.00]
Wong 2002 (20)	51.1	46.1	24	24.7	20.2	25	16.5%	26.40 [6.33 , 46.47]
Subtotal (95% CI)			**478**			**478**	**100.0%**	**1.44 [-6.70 , 9.58]**
Heterogeneity: Chi² = 12.78, df = 2 (P = 0.002); I² = 84%								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.21.12 Combined antioxidants								
Ardestani 2019 (21)	41.3	24.5	30	35.8	23.2	30	0.5%	5.50 [-6.57 , 17.57]
Busetto 2018 (22)	51.4	13.9	52	43.7	13.6	52	2.8%	7.70 [2.41 , 12.99]
Gamidov 2019 (23)	42.7	28.5	60	38.2	34.3	20	0.3%	4.50 [-12.17 , 21.17]
Gopinath 2013 (24)	31.7	9.7	43	15.9	7.7	18	3.7%	15.80 [11.21 , 20.39]
Gopinath 2013 (25)	33.2	12.4	46	15.9	7.7	18	3.1%	17.30 [12.25 , 22.35]
Kizilay 2019 (26)	14.1	2.1	62	12.1	2.1	28	89.4%	2.00 [1.06 , 2.94]
Stenqvist 2018 (27)	40.7	50.3	36	43.3	49.9	39	0.2%	-2.60 [-25.30 , 20.10]
Subtotal (95% CI)			**329**			**205**	**100.0%**	**3.16 [2.28 , 4.05]**
Heterogeneity: Chi² = 68.41, df = 6 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 7.00 (P < 0.00001)								
Test for subgroup differences: Chi² = 246.11, df = 11 (P < 0.00001), I² = 95.5%								



Footnotes

(1) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(2) L-carnitine 3000 mg.
(3) L-acetyl carnitine 3000 mg.
(4) L-carnitine 2000 mg + L-acetyl-carnitine 1000 mg.
(5) Coenzyme Q10 200 mg.
(6) Coenzyme Q10 300 mg.
(7) Folic acid 5 mg. After varicocelectomy.
(8) Folic acid 5 mg.
(9) Folic acid. At 26 weeks.
(10) N-acetylcysteine (NAC) 600 mg. 26 weeks.
(11) DHA 0.72 g + EPA 1.12 g. At 8 months.
(12) Selenium 200 µg. 26 weeks.
(13) Selenium 200 µg + N-acetylcysteine 600 mg. 26 weeks.
(14) Vitamin D 1400 IU + calcium 500 mg plus vitamin D 300,000 IU one dose. At 5 months.
(15) Vitamin E 600 mg. After varicocelectomy.
(16) Zinc 66 mg. After varicocelectomy.
(17) Zinc 66 mg. At 26 weeks.
(18) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(19) Zinc 30 mg + Folic acid 5 mg.
(20) Zinc 66 mg + Folic acid 5 mg. At 26 weeks.
(21) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU. After varicocelectomy.
(22) Proxeed Plus (l-carnitine, fumarate, acetyl-l-carnitine, fructose, CoQ10, vitamin C, zinc, folic acid and vitamin B12). Varicocele patients.
(23) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg)
(24) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(25) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(26) L-carnitine + acetyl-L-carnitine + fructose + citric acid + vitamin C + zinc + folic acid + selenium + coenzyme Q10 + vitamin B12. After varicocelectomy.
(27) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).

Analysis 1.22. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 22: Sperm concentration at 6 months (data not suitable for meta analysis)

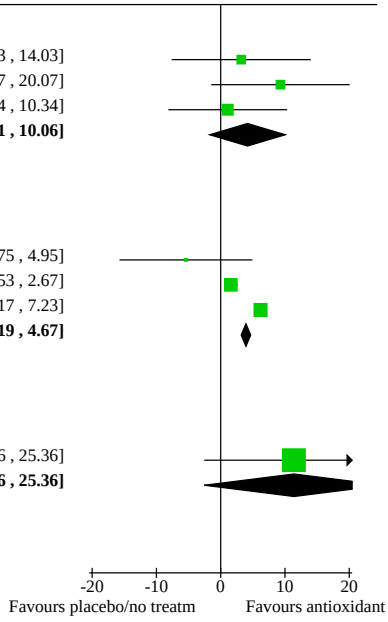
Sperm concentration at 6 months (data not suitable for meta analysis)

Study	Intervention	Control	P value

Glutathione			
Saeed Alkumait 2020	**Glutathione 250 mg** % improvement = 26 (n = 51)	**Placebo** % improvement = 2 (n = 50)	0.01
Coenzyme Q10			
Saeed Alkumait 2020	**Coenzyme Q10 200 mg** % improvement = 24 (n = 50)	**Placebo** % improvement = 2 (n = 50)	0.01

Analysis 1.23. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 23: Sperm concentration at 9 months or more; type of antioxidant

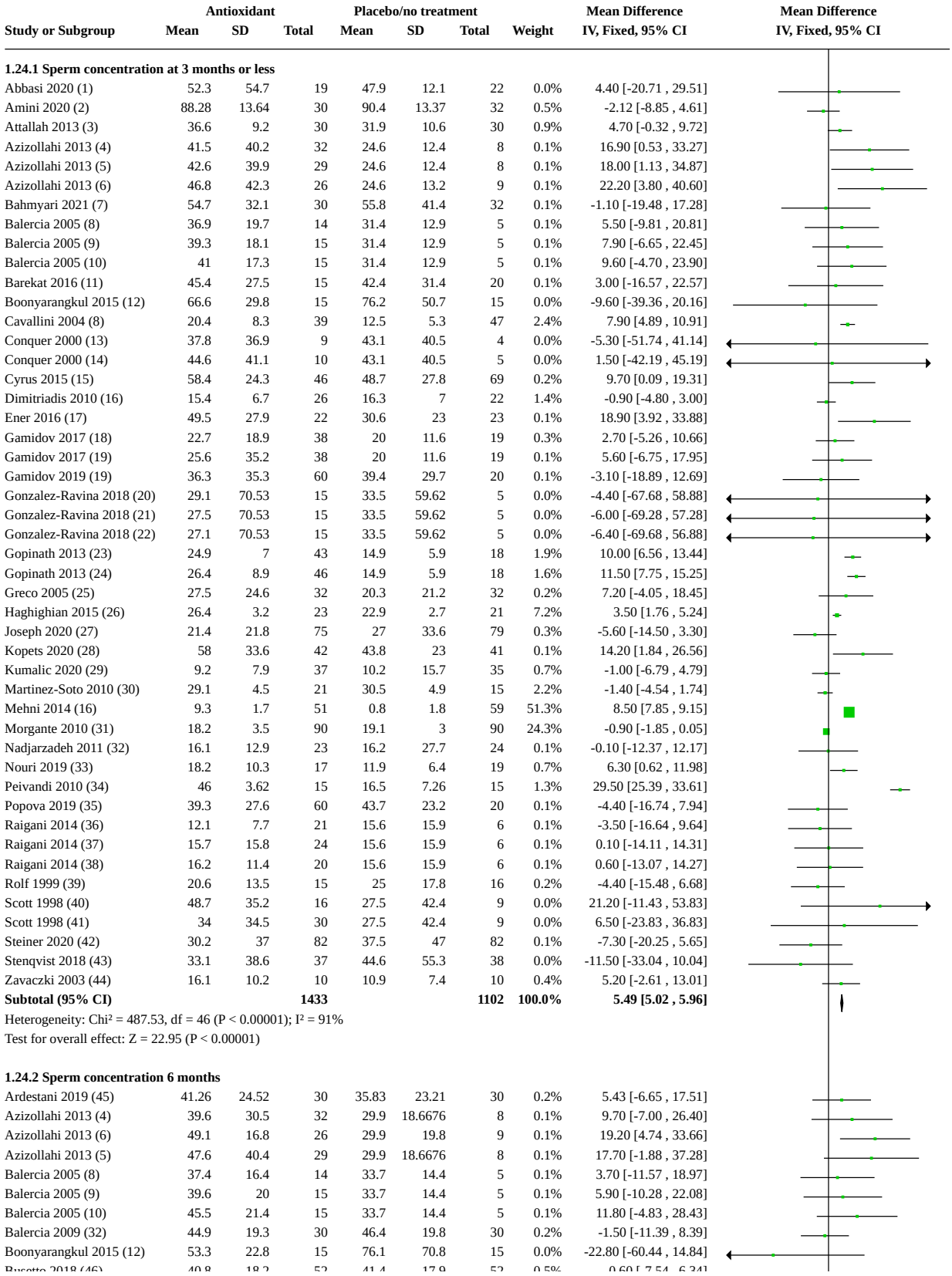
Study or Subgroup	Favours placebo/no treatm Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.23.1 Carnitines								
Balercia 2005 (1)	33.3	13.6	14	30.1	9.3	5	29.6%	3.20 [-7.63 , 14.03]
Balercia 2005 (2)	39.4	13.9	15	30.1	9.3	5	29.9%	9.30 [-1.47 , 20.07]
Balercia 2005 (3)	31.2	8.6	15	30.1	9.3	5	40.6%	1.10 [-8.14 , 10.34]
Subtotal (95% CI)			**44**			**15**	**100.0%**	**4.17 [-1.71 , 10.06]**
Heterogeneity: Chi² = 1.33, df = 2 (P = 0.52); I² = 0%								
Test for overall effect: Z = 1.39 (P = 0.16)								
1.23.2 Coenzyme Q10								
Balercia 2009 (4)	44.2	20.4	30	49.6	20.5	30	0.5%	-5.40 [-15.75 , 4.95]
Safarinejad 2009a (5)	22.8	3.8	98	21.2	3.8	96	48.1%	1.60 [0.53 , 2.67]
Safarinejad 2012 (4)	22.4	4.2	112	16.2	3.7	113	51.4%	6.20 [5.17 , 7.23]
Subtotal (95% CI)			**240**			**239**	**100.0%**	**3.93 [3.19 , 4.67]**
Heterogeneity: Chi² = 39.85, df = 2 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 10.38 (P < 0.00001)								
1.23.3 Vitamin E								
Ener 2016 (6)	58.6	20.2	22	47.2	27.2	23	100.0%	11.40 [-2.56 , 25.36]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**11.40 [-2.56 , 25.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.60 (P = 0.11)								
Test for subgroup differences: Chi² = 1.10, df = 2 (P = 0.58), I² = 0%								



Footnotes

(1) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(2) L-carnitine 3000 mg.
(3) L-acetyl carnitine 3000 mg.
(4) Coenzyme Q10 200 mg.
(5) Coenzyme Q10 300 mg.
(6) Vitamin E 600 mg. Varicocele patients. At 12 months.

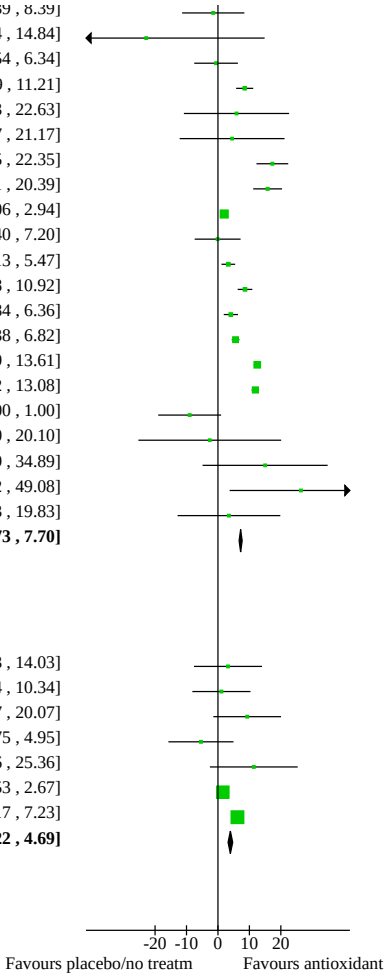
Analysis 1.24. Comparison 1: Antioxidant(s) versus placebo or no treatment, Outcome 24: Sperm concentration over time



Study or Subgroup	Antioxidant Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.24.1 Sperm concentration at 3 months or less								
Abbasi 2020 (1)	52.3	54.7	19	47.9	12.1	22	0.0%	4.40 [-20.71 , 29.51]
Amini 2020 (2)	88.28	13.64	30	90.4	13.37	32	0.5%	-2.12 [-8.85 , 4.61]
Attallah 2013 (3)	36.6	9.2	30	31.9	10.6	30	0.9%	4.70 [-0.32 , 9.72]
Azizollahi 2013 (4)	41.5	40.2	32	24.6	12.4	8	0.1%	16.90 [0.53 , 33.27]
Azizollahi 2013 (5)	42.6	39.9	29	24.6	12.4	8	0.1%	18.00 [1.13 , 34.87]
Azizollahi 2013 (6)	46.8	42.3	26	24.6	13.2	9	0.1%	22.20 [3.80 , 40.60]
Bahmyari 2021 (7)	54.7	32.1	30	55.8	41.4	32	0.1%	-1.10 [-19.48 , 17.28]
Balercia 2005 (8)	36.9	19.7	14	31.4	12.9	5	0.1%	5.50 [-9.81 , 20.81]
Balercia 2005 (9)	39.3	18.1	15	31.4	12.9	5	0.1%	7.90 [-6.65 , 22.45]
Balercia 2005 (10)	41	17.3	15	31.4	12.9	5	0.1%	9.60 [-4.70 , 23.90]
Barekat 2016 (11)	45.4	27.5	15	42.4	31.4	20	0.1%	3.00 [-16.57 , 22.57]
Boonyarangkul 2015 (12)	66.6	29.8	15	76.2	50.7	15	0.0%	-9.60 [-39.36 , 20.16]
Cavallini 2004 (8)	20.4	8.3	39	12.5	5.3	47	2.4%	7.90 [4.89 , 10.91]
Conquer 2000 (13)	37.8	36.9	9	43.1	40.5	4	0.0%	-5.30 [-51.74 , 41.14]
Conquer 2000 (14)	44.6	41.1	10	43.1	40.5	5	0.0%	1.50 [-42.19 , 45.19]
Cyrus 2015 (15)	58.4	24.3	46	48.7	27.8	69	0.2%	9.70 [0.09 , 19.31]
Dimitriadis 2010 (16)	15.4	6.7	26	16.3	7	22	1.4%	-0.90 [-4.80 , 3.00]
Ener 2016 (17)	49.5	27.9	22	30.6	23	23	0.1%	18.90 [3.92 , 33.88]
Gamidov 2017 (18)	22.7	18.9	38	20	11.6	19	0.3%	2.70 [-5.26 , 10.66]
Gamidov 2017 (19)	25.6	35.2	38	20	11.6	19	0.1%	5.60 [-6.75 , 17.95]
Gamidov 2019 (19)	36.3	35.3	60	39.4	29.7	20	0.1%	-3.10 [-18.89 , 12.69]
Gonzalez-Ravina 2018 (20)	29.1	70.53	15	33.5	59.62	5	0.0%	-4.40 [-67.68 , 58.88]
Gonzalez-Ravina 2018 (21)	27.5	70.53	15	33.5	59.62	5	0.0%	-6.00 [-69.28 , 57.28]
Gonzalez-Ravina 2018 (22)	27.1	70.53	15	33.5	59.62	5	0.0%	-6.40 [-69.68 , 56.88]
Gopinath 2013 (23)	24.9	7	43	14.9	5.9	18	1.9%	10.00 [6.56 , 13.44]
Gopinath 2013 (24)	26.4	8.9	46	14.9	5.9	18	1.6%	11.50 [7.75 , 15.25]
Greco 2005 (25)	27.5	24.6	32	20.3	21.2	32	0.2%	7.20 [-4.05 , 18.45]
Haghighian 2015 (26)	26.4	3.2	23	22.9	2.7	21	7.2%	3.50 [1.76 , 5.24]
Joseph 2020 (27)	21.4	21.8	75	27	33.6	79	0.3%	-5.60 [-14.50 , 3.30]
Kopets 2020 (28)	58	33.6	42	43.8	23	41	0.1%	14.20 [1.84 , 26.56]
Kumalic 2020 (29)	9.2	7.9	37	10.2	15.7	35	0.7%	-1.00 [-6.79 , 4.79]
Martinez-Soto 2010 (30)	29.1	4.5	21	30.5	4.9	15	2.2%	-1.40 [-4.54 , 1.74]
Mehni 2014 (16)	9.3	1.7	51	0.8	1.8	59	51.3%	8.50 [7.85 , 9.15]
Morgante 2010 (31)	18.2	3.5	90	19.1	3	90	24.3%	-0.90 [-1.85 , 0.05]
Nadjarzadeh 2011 (32)	16.1	12.9	23	16.2	27.7	24	0.1%	-0.10 [-12.37 , 12.17]
Nouri 2019 (33)	18.2	10.3	17	11.9	6.4	19	0.7%	6.30 [0.62 , 11.98]
Peivandi 2010 (34)	46	3.62	15	16.5	7.26	15	1.3%	29.50 [25.39 , 33.61]
Popova 2019 (35)	39.3	27.6	60	43.7	23.2	20	0.1%	-4.40 [-16.74 , 7.94]
Raigani 2014 (36)	12.1	7.7	21	15.6	15.9	6	0.1%	-3.50 [-16.64 , 9.64]
Raigani 2014 (37)	15.7	15.8	24	15.6	15.9	6	0.1%	0.10 [-14.11 , 14.31]
Raigani 2014 (38)	16.2	11.4	20	15.6	15.9	6	0.1%	0.60 [-13.07 , 14.27]
Rolf 1999 (39)	20.6	13.5	15	25	17.8	16	0.2%	-4.40 [-15.48 , 6.68]
Scott 1998 (40)	48.7	35.2	16	27.5	42.4	9	0.0%	21.20 [-11.43 , 53.83]
Scott 1998 (41)	34	34.5	30	27.5	42.4	9	0.0%	6.50 [-23.83 , 36.83]
Steiner 2020 (42)	30.2	37	82	37.5	47	82	0.1%	-7.30 [-20.25 , 5.65]
Stenqvist 2018 (43)	33.1	38.6	37	44.6	55.3	38	0.0%	-11.50 [-33.04 , 10.04]
Zavaczki 2003 (44)	16.1	10.2	10	10.9	7.4	10	0.4%	5.20 [-2.61 , 13.01]
Subtotal (95% CI)			**1433**			**1102**	**100.0%**	**5.49 [5.02 , 5.96]**
Heterogeneity: Chi² = 487.53, df = 46 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 22.95 (P < 0.00001)								
1.24.2 Sperm concentration 6 months								
Ardestani 2019 (45)	41.26	24.52	30	35.83	23.21	30	0.2%	5.43 [-6.65 , 17.51]
Azizollahi 2013 (4)	39.6	30.5	32	29.9	18.6676	8	0.1%	9.70 [-7.00 , 26.40]
Azizollahi 2013 (6)	49.1	16.8	26	29.9	19.8	9	0.1%	19.20 [4.74 , 33.66]
Azizollahi 2013 (5)	47.6	40.4	29	29.9	18.6676	8	0.1%	17.70 [-1.88 , 37.28]
Balercia 2005 (8)	37.4	16.4	14	33.7	14.4	5	0.1%	3.70 [-11.57 , 18.97]
Balercia 2005 (9)	39.6	20	15	33.7	14.4	5	0.1%	5.90 [-10.28 , 22.08]
Balercia 2005 (10)	45.5	21.4	15	33.7	14.4	5	0.1%	11.80 [-4.83 , 28.43]
Balercia 2009 (32)	44.9	19.3	30	46.4	19.8	30	0.2%	-1.50 [-11.39 , 8.39]
Boonyarangkul 2015 (12)	53.3	22.8	15	76.1	70.8	15	0.0%	-22.80 [-60.44 , 14.84]
Busetto 2018 (46)	40.8	18.2	52	41.4	17.9	52	0.5%	0.60 [-7.54 , 6.34]

Analysis 1.24. (Continued)

Balercia 2009 (32)	44.9	19.3	30	46.4	19.8	30	0.2%	-1.50 [-11.39 , 8.39]
Boonyarangkul 2015 (12)	53.3	22.8	15	76.1	70.8	15	0.0%	-22.80 [-60.44 , 14.84]
Busetto 2018 (46)	40.8	18.2	52	41.4	17.9	52	0.5%	-0.60 [-7.54 , 6.34]
Cavallini 2004 (8)	20.2	7.5	39	11.7	4.7	47	3.2%	8.50 [5.79 , 11.21]
Ener 2016 (17)	53.9	22	22	48	34.2	23	0.1%	5.90 [-10.83 , 22.63]
Gamidov 2019 (19)	42.7	28.5	60	38.2	34.3	20	0.1%	4.50 [-12.17 , 21.17]
Gopinath 2013 (24)	33.2	12.4	46	15.9	7.7	18	0.9%	17.30 [12.25 , 22.35]
Gopinath 2013 (23)	31.7	9.7	43	15.9	7.7	18	1.1%	15.80 [11.21 , 20.39]
Kizilay 2019 (47)	14.1	2.1	62	12.1	2.1	28	26.7%	2.00 [1.06 , 2.94]
Lenzi 2004 (48)	22.1	9.1	30	22.2	17	26	0.4%	-0.10 [-7.40 , 7.20]
Safarinejad 2009 (49)	26.8	5.3	105	23.5	5.8	35	5.0%	3.30 [1.13 , 5.47]
Safarinejad 2009 (50)	32.1	6.8	104	23.5	5.8	35	4.3%	8.60 [6.28 , 10.92]
Safarinejad 2009 (51)	27.6	6.4	105	23.5	5.8	36	4.6%	4.10 [1.84 , 6.36]
Safarinejad 2009a (52)	26.4	4.4	98	20.8	4.3	96	15.6%	5.60 [4.38 , 6.82]
Safarinejad 2011b (53)	28.7	4.4	113	16.2	4.1	114	19.1%	12.50 [11.39 , 13.61]
Safarinejad 2012 (32)	28.7	4.6	112	16.8	4.4	113	16.9%	11.90 [10.72 , 13.08]
Schisterman 2020 (54)	54.4	70.1	425	63.4	78.7	428	0.2%	-9.00 [-19.00 , 1.00]
Stenqvist 2018 (43)	40.7	50.3	36	43.3	49.9	39	0.0%	-2.60 [-25.30 , 20.10]
Wong 2002 (55)	39.7	33.8	22	24.7	20.2	8	0.1%	15.00 [-4.89 , 34.89]
Wong 2002 (56)	51.1	46.1	24	24.7	20.2	9	0.0%	26.40 [3.72 , 49.08]
Wong 2002 (57)	28.2	20.6	23	24.7	20.2	8	0.1%	3.50 [-12.83 , 19.83]
Subtotal (95% CI)			**1727**			**1268**	**100.0%**	**7.21 [6.73 , 7.70]**
Heterogeneity: Chi² = 358.04, df = 27 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 29.21 (P < 0.00001)								
1.24.3 Sperm concentration at 9 months or more								
Balercia 2005 (8)	33.3	13.6	14	30.1	9.3	5	0.5%	3.20 [-7.63 , 14.03]
Balercia 2005 (9)	31.2	8.6	15	30.1	9.3	5	0.6%	1.10 [-8.14 , 10.34]
Balercia 2005 (10)	39.4	13.9	15	30.1	9.3	5	0.5%	9.30 [-1.47 , 20.07]
Balercia 2009 (32)	44.2	20.4	30	49.6	20.5	30	0.5%	-5.40 [-15.75 , 4.95]
Ener 2016 (58)	58.6	20.2	22	47.2	27.2	23	0.3%	11.40 [-2.56 , 25.36]
Safarinejad 2009a (52)	22.8	3.8	98	21.2	3.8	96	47.2%	1.60 [0.53 , 2.67]
Safarinejad 2012 (32)	22.4	4.2	112	16.2	3.7	113	50.4%	6.20 [5.17 , 7.23]
Subtotal (95% CI)			**306**			**277**	**100.0%**	**3.95 [3.22 , 4.69]**
Heterogeneity: Chi² = 42.28, df = 6 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 10.54 (P < 0.00001)								



Footnotes

(1) Alpha-lipoic acid (ALA) 600 mg. At 80 days.
(2) Vitamin D3 50,000 IU.
(3) N-acetylcysteine (NAC) 600 mg.
(4) Zinc 66 mg. After varicocelectomy.
(5) Zinc 66 mg + Folic acid 5 mg. After varicocelectomy.
(6) Folic acid 5 mg. After varicocelectomy.
(7) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU.
(8) L-carnitine 2000 mg + L-acetyl carnitine 1000 mg.
(9) L-acetyl carnitine 3000 mg.
(10) L-carnitine 3000 mg.
(11) N-acetylcysteine (NAC) 200 mg. After varicocelectomy.
(12) Folic acid 5 mg.
(13) Docosahexaenoic acid (DHA) 400 mg.
(14) Docosahexaenoic acid (DHA) 800 mg.
(15) Vitamin C 500 mg. After varicocelectomy.
(16) L-carnitine 1000 mg.
(17) Vitamin E 600 mg. After varicocelectomy.
(18) SpermActin Forte + Vitamin complex 'Man's formula'. After varicocelectomy.
(19) SpermActin Forte (l-carnitine fumarate 2000 mg + acetyl-L-carnitine 1000 mg + alpha-lipoic acid 100 mg + vitamin C 100 mg).
(20) Docosahexaenoic acid (DHA) 2 g.
(21) Docosahexaenoic acid (DHA) 0.5 g.
(22) Docosahexaenoic acid (DHA) 1 g.
(23) 1 tablet FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(24) 2 tablets FDC (Coenzyme Q10 50 mg + L-carnitine 500 mg + lycopene 2.5 mg + zinc 12.5 mg).
(25) Vitamin C 1000 mg + Vitamin E 1000 mg.
(26) Alpha-lipoic acid (ALA) 600 mg.
(27) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.

Analysis 1.24. (Continued)

(26) Alpha-lipoic acid (ALA) 600 mg.
(27) Vitamin C 500 mg + vitamin E 400 mg + zinc 140 mg.
(28) L-carnitine/ l-acetyl-carnitine + l-arginine + glutathione + coenzyme Q10 + zinc + vitamin B9 + vitamin B12 + selenium. At 2 months.
(29) Astaxanthin 16 mg + Vitamin E 40 mg.
(30) Docosahexaenoic acid (DHA) 1000 mg. 10 weeks.
(31) L-arginine 1660 mg + carnitine 150 mg + acetyl-carnitine 50 mg + ginseng 200 mg.
(32) Coenzyme Q10 200 mg.
(33) Lycopene 25 mg.
(34) L-carnitine 2000 mg. 2 months (crossover trial). According to author really SD used (not SE).
(35) Androdoz (l-arginine 720 mg + l-carnitine 240 mg + l-carnosine 92 mg + coenzyme Q10 10 mg + glycyrrhizic acid 6 mg).
(36) Zinc 220 mg + Folic acid 5 mg. 16 weeks.
(37) Zinc 220 mg. 16 weeks.
(38) Folic acid 5 mg. 16 weeks.
(39) Vitamin C 1000 mg + Vitamin E 800 mg.
(40) Selenium 100 mcg.
(41) Selenium 100 µg + vitamin A 1 mg + vitamin C 10 mg + vitamin E 15 mg.
(42) Vitamin C + vitamin E + selenium + l-carnitine + zinc + folic acid + lycopene + vitamin D.
(43) Androferti (vitamin C + vitamin E + vitamin B12 + l-carnitine + coenzyme Q10 + folic acid + zinc + selenium).
(44) Magnesium 3000 mg.
(45) Folic acid 5 mg + selenium 200 mcg + vitamin E 400 IU. After varicocelectomy.
(46) Proxeed Plus (l-carnitine, fumarate, acetyl-L-carnitine, fructose, CoQ10, vitamin C, zinc, folic acid and vitamin B12). Varicocele patients.
(47) L-carnitine + acetyl-L-carnitine + fructose + citric acid + vitamin C + zinc + folic acid + selenium + coenzyme Q10 + vitamin B12. After varicocelectomy.
(48) L-carnitine 2000 mg.
(49) N-acetylcysteine (NAC) 600 mg. 26 weeks.
(50) Selenium 200 µg + N-acetylcysteine 600 mg. 26 weeks.
(51) Selenium 200 µg. 26 weeks.
(52) Coenzyme Q10 300 mg.
(53) DHA 0.72 g + EPA 1.12 g. At 8 months.
(54) Zinc 30 mg + Folic acid 5 mg.
(55) Folic acid 5 mg. 26 weeks.
(56) Zinc 66 mg + Folic acid 5 mg. 26 weeks.
(57) Zinc 66 mg. 26 weeks.
(58) 12 months. Vitamin E 600 mg. Varicocele patients.

Comparison 2. Head-to-head antioxidant(s)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth; type of antioxidant	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1.1 L-carnitine vs L-acetyl carnitine	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.13, 7.92]
2.1.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.06, 1.79]
2.1.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.06, 1.79]
2.2 Clinical pregnancy; type of antioxidant	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.2.1 L-carnitine vs L-acetyl carnitine	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.13, 7.92]
2.2.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.06, 1.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.06, 1.79]
2.2.4 L-carnitine vs Coenzyme Q10	1	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.54, 4.05]
2.2.5 L-carnitine vs L-carnitine + Coenzyme Q10	1	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.27, 1.46]
2.2.6 Coenzyme Q10 vs L-carnitine + Coenzyme Q10	1	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.18, 1.06]
2.2.7 Vitamin D + Calcium vs Vitamin E + Vitamin C	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.13 [1.21, 21.79]
2.2.8 Combined antioxidants vs L-carnitine	1	89	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [0.20, 19.08]
2.3 Sperm DNA fragmentation; type of antioxidant	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 L-carnitine vs Coenzyme Q10	1	125	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.22, 0.62]
2.3.2 L-carnitine vs L-carnitine + Coenzyme Q10	1	125	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.14, 1.94]
2.3.3 Coenzyme Q10 vs L-carnitine + Coenzyme Q10	1	126	Mean Difference (IV, Fixed, 95% CI)	1.20 [-0.25, 2.65]
2.3.4 L-carnitine vs Vitamin B1	1	136	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.22, 0.22]
2.3.5 Coenzyme Q10 vs Vitamin B1	1	137	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.34, 0.94]
2.3.6 Vitamin B1 vs L-carnitine + Coenzyme Q10	1	137	Mean Difference (IV, Fixed, 95% CI)	1.90 [0.16, 3.64]
2.4 Total sperm motility at 3 months or less; type of antioxidant	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.4.1 Coenzyme Q10 200 mg vs Coenzyme Q10 400 mg	1	65	Mean Difference (IV, Fixed, 95% CI)	-4.86 [-10.60, 0.88]
2.4.2 Docosahexaenoic acid (DHA) 400 mg vs Docosahexaenoic acid 800 mg	1	19	Mean Difference (IV, Fixed, 95% CI)	7.40 [-11.35, 26.15]
2.4.3 DHA vs DHA + Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	-3.77 [-5.42, -2.12]
2.4.4 DHA versus Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.30, 0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.5 DHA + Vitamin E vs Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	2.17 [0.54, 3.80]
2.4.6 Ethylcysteine vs Vitamin E	1	10	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-41.97, 38.17]
2.4.7 L-acetyl carnitine + L-carnitine vs Vitamin E + Vitamin C	1	138	Mean Difference (IV, Fixed, 95% CI)	23.10 [20.14, 26.06]
2.4.8 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	3.40 [-3.73, 10.53]
2.4.9 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	4.80 [-1.76, 11.36]
2.4.10 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	1.40 [-6.42, 9.22]
2.4.11 Selenium vs combined antioxidants	1	46	Mean Difference (IV, Fixed, 95% CI)	3.20 [-10.13, 16.53]
2.4.12 Vitamin C 200mg vs Vitamin C 1000mg	1	20	Mean Difference (IV, Fixed, 95% CI)	-43.00 [-67.10, -18.90]
2.4.13 Vitamin E + 'Compound amino acids' vs Vitamin E	1	120	Mean Difference (IV, Fixed, 95% CI)	11.90 [8.71, 15.09]
2.4.14 Zinc vs Folic acid	2	124	Mean Difference (IV, Fixed, 95% CI)	-3.01 [-11.38, 5.35]
2.4.15 Zinc vs Zinc + Folic acid	2	125	Mean Difference (IV, Fixed, 95% CI)	-2.91 [-10.92, 5.10]
2.4.16 Zinc + Folic acid vs Folic acid	2	121	Mean Difference (IV, Fixed, 95% CI)	0.24 [-6.17, 6.66]
2.4.17 Zinc vs Zinc + Vitamin E	1	18	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-15.00, 13.00]
2.4.18 Zinc vs Zinc + Vitamin E + Vitamin C	1	12	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-19.66, 17.66]
2.4.19 Zinc + Vitamin E vs Zinc + Vitamin E + Vitamin C	1	18	Mean Difference (IV, Fixed, 95% CI)	0.00 [-18.97, 18.97]
2.5 Total sperm motility at 6 months; type of antioxidant	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.5.1 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	4.10 [-2.70, 10.90]
2.5.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	3.40 [-2.87, 9.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-7.73, 6.33]
2.5.4 N-acetylcysteine (NAC) vs Selenium + N-acetylcysteine (NAC)	1	234	Mean Difference (IV, Fixed, 95% CI)	-4.40 [-5.14, -3.66]
2.5.5 Selenium vs N-acetylcysteine (NAC)	1	234	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.56, 2.04]
2.5.6 Selenium vs Selenium + N-acetylcysteine (NAC)	1	232	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-3.85, -2.35]
2.5.7 Zinc vs Folic acid	2	125	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-5.18, 3.13]
2.5.8 Zinc vs Zinc + Folic acid	2	127	Mean Difference (IV, Fixed, 95% CI)	-1.69 [-6.95, 3.58]
2.5.9 Zinc + Folic acid vs Folic acid	2	126	Mean Difference (IV, Fixed, 95% CI)	1.03 [-4.23, 6.29]
2.6 Total sperm motility at 9 months or more; type of antioxidant	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.6.1 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	3.70 [-1.69, 9.09]
2.6.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	5.30 [-0.73, 11.33]
2.6.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	1.60 [-3.29, 6.49]
2.7 Progessive sperm motility at 3 months or less; type of antioxidant	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.7.1 Coenzyme Q10 200 mg vs Coenzyme Q10 400 mg	1	65	Mean Difference (IV, Fixed, 95% CI)	-3.52 [-9.71, 2.67]
2.7.2 Docosahexaenoic acid (DHA) vs DHA + Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	-2.22 [-3.50, -0.94]
2.7.3 DHA vs Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.67, 0.89]
2.7.4 DHA + Vitamin E vs Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	1.83 [0.68, 2.98]
2.7.5 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	4.00 [-1.88, 9.88]
2.7.6 L-carnitine vs L-carnitine + L-acetyl carnitine	1	29	Mean Difference (IV, Fixed, 95% CI)	5.00 [-0.68, 10.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.7 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	29	Mean Difference (IV, Fixed, 95% CI)	1.00 [-5.41, 7.41]
2.7.8 L-carnitine vs Vitamin B1	1	136	Mean Difference (IV, Fixed, 95% CI)	1.70 [-1.54, 4.94]
2.7.9 L-carnitine vs Coenzyme Q10	1	125	Mean Difference (IV, Fixed, 95% CI)	1.30 [-1.70, 4.30]
2.7.10 L-carnitine vs L-carnitine + Coenzyme Q10	1	125	Mean Difference (IV, Fixed, 95% CI)	-8.20 [-12.31, -4.09]
2.7.11 Coenzyme Q10 vs L-carnitine + Coenzyme Q10	1	126	Mean Difference (IV, Fixed, 95% CI)	-9.50 [-13.54, -5.46]
2.7.12 Coenzyme Q10 vs Vitamin B1	1	137	Mean Difference (IV, Fixed, 95% CI)	0.40 [-2.75, 3.55]
2.7.13 Vitamin B1 vs L-carnitine + Coenzyme Q10	1	137	Mean Difference (IV, Fixed, 95% CI)	-9.90 [-14.12, -5.68]
2.7.14 L-acetyl carnitine + L-carnitine vs Vitamin E + Vitamin C	1	138	Mean Difference (IV, Fixed, 95% CI)	13.30 [11.21, 15.39]
2.7.15 L-carnitine vs Vitamin E + Vitamin C	1	63	Mean Difference (IV, Fixed, 95% CI)	30.50 [27.70, 33.30]
2.7.16 L-carnitine vs Vitamin E	1	212	Mean Difference (IV, Fixed, 95% CI)	1.90 [1.31, 2.49]
2.7.17 L-carnitine + Vitamin E vs Vitamin E	1	113	Mean Difference (IV, Fixed, 95% CI)	14.10 [10.11, 18.09]
2.7.18 Vitamin D + Calcium vs Vitamin E + Vitamin C	1	86	Mean Difference (IV, Fixed, 95% CI)	6.90 [5.38, 8.42]
2.7.19 Vitamin E + 'Compound amino acids' vs Vitamin E	1	120	Mean Difference (IV, Fixed, 95% CI)	6.10 [3.87, 8.33]
2.8 Progressive sperm motility at 6 months; type of antioxidant	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.8.1 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	6.30 [0.42, 12.18]
2.8.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	29	Mean Difference (IV, Fixed, 95% CI)	5.70 [0.10, 11.30]
2.8.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	29	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-6.93, 5.73]
2.9 Progressive motility at 6 months (data not suitable for meta-analysis)	1		Other data	No numeric data

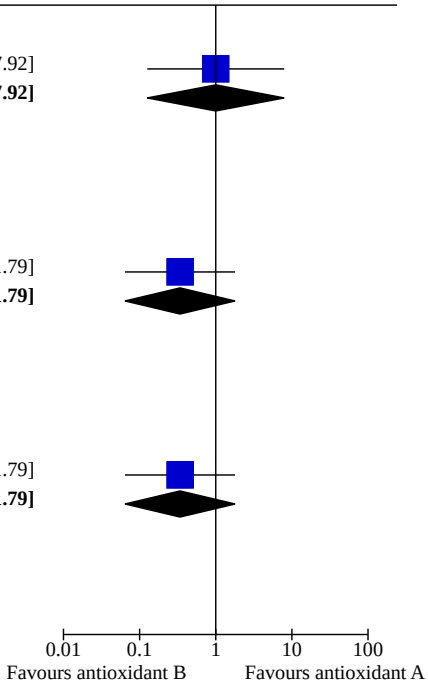
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.10 Progressive sperm motility at 9 months; type of antioxidant	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.10.1 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	3.80 [-1.50, 9.10]
2.10.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	29	Mean Difference (IV, Fixed, 95% CI)	5.50 [-0.11, 11.11]
2.10.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	29	Mean Difference (IV, Fixed, 95% CI)	1.70 [-4.17, 7.57]
2.11 Sperm concentration at 3 months or less; type of antioxidant	11		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.11.1 Coenzyme Q10 200 mg vs Coenzyme Q10 400 mg	1	65	Mean Difference (IV, Fixed, 95% CI)	0.20 [-3.26, 3.66]
2.11.2 Docosahexaenoic acid (DHA) 400 mg vs Docosahexaenoic acid (DHA) 800 mg	1	19	Mean Difference (IV, Fixed, 95% CI)	-6.80 [-41.87, 28.27]
2.11.3 DHA vs DHA + Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.47, -0.43]
2.11.4 DHA vs Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-1.26, 0.78]
2.11.5 DHA + Vitamin E vs Vitamin E	1	90	Mean Difference (IV, Fixed, 95% CI)	1.21 [0.28, 2.14]
2.11.6 Ethylcysteine vs Vitamin E	1	10	Mean Difference (IV, Fixed, 95% CI)	2.20 [-16.65, 21.05]
2.11.7 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	1.70 [-10.97, 14.37]
2.11.8 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	4.10 [-9.17, 17.37]
2.11.9 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	2.40 [-11.14, 15.94]
2.11.10 L-carnitine vs Vitamin E + Vitamin C	1	63	Mean Difference (IV, Fixed, 95% CI)	15.50 [12.49, 18.51]
2.11.11 L-carnitine vs Vitamin E	1	212	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.34, 1.74]
2.11.12 L-carnitine + Vitamin E vs Vitamin E	1	113	Mean Difference (IV, Fixed, 95% CI)	1.90 [-10.52, 14.32]
2.11.13 Selenium vs Combined antioxidants	1	46	Mean Difference (IV, Fixed, 95% CI)	14.70 [-6.51, 35.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.11.14 Zinc vs Folic acid	2	124	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-8.65, 6.06]
2.11.15 Zinc vs Zinc + Folic acid	2	125	Mean Difference (IV, Fixed, 95% CI)	2.93 [-3.67, 9.54]
2.11.16 Zinc + Folic acid vs Folic acid	2	121	Mean Difference (IV, Fixed, 95% CI)	-4.11 [-9.79, 1.57]
2.12 Sperm concentration at 6 months; type of antioxidant	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.12.1 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	5.90 [-8.92, 20.72]
2.12.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	8.10 [-5.54, 21.74]
2.12.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Fixed, 95% CI)	2.20 [-10.89, 15.29]
2.12.4 N-acetylcysteine (NAC) vs Selenium + N-acetylcysteine (NAC)	1	234	Mean Difference (IV, Fixed, 95% CI)	-5.30 [-6.86, -3.74]
2.12.5 Selenium vs N-acetylcysteine (NAC)	1	234	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.71, 2.31]
2.12.6 Selenium vs Selenium + N-acetylcysteine (NAC)	1	232	Mean Difference (IV, Fixed, 95% CI)	-4.50 [-6.20, -2.80]
2.12.7 Zinc vs Folic acid	2	125	Mean Difference (IV, Fixed, 95% CI)	-10.10 [-19.12, -1.08]
2.12.8 Zinc vs Zinc + Folic acid	2	127	Mean Difference (IV, Fixed, 95% CI)	-13.58 [-25.99, -1.17]
2.12.9 Zinc + Folic acid vs Folic acid	2	126	Mean Difference (IV, Fixed, 95% CI)	1.78 [-9.93, 13.49]
2.13 Sperm concentration at 6 months (data not suitable for meta-analysis)	1		Other data	No numeric data
2.14 Sperm concentration at 9 months or more; type of antioxidant	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.14.1 L-carnitine vs L-acetyl carnitine	1	30	Mean Difference (IV, Random, 95% CI)	8.20 [-0.07, 16.47]
2.14.2 L-carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Random, 95% CI)	6.10 [-3.74, 15.94]
2.14.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine	1	30	Mean Difference (IV, Random, 95% CI)	-2.10 [-10.24, 6.04]

Analysis 2.1. Comparison 2: Head-to-head antioxidant(s), Outcome 1: Live birth; type of antioxidant

Study or Subgroup	Antioxidant A Events	Antioxidant A Total	Antioxidant B Events	Antioxidant B Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.1.1 L-carnitine vs L-acetyl carnitine						
Balercia 2005 (1)	2	15	2	15	100.0%	1.00 [0.13 , 7.92]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**1.00 [0.13 , 7.92]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.1.2 L-carnitine vs L-carnitine + L-acetyl carnitine						
Balercia 2005 (1)	2	15	5	15	100.0%	0.34 [0.06 , 1.79]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.34 [0.06 , 1.79]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
2.1.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine						
Balercia 2005 (1)	2	15	5	15	100.0%	0.34 [0.06 , 1.79]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**0.34 [0.06 , 1.79]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						

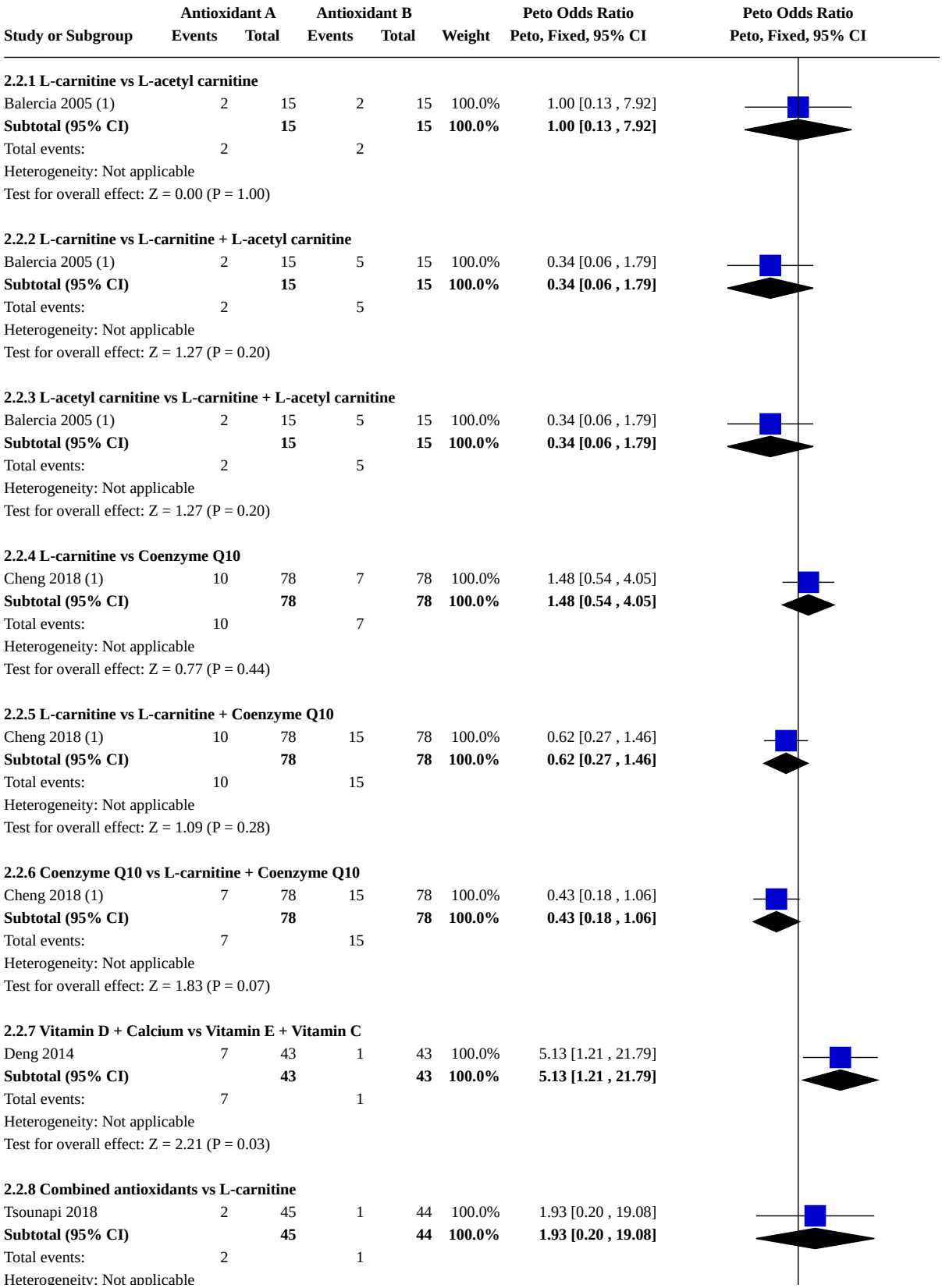
Test for subgroup differences: Chi² = 0.79, df = 2 (P = 0.67), I² = 0%



Footnotes

(1) Spontaneous pregnancy

Analysis 2.2. Comparison 2: Head-to-head antioxidant(s), Outcome 2: Clinical pregnancy; type of antioxidant

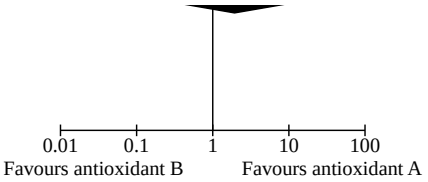


Analysis 2.2. (Continued)

Total events:	2	1

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)

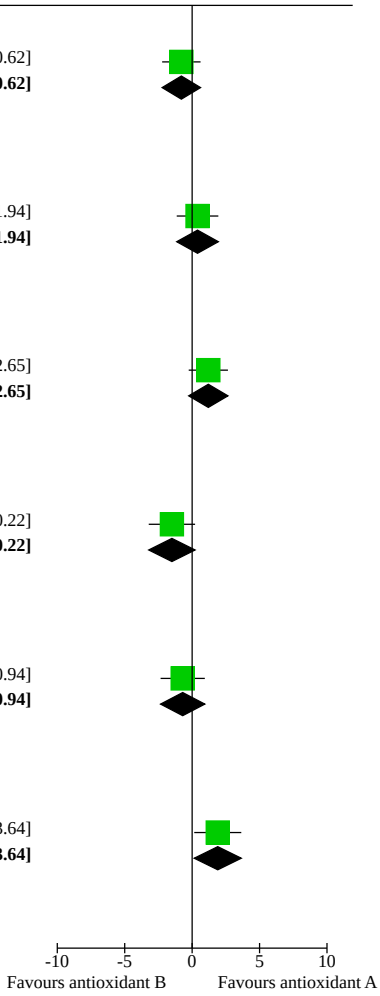
Test for subgroup differences: Chi² = 12.59, df = 7 (P = 0.08), I² = 44.4%



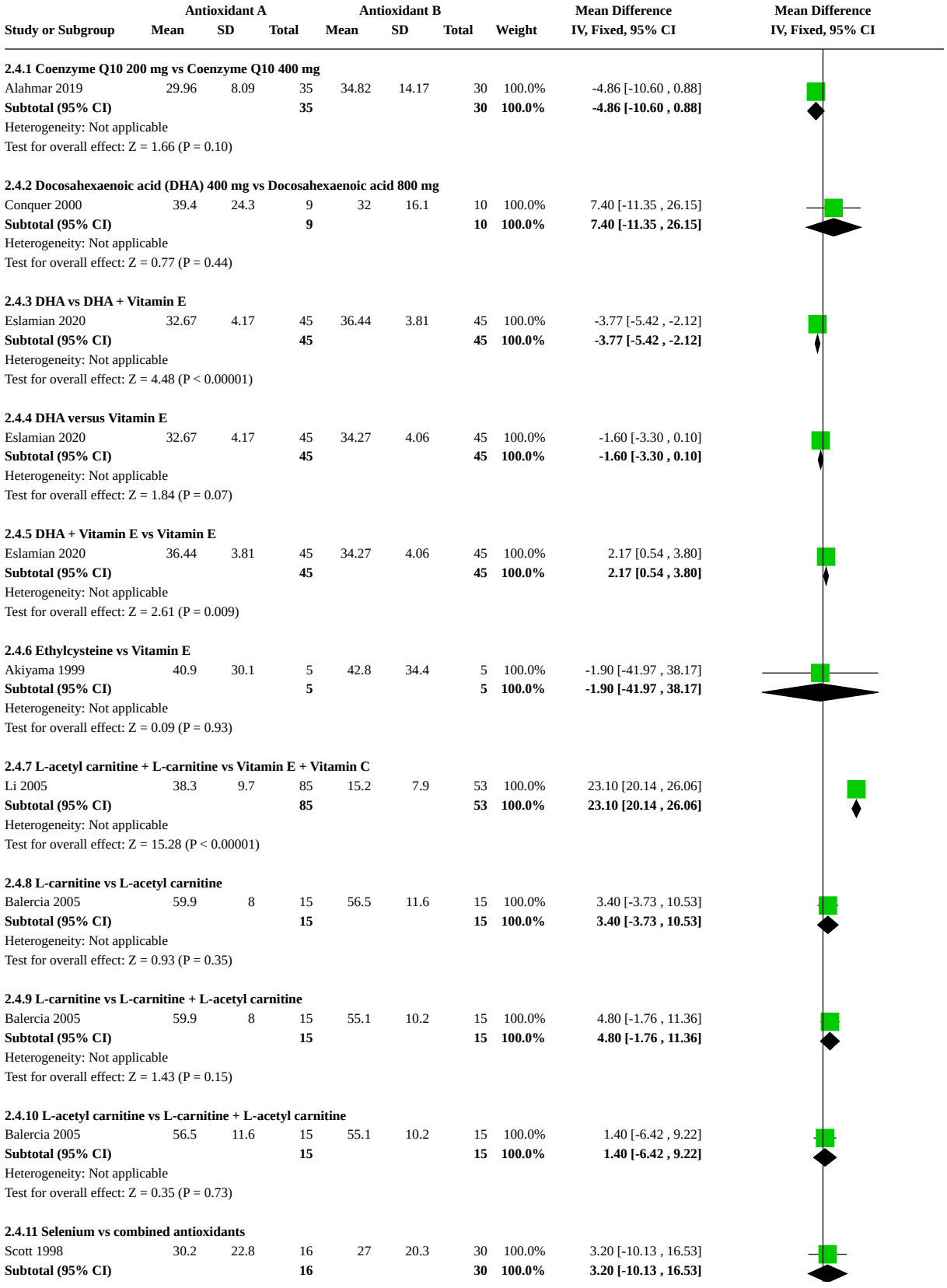
Footnotes
(1) Spontaneous pregnancy

Analysis 2.3. Comparison 2: Head-to-head antioxidant(s), Outcome 3: Sperm DNA fragmentation; type of antioxidant

Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 L-carnitine vs Coenzyme Q10								
Cheng 2018	9.5	4.3	62	10.3	3.8	63	100.0%	-0.80 [-2.22 , 0.62]
Subtotal (95% CI)			**62**			**63**	**100.0%**	**-0.80 [-2.22 , 0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.10 (P = 0.27)								
2.3.2 L-carnitine vs L-carnitine + Coenzyme Q10								
Cheng 2018	9.5	4.3	62	9.1	4.5	63	100.0%	0.40 [-1.14 , 1.94]
Subtotal (95% CI)			**62**			**63**	**100.0%**	**0.40 [-1.14 , 1.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.51 (P = 0.61)								
2.3.3 Coenzyme Q10 vs L-carnitine + Coenzyme Q10								
Cheng 2018	10.3	3.8	63	9.1	4.5	63	100.0%	1.20 [-0.25 , 2.65]
Subtotal (95% CI)			**63**			**63**	**100.0%**	**1.20 [-0.25 , 2.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.62 (P = 0.11)								
2.3.4 L-carnitine vs Vitamin B1								
Cheng 2018	9.5	4.3	62	11	5.9	74	100.0%	-1.50 [-3.22 , 0.22]
Subtotal (95% CI)			**62**			**74**	**100.0%**	**-1.50 [-3.22 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.71 (P = 0.09)								
2.3.5 Coenzyme Q10 vs Vitamin B1								
Cheng 2018	10.3	3.8	63	11	5.9	74	100.0%	-0.70 [-2.34 , 0.94]
Subtotal (95% CI)			**63**			**74**	**100.0%**	**-0.70 [-2.34 , 0.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								
2.3.6 Vitamin B1 vs L-carnitine + Coenzyme Q10								
Cheng 2018	11	5.9	74	9.1	4.5	63	100.0%	1.90 [0.16 , 3.64]
Subtotal (95% CI)			**74**			**63**	**100.0%**	**1.90 [0.16 , 3.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.14 (P = 0.03)								

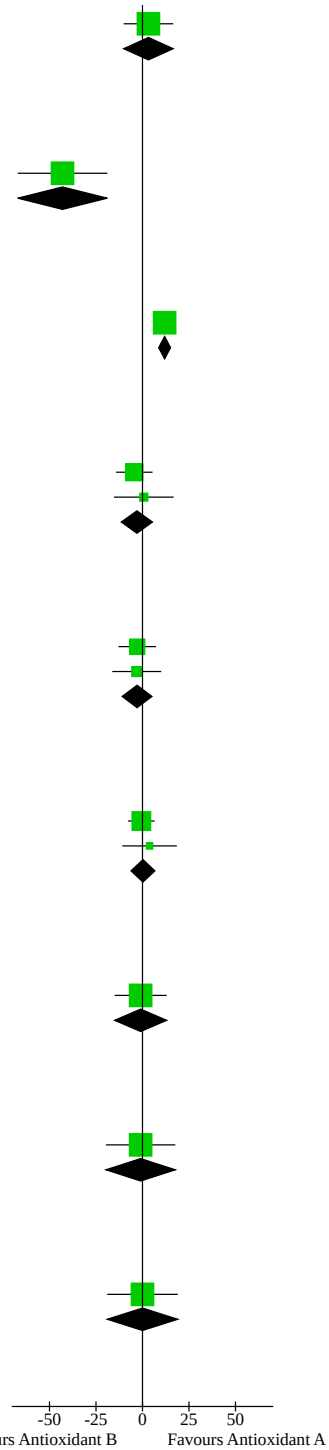


Analysis 2.4. Comparison 2: Head-to-head antioxidant(s), Outcome 4: Total sperm motility at 3 months or less; type of antioxidant



Analysis 2.4. (Continued)

Scott 1998	30.2	22.8	16	27	20.3	30	100.0%	3.20 [-10.13 , 16.53]
Subtotal (95% CI)			**16**			**30**	**100.0%**	**3.20 [-10.13 , 16.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
2.4.12 Vitamin C 200mg vs Vitamin C 1000mg								
Dawson 1990	51	22.1	10	94	32	10	100.0%	-43.00 [-67.10 , -18.90]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**-43.00 [-67.10 , -18.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.50 (P = 0.0005)								
2.4.13 Vitamin E + 'Compound amino acids' vs Vitamin E								
Zhou 2016	49.6	9.8	70	37.7	8	50	100.0%	11.90 [8.71 , 15.09]
Subtotal (95% CI)			**70**			**50**	**100.0%**	**11.90 [8.71 , 15.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.31 (P < 0.00001)								
2.4.14 Zinc vs Folic acid								
Azizollahi 2013 (1)	48.9	27.7	40	53.3	15.3	40	72.8%	-4.40 [-14.21 , 5.41]
Raigani 2014 (2)	34	26	24	33.3	27.9	20	27.2%	0.70 [-15.35 , 16.75]
Subtotal (95% CI)			**64**			**60**	**100.0%**	**-3.01 [-11.38 , 5.35]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.71 (P = 0.48)								
2.4.15 Zinc vs Zinc + Folic acid								
Azizollahi 2013 (1)	48.9	27.7	40	51.7	17.2	40	62.9%	-2.80 [-12.90 , 7.30]
Raigani 2014 (2)	34	26	24	37.1	18.8	21	37.1%	-3.10 [-16.25 , 10.05]
Subtotal (95% CI)			**64**			**61**	**100.0%**	**-2.91 [-10.92 , 5.10]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%								
Test for overall effect: Z = 0.71 (P = 0.48)								
2.4.16 Zinc + Folic acid vs Folic acid								
Azizollahi 2013 (1)	51.7	17.2	40	52.3	15.3	40	80.8%	-0.60 [-7.73 , 6.53]
Raigani 2014 (2)	37.1	18.8	21	33.3	27.9	20	19.2%	3.80 [-10.83 , 18.43]
Subtotal (95% CI)			**61**			**60**	**100.0%**	**0.24 [-6.17 , 6.66]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.07 (P = 0.94)								
2.4.17 Zinc vs Zinc + Vitamin E								
Omu 2008	49	12	6	50	18	12	100.0%	-1.00 [-15.00 , 13.00]
Subtotal (95% CI)			**6**			**12**	**100.0%**	**-1.00 [-15.00 , 13.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								
2.4.18 Zinc vs Zinc + Vitamin E + Vitamin C								
Omu 2008	49	12	6	50	20	6	100.0%	-1.00 [-19.66 , 17.66]
Subtotal (95% CI)			**6**			**6**	**100.0%**	**-1.00 [-19.66 , 17.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.92)								
2.4.19 Zinc + Vitamin E vs Zinc + Vitamin E + Vitamin C								
Omu 2008	50	18	12	50	20	6	100.0%	0.00 [-18.97 , 18.97]
Subtotal (95% CI)			**12**			**6**	**100.0%**	**0.00 [-18.97 , 18.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								

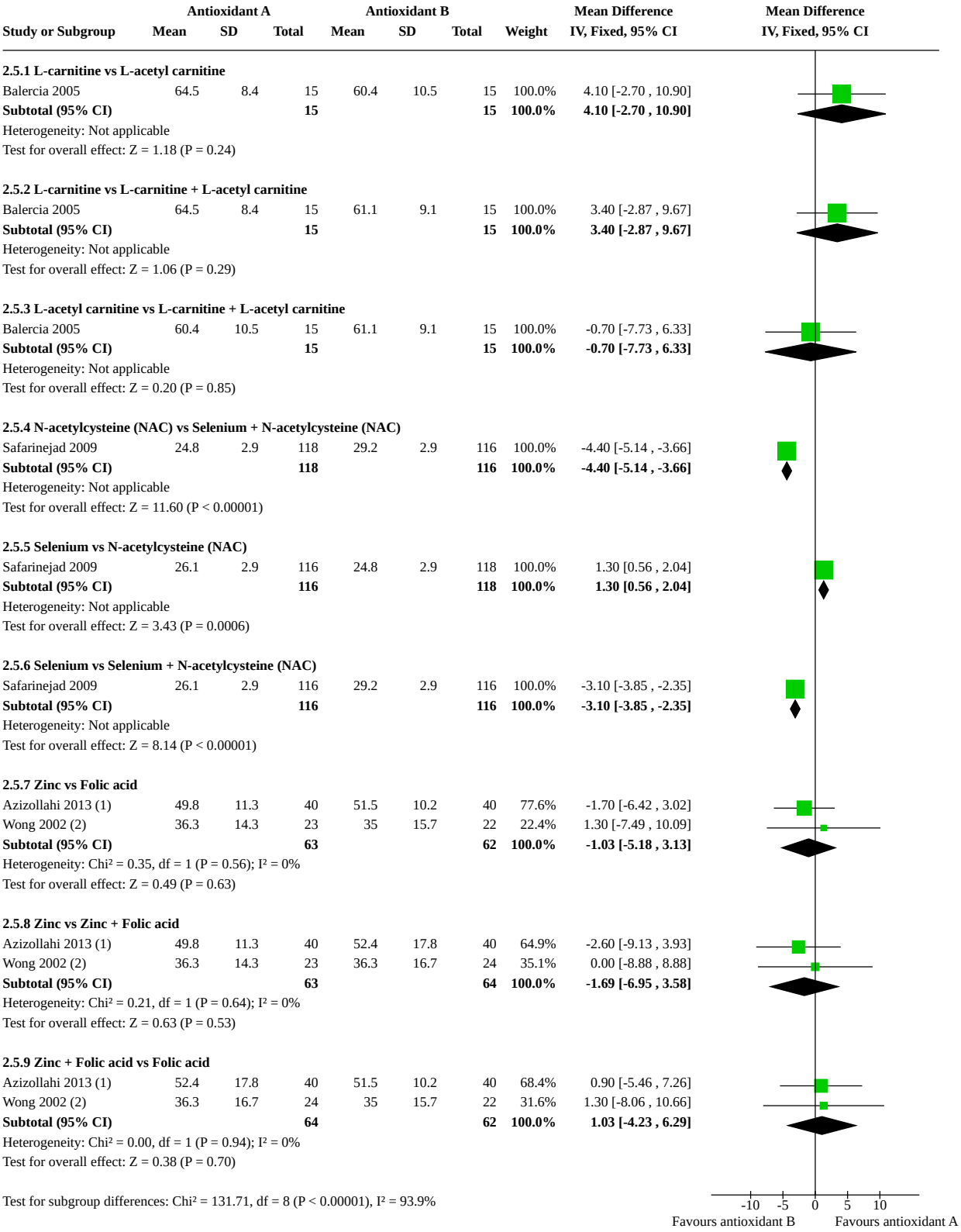


Footnotes

(1) After varicocelectomy.

(2) At 16 weeks.

Analysis 2.5. Comparison 2: Head-to-head antioxidant(s), Outcome 5: Total sperm motility at 6 months; type of antioxidant



Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 L-carnitine vs L-acetyl carnitine								
Balercia 2005	64.5	8.4	15	60.4	10.5	15	100.0%	4.10 [-2.70 , 10.90]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**4.10 [-2.70 , 10.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.18 (P = 0.24)								
2.5.2 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	64.5	8.4	15	61.1	9.1	15	100.0%	3.40 [-2.87 , 9.67]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**3.40 [-2.87 , 9.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
2.5.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	60.4	10.5	15	61.1	9.1	15	100.0%	-0.70 [-7.73 , 6.33]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**-0.70 [-7.73 , 6.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.85)								
2.5.4 N-acetylcysteine (NAC) vs Selenium + N-acetylcysteine (NAC)								
Safarinejad 2009	24.8	2.9	118	29.2	2.9	116	100.0%	-4.40 [-5.14 , -3.66]
Subtotal (95% CI)			**118**			**116**	**100.0%**	**-4.40 [-5.14 , -3.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 11.60 (P < 0.00001)								
2.5.5 Selenium vs N-acetylcysteine (NAC)								
Safarinejad 2009	26.1	2.9	116	24.8	2.9	118	100.0%	1.30 [0.56 , 2.04]
Subtotal (95% CI)			**116**			**118**	**100.0%**	**1.30 [0.56 , 2.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.43 (P = 0.0006)								
2.5.6 Selenium vs Selenium + N-acetylcysteine (NAC)								
Safarinejad 2009	26.1	2.9	116	29.2	2.9	116	100.0%	-3.10 [-3.85 , -2.35]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**-3.10 [-3.85 , -2.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.14 (P < 0.00001)								
2.5.7 Zinc vs Folic acid								
Azizollahi 2013 (1)	49.8	11.3	40	51.5	10.2	40	77.6%	-1.70 [-6.42 , 3.02]
Wong 2002 (2)	36.3	14.3	23	35	15.7	22	22.4%	1.30 [-7.49 , 10.09]
Subtotal (95% CI)			**63**			**62**	**100.0%**	**-1.03 [-5.18 , 3.13]**
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 0.49 (P = 0.63)								
2.5.8 Zinc vs Zinc + Folic acid								
Azizollahi 2013 (1)	49.8	11.3	40	52.4	17.8	40	64.9%	-2.60 [-9.13 , 3.93]
Wong 2002 (2)	36.3	14.3	23	36.3	16.7	24	35.1%	0.00 [-8.88 , 8.88]
Subtotal (95% CI)			**63**			**64**	**100.0%**	**-1.69 [-6.95 , 3.58]**
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.64); I² = 0%								
Test for overall effect: Z = 0.63 (P = 0.53)								
2.5.9 Zinc + Folic acid vs Folic acid								
Azizollahi 2013 (1)	52.4	17.8	40	51.5	10.2	40	68.4%	0.90 [-5.46 , 7.26]
Wong 2002 (2)	36.3	16.7	24	35	15.7	22	31.6%	1.30 [-8.06 , 10.66]
Subtotal (95% CI)			**64**			**62**	**100.0%**	**1.03 [-4.23 , 6.29]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.38 (P = 0.70)								
Test for subgroup differences: Chi² = 131.71, df = 8 (P < 0.00001), I² = 93.9%								

Footnotes

(1) After varicocelectomy.

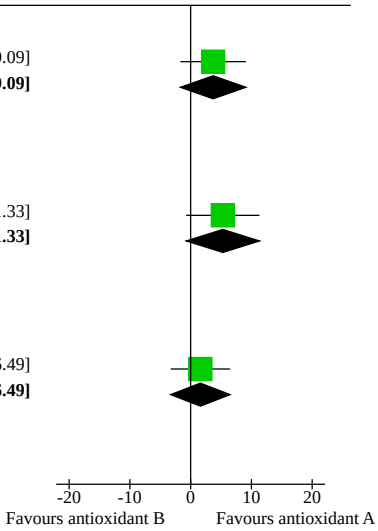
Analysis 2.5. (Continued)

Footnotes
(1) After varicocelectomy.
(2) At 26 weeks.

Analysis 2.6. Comparison 2: Head-to-head antioxidant(s), Outcome 6: Total sperm motility at 9 months or more; type of antioxidant

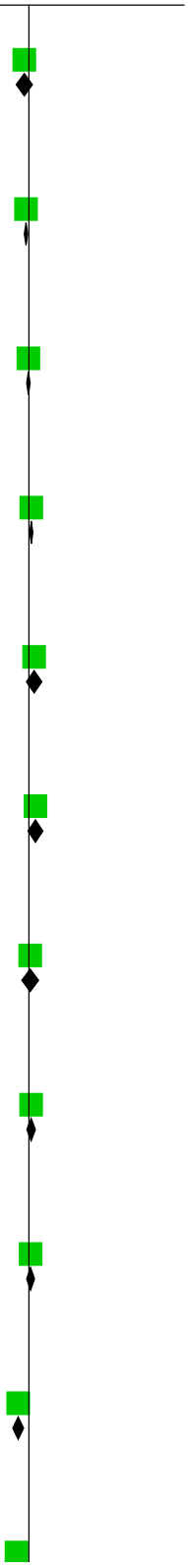
Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.6.1 L-carnitine vs L-acetyl carnitine								
Balercia 2005	54.3	9	15	50.6	5.7	15	100.0%	3.70 [-1.69 , 9.09]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**3.70 [-1.69 , 9.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.35 (P = 0.18)								
2.6.2 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	54.3	9	15	49	7.8	15	100.0%	5.30 [-0.73 , 11.33]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**5.30 [-0.73 , 11.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.72 (P = 0.08)								
2.6.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	50.6	5.7	15	49	7.8	15	100.0%	1.60 [-3.29 , 6.49]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**1.60 [-3.29 , 6.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								

Test for subgroup differences: Chi² = 0.91, df = 2 (P = 0.63), I² = 0%



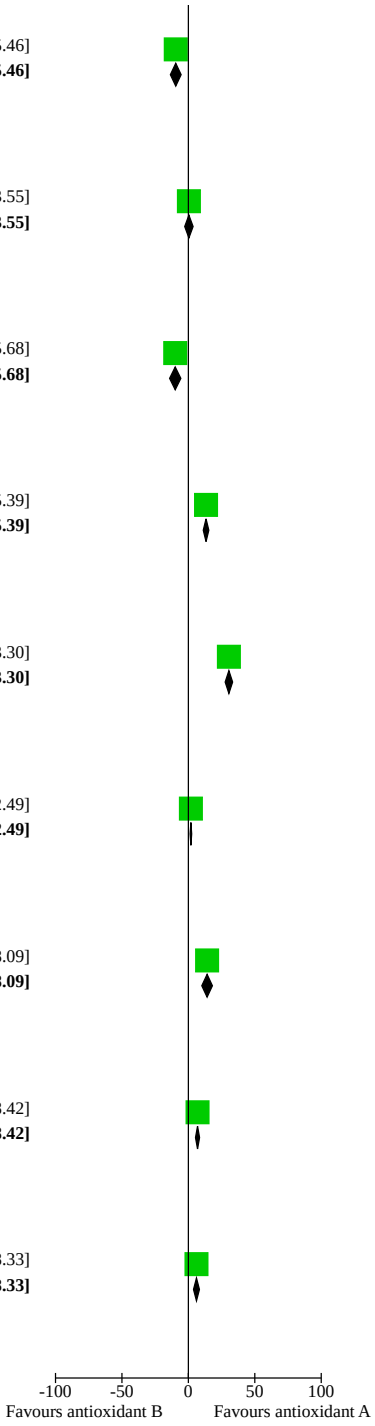
Analysis 2.7. Comparison 2: Head-to-head antioxidant(s), Outcome 7: Progessive sperm motility at 3 months or less; type of antioxidant

Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.7.1 Coenzyme Q10 200 mg vs Coenzyme Q10 400 mg								
Alahmar 2019	22.58	10.15	35	26.1	14.52	30	100.0%	-3.52 [-9.71 , 2.67]
Subtotal (95% CI)			**35**			**30**	**100.0%**	**-3.52 [-9.71 , 2.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.26)								
2.7.2 Docosahexaenoic acid (DHA) vs DHA + Vitamin E								
Eslamian 2020	25.71	3.39	45	27.93	2.78	45	100.0%	-2.22 [-3.50 , -0.94]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**-2.22 [-3.50 , -0.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.40 (P = 0.0007)								
2.7.3 DHA vs Vitamin E								
Eslamian 2020	25.71	3.39	45	26.1	2.78	45	100.0%	-0.39 [-1.67 , 0.89]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**-0.39 [-1.67 , 0.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
2.7.4 DHA + Vitamin E vs Vitamin E								
Eslamian 2020	27.93	2.78	45	26.1	2.78	45	100.0%	1.83 [0.68 , 2.98]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**1.83 [0.68 , 2.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.12 (P = 0.002)								
2.7.5 L-carnitine vs L-acetyl carnitine								
Balercia 2005	38.9	7.1	15	34.9	9.2	15	100.0%	4.00 [-1.88 , 9.88]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**4.00 [-1.88 , 9.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.33 (P = 0.18)								
2.7.6 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	38.9	7.1	15	33.9	8.4	14	100.0%	5.00 [-0.68 , 10.68]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**5.00 [-0.68 , 10.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.73 (P = 0.08)								
2.7.7 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	34.9	9.2	15	33.9	8.4	14	100.0%	1.00 [-5.41 , 7.41]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**1.00 [-5.41 , 7.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
2.7.8 L-carnitine vs Vitamin B1								
Cheng 2018	20.1	8.8	62	18.4	10.5	74	100.0%	1.70 [-1.54 , 4.94]
Subtotal (95% CI)			**62**			**74**	**100.0%**	**1.70 [-1.54 , 4.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.03 (P = 0.30)								
2.7.9 L-carnitine vs Coenzyme Q10								
Cheng 2018	20.1	8.8	62	18.8	8.3	63	100.0%	1.30 [-1.70 , 4.30]
Subtotal (95% CI)			**62**			**63**	**100.0%**	**1.30 [-1.70 , 4.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.85 (P = 0.40)								
2.7.10 L-carnitine vs L-carnitine + Coenzyme Q10								
Cheng 2018	20.1	8.8	62	28.3	14.1	63	100.0%	-8.20 [-12.31 , -4.09]
Subtotal (95% CI)			**62**			**63**	**100.0%**	**-8.20 [-12.31 , -4.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.91 (P < 0.0001)								
2.7.11 Coenzyme Q10 vs L-carnitine + Coenzyme Q10								
Cheng 2018	18.8	8.3	63	28.3	14.1	63	100.0%	-9.50 [-13.54 , -5.46]



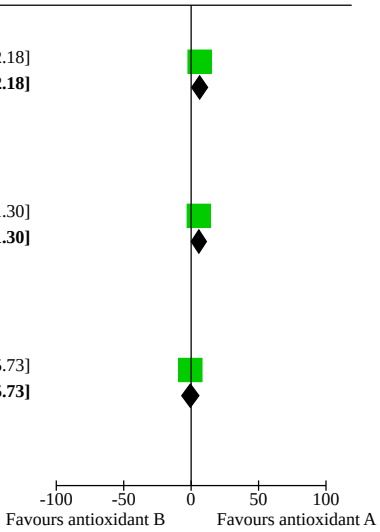
Analysis 2.7. (Continued)

2.7.11 Coenzyme Q10 vs L-carnitine + Coenzyme Q10								
Cheng 2018	18.8	8.3	63	28.3	14.1	63	100.0%	-9.50 [-13.54 , -5.46]
Subtotal (95% CI)			**63**			**63**	**100.0%**	**-9.50 [-13.54 , -5.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.61 (P < 0.00001)								
2.7.12 Coenzyme Q10 vs Vitamin B1								
Cheng 2018	18.8	8.3	63	18.4	10.5	74	100.0%	0.40 [-2.75 , 3.55]
Subtotal (95% CI)			**63**			**74**	**100.0%**	**0.40 [-2.75 , 3.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
2.7.13 Vitamin B1 vs L-carnitine + Coenzyme Q10								
Cheng 2018	18.4	10.5	74	28.3	14.1	63	100.0%	-9.90 [-14.12 , -5.68]
Subtotal (95% CI)			**74**			**63**	**100.0%**	**-9.90 [-14.12 , -5.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.59 (P < 0.00001)								
2.7.14 L-acetyl carnitine + L-carnitine vs Vitamin E + Vitamin C								
Li 2005	23.4	7.9	85	10.1	4.6	53	100.0%	13.30 [11.21 , 15.39]
Subtotal (95% CI)			**85**			**53**	**100.0%**	**13.30 [11.21 , 15.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 12.49 (P < 0.00001)								
2.7.15 L-carnitine vs Vitamin E + Vitamin C								
Li 2005a	58.3	7.1	32	27.8	3.8	31	100.0%	30.50 [27.70 , 33.30]
Subtotal (95% CI)			**32**			**31**	**100.0%**	**30.50 [27.70 , 33.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 21.35 (P < 0.00001)								
2.7.16 L-carnitine vs Vitamin E								
Sun 2018	36.4	1.3	156	34.5	2.1	56	100.0%	1.90 [1.31 , 2.49]
Subtotal (95% CI)			**156**			**56**	**100.0%**	**1.90 [1.31 , 2.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.35 (P < 0.00001)								
2.7.17 L-carnitine + Vitamin E vs Vitamin E								
Wang 2010	45.4	11.1	61	31.3	10.5	52	100.0%	14.10 [10.11 , 18.09]
Subtotal (95% CI)			**61**			**52**	**100.0%**	**14.10 [10.11 , 18.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.93 (P < 0.00001)								
2.7.18 Vitamin D + Calcium vs Vitamin E + Vitamin C								
Deng 2014	28.3	4.5	43	21.4	2.4	43	100.0%	6.90 [5.38 , 8.42]
Subtotal (95% CI)			**43**			**43**	**100.0%**	**6.90 [5.38 , 8.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.87 (P < 0.00001)								
2.7.19 Vitamin E + 'Compound amino acids' vs Vitamin E								
Zhou 2016	33.3	5.6	70	27.2	6.5	50	100.0%	6.10 [3.87 , 8.33]
Subtotal (95% CI)			**70**			**50**	**100.0%**	**6.10 [3.87 , 8.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.36 (P < 0.00001)								
Test for subgroup differences: Chi² = 738.95, df = 18 (P < 0.00001), I² = 97.6%								



Analysis 2.8. Comparison 2: Head-to-head antioxidant(s), Outcome 8: Progressive sperm motility at 6 months; type of antioxidant

Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.8.1 L-carnitine vs L-acetyl carnitine								
Balercia 2005	43.8	7.1	15	37.5	9.2	15	100.0%	6.30 [0.42 , 12.18]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**6.30 [0.42 , 12.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.10 (P = 0.04)								
2.8.2 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	43.8	7.1	15	38.1	8.2	14	100.0%	5.70 [0.10 , 11.30]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**5.70 [0.10 , 11.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.99 (P = 0.05)								
2.8.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	37.5	9.2	15	38.1	8.2	14	100.0%	-0.60 [-6.93 , 5.73]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**-0.60 [-6.93 , 5.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.19 (P = 0.85)								
Test for subgroup differences: Chi² = 2.97, df = 2 (P = 0.23), I² = 32.6%								



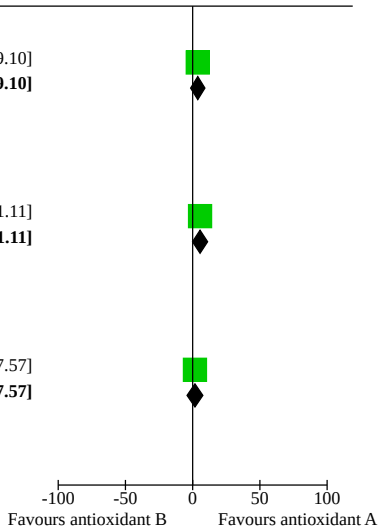
Analysis 2.9. Comparison 2: Head-to-head antioxidant(s), Outcome 9: Progressive motility at 6 months (data not suitable for meta-analysis)

Progressive motility at 6 months (data not suitable for meta-analysis)

Study	Coenzyme Q10 (n=50	Glutathione (n=51)	P value
Saeed Alkumait 2020	% improvement = 36	% improvement = 38	Not provided

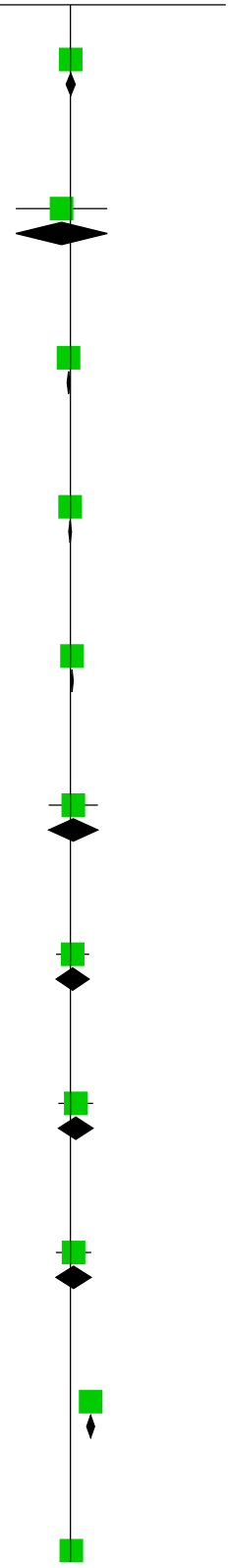
Analysis 2.10. Comparison 2: Head-to-head antioxidant(s), Outcome 10: Progressive sperm motility at 9 months; type of antioxidant

Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.10.1 L-carnitine vs L-acetyl carnitine								
Balercia 2005	34	7	15	30.2	7.8	15	100.0%	3.80 [-1.50 , 9.10]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**3.80 [-1.50 , 9.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.40 (P = 0.16)								
2.10.2 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	34	7	15	28.5	8.3	14	100.0%	5.50 [-0.11 , 11.11]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**5.50 [-0.11 , 11.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.92 (P = 0.05)								
2.10.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	30.2	7.8	15	28.5	8.3	14	100.0%	1.70 [-4.17 , 7.57]
Subtotal (95% CI)			**15**			**14**	**100.0%**	**1.70 [-4.17 , 7.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
Test for subgroup differences: Chi² = 0.84, df = 2 (P = 0.66), I² = 0%								



Analysis 2.11. Comparison 2: Head-to-head antioxidant(s), Outcome 11: Sperm concentration at 3 months or less; type of antioxidant

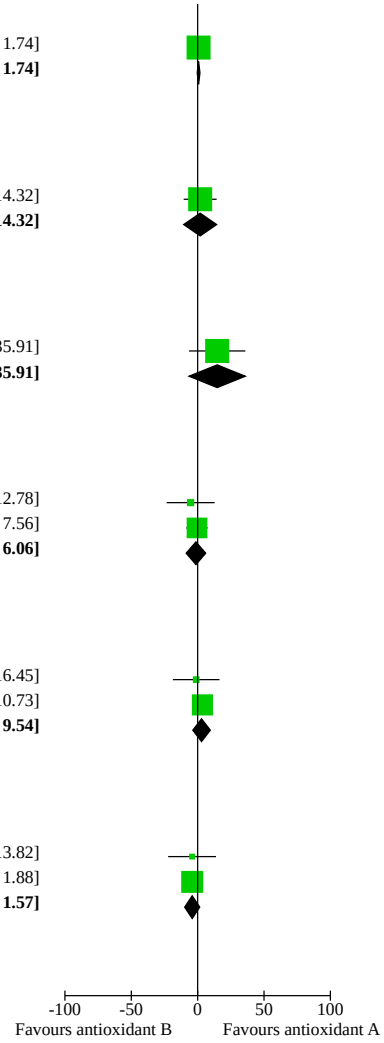
Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.11.1 Coenzyme Q10 200 mg vs Coenzyme Q10 400 mg								
Alahmar 2019	12.53	8.11	35	12.33	6.1	30	100.0%	0.20 [-3.26 , 3.66]
Subtotal (95% CI)			**35**			**30**	**100.0%**	**0.20 [-3.26 , 3.66]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								
2.11.2 Docosahexaenoic acid (DHA) 400 mg vs Docosahexaenoic acid (DHA) 800 mg								
Conquer 2000	37.8	36.9	9	44.6	41.1	10	100.0%	-6.80 [-41.87 , 28.27]
Subtotal (95% CI)			**9**			**10**	**100.0%**	**-6.80 [-41.87 , 28.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
2.11.3 DHA vs DHA + Vitamin E								
Eslamian 2020	21.21	2.66	45	22.66	2.27	45	100.0%	-1.45 [-2.47 , -0.43]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**-1.45 [-2.47 , -0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.78 (P = 0.005)								
2.11.4 DHA vs Vitamin E								
Eslamian 2020	21.21	2.66	45	21.45	2.25	45	100.0%	-0.24 [-1.26 , 0.78]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**-0.24 [-1.26 , 0.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
2.11.5 DHA + Vitamin E vs Vitamin E								
Eslamian 2020	22.66	2.27	45	21.45	2.25	45	100.0%	1.21 [0.28 , 2.14]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**1.21 [0.28 , 2.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.54 (P = 0.01)								
2.11.6 Ethylcysteine vs Vitamin E								
Akiyama 1999	20.1	14.8	5	17.9	15.6	5	100.0%	2.20 [-16.65 , 21.05]
Subtotal (95% CI)			**5**			**5**	**100.0%**	**2.20 [-16.65 , 21.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.23 (P = 0.82)								
2.11.7 L-carnitine vs L-acetyl carnitine								
Balercia 2005	41	17.3	15	39.3	18.1	15	100.0%	1.70 [-10.97 , 14.37]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**1.70 [-10.97 , 14.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.79)								
2.11.8 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	41	17.3	15	36.9	19.7	15	100.0%	4.10 [-9.17 , 17.37]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**4.10 [-9.17 , 17.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
2.11.9 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	39.3	18.1	15	36.9	19.7	15	100.0%	2.40 [-11.14 , 15.94]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**2.40 [-11.14 , 15.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								
2.11.10 L-carnitine vs Vitamin E + Vitamin C								
Li 2005a	34.6	7.4	32	19.1	4.5	31	100.0%	15.50 [12.49 , 18.51]
Subtotal (95% CI)			**32**			**31**	**100.0%**	**15.50 [12.49 , 18.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 10.08 (P < 0.00001)								
2.11.11 L-carnitine vs Vitamin E								
Sun 2018	40.6	2.4	156	39.9	3.7	56	100.0%	0.70 [-0.34 , 1.74]



Analysis 2.11. (Continued)

2.11.11 L-carnitine vs Vitamin E								
Sun 2018	40.6	2.4	156	39.9	3.7	56	100.0%	0.70 [-0.34 , 1.74]
Subtotal (95% CI)			**156**			**56**	**100.0%**	**0.70 [-0.34 , 1.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								
2.11.12 L-carnitine + Vitamin E vs Vitamin E								
Wang 2010	58.5	34.7	61	56.6	32.6	52	100.0%	1.90 [-10.52 , 14.32]
Subtotal (95% CI)			**61**			**52**	**100.0%**	**1.90 [-10.52 , 14.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								
2.11.13 Selenium vs Combined antioxidants								
Scott 1998	48.7	35.2	16	34	34.5	30	100.0%	14.70 [-6.51 , 35.91]
Subtotal (95% CI)			**16**			**30**	**100.0%**	**14.70 [-6.51 , 35.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								
2.11.14 Zinc vs Folic acid								
Azizollahi 2013 (1)	41.5	40.2	40	46.8	42.3	40	16.6%	-5.30 [-23.38 , 12.78]
Raigani 2014 (2)	15.7	15.8	24	16.2	11.4	20	83.4%	-0.50 [-8.56 , 7.56]
Subtotal (95% CI)			**64**			**60**	**100.0%**	**-1.30 [-8.65 , 6.06]**
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 0.34 (P = 0.73)								
2.11.15 Zinc vs Zinc + Folic acid								
Azizollahi 2013 (1)	41.5	40.2	40	42.6	39.9	40	14.2%	-1.10 [-18.65 , 16.45]
Raigani 2014 (2)	15.7	15.8	24	12.1	7.7	21	85.8%	3.60 [-3.53 , 10.73]
Subtotal (95% CI)			**64**			**61**	**100.0%**	**2.93 [-3.67 , 9.54]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 0.87 (P = 0.38)								
2.11.16 Zinc + Folic acid vs Folic acid								
Azizollahi 2013 (1)	42.6	39.9	40	46.8	42.3	40	9.9%	-4.20 [-22.22 , 13.82]
Raigani 2014 (2)	12.1	7.7	21	16.2	11.4	20	90.1%	-4.10 [-10.08 , 1.88]
Subtotal (95% CI)			**61**			**60**	**100.0%**	**-4.11 [-9.79 , 1.57]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 1.42 (P = 0.16)								

Test for subgroup differences: Chi² = 119.22, df = 15 (P < 0.00001), I² = 87.4%

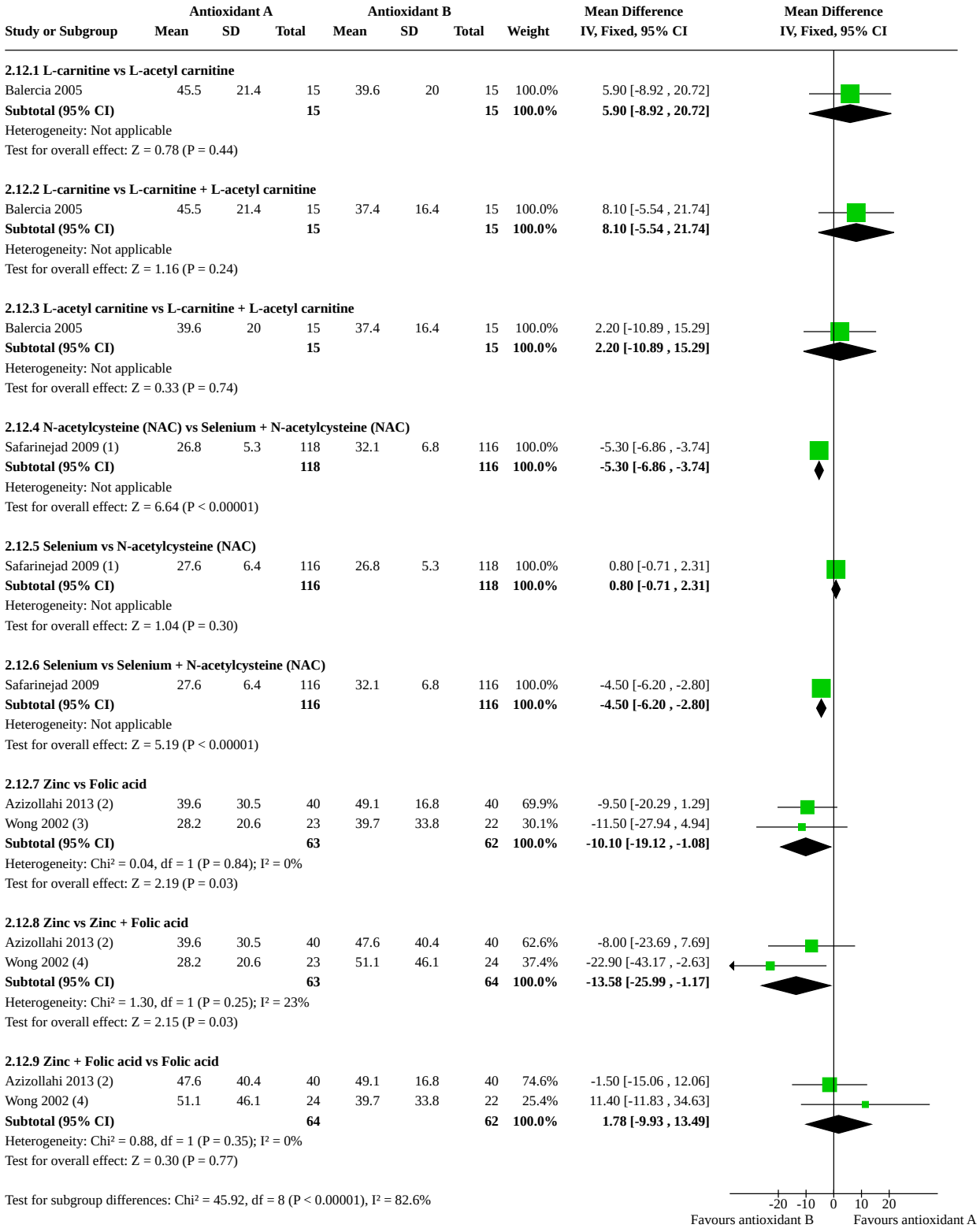


Footnotes

(1) After varicocelectomy.

(2) At 16 weeks.

Analysis 2.12. Comparison 2: Head-to-head antioxidant(s), Outcome 12: Sperm concentration at 6 months; type of antioxidant



Study or Subgroup	Antioxidant A Mean	SD	Total	Antioxidant B Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.12.1 L-carnitine vs L-acetyl carnitine								
Balercia 2005	45.5	21.4	15	39.6	20	15	100.0%	5.90 [-8.92 , 20.72]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**5.90 [-8.92 , 20.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.44)								
2.12.2 L-carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	45.5	21.4	15	37.4	16.4	15	100.0%	8.10 [-5.54 , 21.74]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**8.10 [-5.54 , 21.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.16 (P = 0.24)								
2.12.3 L-acetyl carnitine vs L-carnitine + L-acetyl carnitine								
Balercia 2005	39.6	20	15	37.4	16.4	15	100.0%	2.20 [-10.89 , 15.29]
Subtotal (95% CI)			**15**			**15**	**100.0%**	**2.20 [-10.89 , 15.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
2.12.4 N-acetylcysteine (NAC) vs Selenium + N-acetylcysteine (NAC)								
Safarinejad 2009 (1)	26.8	5.3	118	32.1	6.8	116	100.0%	-5.30 [-6.86 , -3.74]
Subtotal (95% CI)			**118**			**116**	**100.0%**	**-5.30 [-6.86 , -3.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.64 (P < 0.00001)								
2.12.5 Selenium vs N-acetylcysteine (NAC)								
Safarinejad 2009 (1)	27.6	6.4	116	26.8	5.3	118	100.0%	0.80 [-0.71 , 2.31]
Subtotal (95% CI)			**116**			**118**	**100.0%**	**0.80 [-0.71 , 2.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.04 (P = 0.30)								
2.12.6 Selenium vs Selenium + N-acetylcysteine (NAC)								
Safarinejad 2009	27.6	6.4	116	32.1	6.8	116	100.0%	-4.50 [-6.20 , -2.80]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**-4.50 [-6.20 , -2.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.19 (P < 0.00001)								
2.12.7 Zinc vs Folic acid								
Azizollahi 2013 (2)	39.6	30.5	40	49.1	16.8	40	69.9%	-9.50 [-20.29 , 1.29]
Wong 2002 (3)	28.2	20.6	23	39.7	33.8	22	30.1%	-11.50 [-27.94 , 4.94]
Subtotal (95% CI)			**63**			**62**	**100.0%**	**-10.10 [-19.12 , -1.08]**
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%								
Test for overall effect: Z = 2.19 (P = 0.03)								
2.12.8 Zinc vs Zinc + Folic acid								
Azizollahi 2013 (2)	39.6	30.5	40	47.6	40.4	40	62.6%	-8.00 [-23.69 , 7.69]
Wong 2002 (4)	28.2	20.6	23	51.1	46.1	24	37.4%	-22.90 [-43.17 , -2.63]
Subtotal (95% CI)			**63**			**64**	**100.0%**	**-13.58 [-25.99 , -1.17]**
Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%								
Test for overall effect: Z = 2.15 (P = 0.03)								
2.12.9 Zinc + Folic acid vs Folic acid								
Azizollahi 2013 (2)	47.6	40.4	40	49.1	16.8	40	74.6%	-1.50 [-15.06 , 12.06]
Wong 2002 (4)	51.1	46.1	24	39.7	33.8	22	25.4%	11.40 [-11.83 , 34.63]
Subtotal (95% CI)			**64**			**62**	**100.0%**	**1.78 [-9.93 , 13.49]**
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.77)								

Test for subgroup differences: Chi² = 45.92, df = 8 (P < 0.00001), I² = 82.6%

Footnotes

(1) 26 weeks.

(2) After varicocelectomy.

(3) At 26 weeks

Analysis 2.12. (Continued)

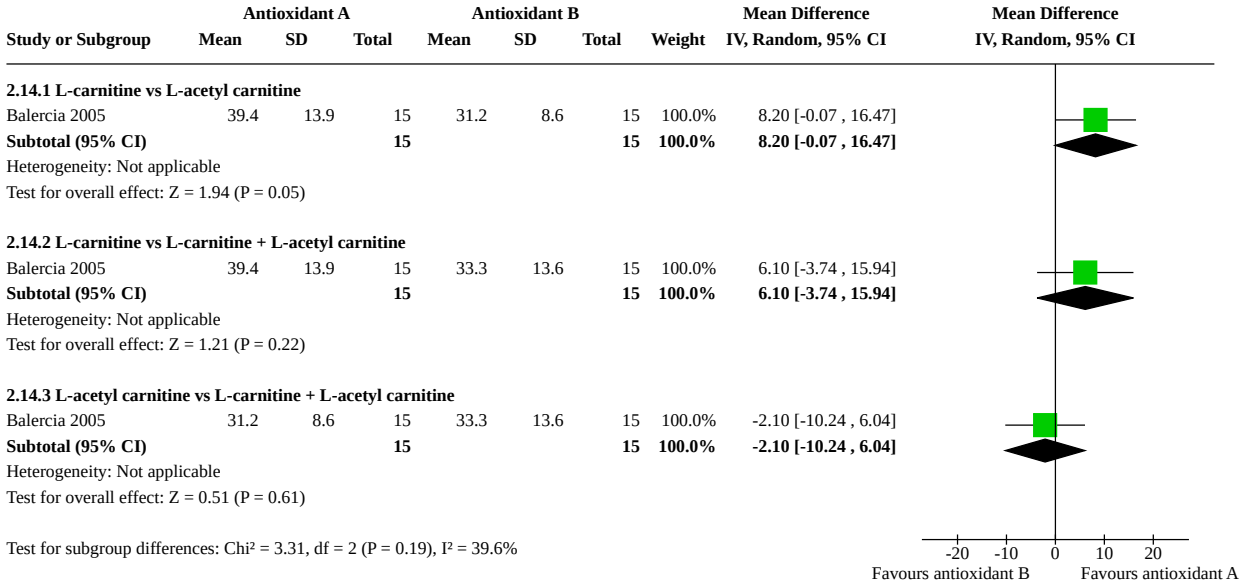
(1) 26 weeks.
(2) After varicocelectomy.
(3) At 26 weeks
(4) At 26 weeks.

Analysis 2.13. Comparison 2: Head-to-head antioxidant(s), Outcome 13: Sperm concentration at 6 months (data not suitable for meta-analysis)

Sperm concentration at 6 months (data not suitable for meta-analysis)

Study	Coenzyme Q10 (n=50)	Glutathione (n=51)	P value
Saeed Alkumait 2020	% improvement = 24	% improvement = 26	Not provided

Analysis 2.14. Comparison 2: Head-to-head antioxidant(s), Outcome 14: Sperm concentration at 9 months or more; type of antioxidant



ADDITIONAL TABLES

Table 1. Data for undefined or biochemical pregnancy

Undefined or biochemical pregnancy	Antioxidant		Control		Peto OR [CI]
Antioxidant(s) versus placebo or no treatment					
Combined antioxidants	Events	Total	Events	Total	
	35	234	32	194	
Galatioto 2008	1	20	0	22	8.17 [0.16 to 413.39]

Table 1. Data for undefined or biochemical pregnancy *(Continued)*

Gopinath 2013	13	92	2	46	2.72 [0.88 to 8.46]
Steiner 2020	18	85	26	86	0.62 [0.32 to 1.24]
Stenqvist 2018	3	37	4	40	0.80 [0.17 to 3.74]
Arginine					
Pryor 1978	2	35	2	29	0.82 [0.11 to 6.16]
Carnitines	25	154	3	145	
Sigman 2006	1	12	1	9	0.74 [0.04 to 13.02]
Peivandi 2010	3	15	0	15	8.57 [0.82 to 89.45]
Lenzi 2003	6	43	0	43	8.37 [1.61 to 43.58]
Lenzi 2004	4	30	0	26	7.20 [0.95 to 54.34]
Cavallini 2004	9	39	1	47	7.50 [2.01 to 27.98]
Coenzyme Q10	6	136	3	136	
Safarinejad 2009a	0	106	0	106	Not estimable
Nadjarzadeh 2011	0	23	0	24	Not estimable
Vitamin C + Vitamin E					
Rolf 1999	0	15	0	16	Not estimable
Vitamin E					
Ener 2016	5	28	5	28	1.00 [0.26 to 3.88]
Head-to-head antioxidant(s)	Events	Total	Events	Total	
L-acetyl carnitine + L-carnitine vs Vitamin E + Vitamin C					
Li 2005	10	85	2	53	2.72 [0.81 to 9.14]
L-carnitine + Vitamin E vs Vitamin E					
Wang 2010	21	68	3	67	6.01 [2.49 to 14.47]
Vitamin E + amino acids vs Vitamin E					
Zhou 2016	4	70	1	50	2.52 [0.41 to 15.35]

Table 2. Outcomes and conclusions from all included studies

Study ID	Design, population	Outcomes described in methods section	Outcomes reported on in results	In meta-analysis Y or N	Results	Conclusions + = positive effect - = negative or no effect
Abbasi 2020	Parallel, placebo Men post-varicocelectomy N = 60	Sperm parameters, DNA fragmentation	Sperm parameters, DNA fragmentation	Y - sperm parameters Y - DNA fragmentation	ALA improved sperm motility compared to baseline. No significant difference in sperm parameters between ALA and placebo.	- ALA does not improve semen quality compared to placebo after varicocelectomy
Akiyama 1999	Cross-over, head-to-head Infertile men, high ROS levels N = 10	Sperm parameters	Sperm parameters	Y - sperm parameters	Ethylcystein did not improve sperm density and motility but "sperm function" increased and ROS levels decreased, compared to vitamin E	+ Ethylcysteine shown to be effective for improvement of sperm parameters when compared to vitamin E
Alahmar 2019	Parallel, head-to-head Idiopathic OAT N = 65	Sperm parameters	Sperm parameters	Y - sperm parameters	CoQ10 200 and 400 mg improved sperm concentration and motility, greater improvement with 400 mg	+ CoQ10 improves sperm parameters, greater improvement with a 400 mg dose compared to 200 mg
Alahmar 2020	Parallel, head-to-head Idiopathic OAT N = 70	Sperm parameters	Sperm parameters	N - number of drop-outs unclear	CoQ10 and selenium each improved sperm concentration and motility, greater improvement with CoQ10	+ CoQ10 and selenium improve sperm parameters, greater improvement with CoQ10
Amini 2020	Parallel, placebo Infertile men N = 72	Sperm parameters	Sperm parameters	Y - sperm parameters	Vitamin D did not improve sperm parameters	- Vitamin D does not improve sperm parameters
Ardestani 2019	Parallel, no treatment Men post-varicocelectomy N = 64	Sperm parameters	Sperm parameters	Y - sperm parameters	Co-administration of folic acid, selenium and vitamin E improved sperm concentration and motility	+ A combination of folic acid + selenium + vitamin E improves sperm parameters after varicocelectomy
Attallah 2013	Parallel, no treatment	Sperm parameters, chemical	Sperm parameters, chemical	Y - sperm parameters	NAC increased sperm concentration and motility.	+

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Idiopathic asthenozospermia, IUI N = 30 Conference abstract	and clinical pregnancy	and clinical pregnancy	Y - pregnancy rate, clinical	Clinical pregnancy was not significantly different between the groups	NAC improves semen quality and improves pregnancy rates prior to IUI, no improvement of pregnancy rate
Azizollahi 2013	Multiple arm trial Men post-varicocelectomy N = 160	Sperm parameters	Sperm parameters	Y - sperm parameters Y - pregnancy rate, clinical	Mild improvement in sperm parameters with the use of antioxidants zinc, folic acid or both	+ Co-administration of zinc and folic acid improved sperm parameters and increased varicocelectomy outcomes, only zinc an improvement in pregnancy rate
Bahmyari 2021	Parallel, placebo Idiopathic OAT N = 70	Sperm parameters	Sperm parameters	Y - sperm parameters	No improvement of sperm parameters with the use of selenium, folic acid and vitamin E	- Co-administration of selenium, folic acid and vitamin E were not effective to improve sperm parameters
Balercia 2005	Multiple arm, placebo Infertile men N = 60	Sperm parameters	Sperm parameters, pregnancy rate	Y - sperm parameters Y - pregnancy rate, clinical Y - live birth	Improvement in motility in LAC group.	+ Long-term carnitine is effective in increasing sperm motility. No evidence of increased live birth or clinical pregnancy.
Balercia 2009	Parallel, placebo Infertile and unexplained N = 60	Sperm parameters	Sperm parameters, pregnancy rate	Y - sperm parameters Y - pregnancy rate, clinical	Co enzyme Q10 increased sperm motility.	+ Q10 is effective in improving sperm kinetic features in asthenospermia. No evidence of increased live birth or clinical pregnancy.
Barekat 2016	Parallel, no treatment Subfertile men with varicocele N = 40	Sperm parameters, DNA fragmentation	Sperm parameters, DNA fragmentation, clinical spontaneous pregnancies	Y - sperm parameters Y - DNA fragmentation Y - pregnancy rate, clinical (SEs converted to SDs)	Sperm parameters significantly improved after surgery compared to before surgery in both the NAC and control groups. NAC might have an additional value by improving sperm motility post-varicocelectomy	+ The results of this study revealed that NAC improved chromatin integrity and pregnancy rate when administered as adjunct therapy post-varicocelectomy

Table 2. Outcomes and conclusions from all included studies *(Continued)*

Biagiotti 2003	Multiple arm, no treatment Severe idiopathic oligoasthenospermia N = 42 Conference abstract	Sperm parameters	Sperm parameters	N - no data available	A significant improvement in morphology concentration, motility in the carnitine group No side effects	+ Quality of semen is positively associated with fertilisation and implantation rates in assisted reproduction
Blomberg Jensen 2018	Parallel, placebo Infertile men with impaired semen quality N = 307	Sperm parameters, reproductive hormones, live birth rate	Sperm parameters, reproductive hormones, live birth rate	Y - sperm parameters, concentration provided as median + IQR and converted to mean + SD Y - live birth rate	Vitamin D was not associated with changes in semen parameters, although spontaneous pregnancies tended to be higher in couples in which the man was in the treatment group	± Vitamin D did not improve semen quality. The positive impact of vitamin D supplementation on live birth rate and serum inhibin B in oligozoospermic and vitamin D–deficient men may be of clinical importance and warrant verification by others.
Boonyarangkul 2015	Multiple arm, placebo, tamoxifen excluded Men with abnormal semen analysis N = 68	Sperm parameters, DNA damage (Comet assay)	Sperm parameters, DNA tail length	Y - sperm parameters	Folate alone significantly decreased DNA tail length at 3-months. Sperm motility was significantly increased after 3-months Folate alone.	+ Our study indicated that folate in combination with Tamoxifen citrate could improve sperm quality including semen parameters and sperm DNA integrity
Busetto 2018	Parallel, placebo Infertile men with OAT, 50% included with varicocele N = 104	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	Y - sperm parameters Y - pregnancy rate, clinical	Sperm concentration, total sperm count, progressive and total motility were significantly increased in supplemented (Proxeed Plus) patients. Increased pregnancy rate	+ Supplementation with metabolic and antioxidant compounds could be efficacious when included in strategies to improve fertility
Cavallini 2004	Multiple arm, placebo Idiopathic OAT men with varicocele N = 325	Sperm parameters, pregnancy rate, adverse events	Sperm parameters, pregnancy rate, adverse events	Y - sperm parameters (median +IQR converted to mean + SD) N - pregnancy rate, unclear if	Significant increase in sperm parameters for carnitines when compared to placebo. Carnitine groups had a significantly higher pregnancy rate than placebo group	+ The antioxidant plus anti-inflammatory group was more effective in improving sperm parameters and pregnancy than those of carnitines alone or place-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

				clinical Table 1 Y - adverse events		bo however carnitines alone were more effective than placebo
Cheng 2018	Multiple arm, head-to-head Idiopathic OAT N = 312	Sperm parameters, DNA fragmentation, pregnancy rate	Sperm parameters, DNA fragmentation, pregnancy rate	Y/N - sperm parameters, results not available for all groups and parameters Y - DNA fragmentation Y - pregnancy rate, clinical	Significant improvement of sperm parameters and DNA fragmentation in the L-carnitine plus CoQ10 group compared to placebo. Combination and L-carnitine groups had remarkably higher pregnancy rate than placebo group	+ Combination of LC and CoQ10 improve semen parameters and outcome of clinical pregnancy
Conquer 2000	Multiple arm, placebo Asthenozoospermic men N = 28	Sperm parameters	Sperm parameters	Y - sperm parameters (SEs converted to SDs)	DHA showed no effect on sperm motility or concentration	± DHA supplementation increased DHA levels in the sperm but not motility or concentration
Cyrus 2015	Parallel, placebo Infertile men with varicocele N = 115	Sperm parameters	Sperm parameters	Y - sperm parameters	Vitamin C was not effective on sperm count but improved sperm motility and morphology significantly	+ Ascorbic acid can play a role as adjuvant treatment after varicocelectomy in infertile men
Dawson 1990	Multiple arm, placebo Men with sperm agglutination N = 30	Sperm parameters	Sperm parameters	Y - sperm parameters (SEs converted to SDs)	The group receiving 1000 mg of AA showed more improvement in parameters than the 200mg group and the placebo	+ Vitamin C can improve sperm parameters, especially dosage of 1000 mg.
Deng 2014	Head-to-head Men with idiopathic oligoasthenozoospermia N = 86	Sperm parameters, adverse reactions, pregnancy rate	Sperm parameters, adverse reactions, pregnancy rate	Y - sperm parameters Y - pregnancy rate, clinical	Vitamin D is a safe option for the treatment of idiopathic oligoasthenozoospermia and can effectively improve the semen quality especially the progressive sperm motility	+ Vitamin D can improve forward movement sperm number and percentage, improve the woman's clinical pregnancy rate, and is well tolerated
Dimitriadis 2010	Multiple arm, no treatment, vardenafil/silde-	Sperm parameters	Sperm parameters	Y - sperm parameters	An improvement in sperm concentration with carnitine versus no treatment	+ Enhancement of Leydig cell secretory function may increase sperm

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	nafil arms excluded Men with oligoasthenospermia N = 75					concentration and motility
Ener 2016	Parallel, no treatment Infertile men with varicocele N = 56	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	Y - sperm parameters N - pregnancy rate, unknown if clinical Table 1	The administration of vitamin E increased all of the parameters; however not statistically significant	- Vitamin E supplementation does not improve the sperm parameters after varicocelectomy
Eslamian 2013	Parallel, placebo Asthenozoospermic men N = 50	Sperm parameters	Sperm parameters, sperm membrane and serum fatty acids	N - sperm parameters, data not usable, no continuous data but categories from 'significantly improvement' to 'worsened'	Sperm parameters improved with DHA + vitamin E supplementation	+ Sperm parameters improve with DHA + vitamin E supplementation
Eslamian 2020	Multiple arm, placebo Asthenozoospermic men N = 180	Sperm parameters	Sperm parameters	N - sperm parameters, only imputed data provided	Significant increase of sperm concentration in the DHA + vitamin E group compared to groups treated with DHA+placebo, vitamin E+placebo and placebo.	+ Combined DHA and vitamin E improve sperm parameters
Exposito 2016	Parallel, placebo Normozoospermic, oligozoospermic and asthenozoospermic men N = 113	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	N - sperm parameters N - pregnancy rate Both not included because data included normospermic men	50% of oligozoospermic men improved sperm concentration and sperm count to normozoospermic levels. This trend was also observed in asthenozoospermic men, but nog significantly	+ Vitamin E treatment by oral administration improves semen parameters
Galatioto 2008	Parallel, no treatment Men with persistent oligospermia after embolisation of varicocele	Sperm parameters, pregnancy rate, adverse events	Sperm parameters, pregnancy rate, adverse events	N - sperm parameters, only medians given N - pregnancy, unclear if clinical Table 1 N - adverse events	Significant difference in sperm count in combined antioxidant group but not in motility. One pregnancy in the NAC group No significant adverse effects	± NAC does not improve pregnancy rate, no significant adverse events, but do significantly increase sperm count

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	N = 42					
Gamidov 2017	Multiple arm, no treatment Men with varicocele N = 114	Sperm parameters, DNA fragmentation, adverse events	Sperm parameters, DNA fragmentation, adverse events	Y - sperm parameters (median+IQR converted to mean+SD) Y - DNA fragmentation (median+IQR converted to mean+ SD) Y - adverse events	SpermActine (SA) resulted in a 22.3% decrease in the level of sperm DNA fragmentation at 3 months. SA + vitamin complex resulted in a 27% increase in the sperm concentration at 3 months. There were no side effects of pharmacotherapy.	+ Antioxidant therapy leads to an improvement in the basic sperm parameters (sperm concentration and motility) and a decrease in the level of sperm DNA fragmentation in the short term. There were no side effects
Gamidov 2019	Parallel, placebo Infertile men with high oxidative stress and DNA fragmentation N = 80	Sperm parameters, DNA fragmentation, pregnancy rate, live birth	Sperm parameters, DNA fragmentation, pregnancy rate, live birth, adverse events	Y - sperm parameters Y - DNA fragmentation Y - pregnancy rate, clinical Y - live births Y - adverse events	Spermactin Forte significantly improvement sperm motility and decreased oxidative stress. There were more pregnancies in the intervention group (13 versus 1)	+ The use of the SpermActin Forte antioxidant improves sperm analysis in most patients. SpermActin Forte is an effective and safe method of treating male infertility
Gonzalez-Ravina 2018	Multiple arm, placebo Infertile men N = 60	Sperm parameters, DNA fragmentation	Sperm parameters, DNA fragmentation	N - sperm parameters, outcomes provided as change + SD Analysis 1.15; Analysis 1.20 N - DNA fragmentation, outcomes provided as change + SD Analysis 1.8	Significant increase of progressive sperm motility in the DHA 1g and 2g groups after 1 month and in the DHA 0.5 group after 3 months. Greater effect in asthenozoospermic men	+ DHA (0.5, 1 and 2g) had beneficial effects on sperm function without producing any adverse effects, obtaining more immediate results with higher doses
Gopinath 2013	Multiple arm, placebo Idiopathic OAT men N = 138	Sperm parameters, pregnancy rate, adverse events	Sperm parameters, pregnancy rate, adverse events	Y - sperm parameters N - pregnancy rate, not clinical Table 1 Y - adverse events	Combined antioxidant significantly improved sperm count and total motility in both treatment arms (1 vs 2 tablets). Mild adverse events were reported, no severe.	+ Exogenous administration of fixed dose combination of antioxidants is safe and effective therapy in improving the male subfertility regarding sperm parameters. Only mild adverse events when using combined antioxidants
Goswami 2015	Multiple arm, placebo	Sperm parameters,	DNA fragmentation	N - sperm parameters, not	No difference in DNA fragmentation between the study groups	+/-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Arm treated with diet enriched in antioxidants not used Men with idiopathic infertility and high ROS N = 175 Conference abstract	DNA fragmentation		reported in results N - DNA fragmentation, no results reported besides p-value		No conclusions on antioxidants versus placebo. A diet rich in antioxidants and lifestyle modifications can bring almost the same effect as antioxidant supplements
Greco 2005	Parallel, placebo Infertile males with high DNA fragmentation N = 64	Sperm parameters	Sperm parameters	Y - sperm parameters	No significant difference in concentration or motility however DNA fragmentation was significantly reduced in the vitamin C + E when compared to placebo	+ A short oral treatment of Vitamin C + E can reduce DNA fragmentation
Haghighian 2015	Parallel, placebo Men with idiopathic asthenozoospermia N = 48	Sperm parameters, adverse events	Sperm parameters, adverse events	Y - sperm parameters N - adverse events, reported "none", however not clear which side effects they aimed for	Sperm parameters were significantly higher in ALA group. No side effects due to the oral administration of ALA were observed in any participants.	+ Medical therapy of asthenoteratospermia with ALA supplement could improve quality of semen parameters
Haje 2015	Multiple arm, placebo, tamoxifen arms excluded Infertile men with idiopathic OAT N = 128	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	N - sperm parameters, range of treatment 3 - 6 months and not divided N - pregnancy rate, unclear if pregnancy and no numbers but percentage	L-carnitine did not improve sperm count or motility. Only tamoxifen or tamoxifen + L-carnitine improved pregnancy rate, not significantly.	± Administration of tamoxifen or L-carnitine can improve sperm parameters and ICSI outcomes. Combining those result in maximum therapeutic effect
Huang 2020	Parallel, placebo Oligozoospermic men N = 769	Sperm parameters, evaluation of MTHFR polymorphism, DNA fragmentation, preg-	Sperm parameters, evaluation of MTHFR polymorphism, DNA fragmentation, preg-	N - sperm parameters N - DNA fragmentation N - pregnancy, clinical	Folic acid significantly increased sperm parameters, decreased oxidative stress and DNA fragmentation and lead to a higher pregnancy and live birth rate in the MTHFR 677 TT group. Effect not seen in	+ Folic acid has a beneficial effect on oligozoospermia with MTHFR 677 TT genotype in terms of sperm parameters, DNA fragmenta-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

		nancy rate, live birth	nancy rate, live birth	N - live births All outcomes reported for MTHFR polymorphism groups only		tion and pregnancy outcomes
Joseph 2020	Parallel, no treatment Infertile men scheduled for ART N = 200	Sperm parameters, pregnancy rate, live birth, adverse events	Sperm parameters, pregnancy rate, live birth, adverse events	Y - sperm parameters (median+IQR converted to mean+SD) Y - pregnancy rate, clinical Y - live births Y - adverse events	No significant difference in clinical pregnancies or live births when combined vitamin C + vitamin E + zinc were compared to no treatment. No improvement of sperm parameters	- No difference in clinical pregnancy and live births. No improvement of sperm parameters
Kessopoulou 1995	Cross-over, placebo Male infertility N = 30	Sperm parameters, adverse events, live birth	Sperm parameters, adverse effects, live birth	N - sperm parameters, only medians given Analysis 1.10; Analysis 1.20 Y - pregnancy rate, clinical Y - live births Y - adverse events	No differences in sperm outcomes were seen between the groups. 1 pregnancy in the vitamin E group and nil in the placebo (first phase data)	+ No difference in semen parameters. There is evidence of increased live birth and clinical pregnancy rate
Kizilay 2019	Parallel, no treatment Varicocele patients with oligozoospermia N = 93	Sperm parameters, clinical pregnancy, adverse events	Sperm parameters, clinical pregnancy, adverse events	Y - sperm parameters Y - pregnancy rate, clinical Y - adverse events	Significant improvement of sperm parameters and higher clinical pregnancy rate in combined antioxidant group compared to no treatment	+ Antioxidant treatment provides an important contribution to varicocelectomy outcomes and improves pregnancy rates
Kopets 2020	Parallel, placebo Idiopathic infertility N = 83	Sperm parameters, clinical pregnancy, adverse events	Sperm parameters, clinical pregnancy, adverse events	Y - sperm parameters Y - pregnancy rate, clinical Y - adverse events	The percentage of normal spermiograms was significantly higher in the combined antioxidant group. Higher spontaneous pregnancy rate in antioxidant group	+ Combined l-carnitine/l-acetyl-carnitine, l-arginine, glutathione, CoQ10, zinc, folic acid, cyanocobalamin, and selenium improves sperm quality and increases pregnancy rates
Korshunov 2018	Parallel, no treatment	Clinical pregnancy, live births	Clinical pregnancy, live birth, embryo	Y - pregnancy rate, clinical Y - live births	Clinical pregnancy and live birth rate were 62,5% vs 59,1% and 54,1% vs 40,9% in the antioxidant and no	+ Antioxidant therapy may have a positive ef-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Obstructive azoospermia, TESA/ICSI candidates N = 46 Conference abstract		quality, early pregnancy loss	N - adverse events, miscarriage. No data provided by authors.	treatment group, respectively. Higher early pregnancy loss rate in control group	fect for patients with obstructive azoospermia. It might improve ART outcome and decrease pregnancy loss
Kumalic 2020	Parallel, placebo Infertile men with OAT N = 80	Sperm parameters, DNA fragmentation, adverse events	Sperm parameters, DNA fragmentation, adverse events, after contact with author: clinical pregnancy rate and live births after ICSI	Y - sperm parameters Y - DNA fragmentation Y - adverse events Y - pregnancy rate, clinical Y - live births	No statistical differences in sperm parameters between astaxanthin + vitamin E group and placebo	- The oral intake of astaxanthin did not affect any semen parameters in patients with OAT
Kumamoto 1988	Multiple arm, placebo Men with abnormal sperm count or motility N = 396	Sperm parameters	Sperm parameters	N - sperm parameters, only scales given	No statistical difference in sperm outcomes in vitamin B 12 groups or placebo	- No improvement in sperm parameters after use of vitamin B12
Lenzi 2003	Cross-over, placebo Infertile men with OAT N = 100	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	Y - sperm parameters N - pregnancy rate, no definition of pregnancy given see Table 1	The patient groups showed no differences in sperm outcomes between therapy (carnitine) and placebo groups. Six pregnancies in the carnitine group and nil in the placebo (first phase)	+ The pregnancies obtained during the carnitine therapy period could suggest that carnitines may also lead to improvement in sperm function and fertilisation
Lenzi 2004	Parallel, placebo Infertile men with OAT N = 60	Sperm parameters, pregnancy rate, adverse events	Sperm parameters, pregnancy rate, adverse events	Y - sperm parameters N - pregnancy rate, no definition of pregnancy given Table 1 N - adverse events	Four participants taking carnitine induced a pregnancy in their partner and nil in the placebo	+ No evidence of improved sperm parameters
Li 2005	Head-to-head	Sperm parameters,	Sperm parameters,	Y - sperm parameters	L-carnitine and acetyl carnitine more effective than	+

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Infertile men with OAT N = 150	pregnancy rate	pregnancy rate	N - pregnancy rate, no definition given Table 1	vitamin E + vitamin C for pregnancy, sperm parameters and no evidence of adverse events	L-carnitine and acetyl carnitine more effective than vitamin E + vitamin C for pregnancy, sperm parameters and no evidence of adverse events
Li 2005a	Head-to-head Infertile men with OAT N = 80	Sperm parameters	Sperm parameters	Y - sperm parameters	Statistical significance for carnitines over vitamin E + C	+ Improvement of sperm parameters for carnitines compared to vitamin E + C
Lombardo 2002	Cross-over Infertile men with OAT N = 100 Conference abstract	Sperm parameters	Sperm parameters	N - sperm parameters, no data available	Sperm parameters (concentration, motility) carnitines versus placebo	+ Improvement of sperm parameters
Martinez 2015	Multiple arm, placebo, SG1002 arm excluded Men with idiopathic OAT N = 54	Sperm parameters	Sperm parameters	N - sperm parameters, no SDs given	Resveratrol treatment did not significantly affect any of the parameters.	- Resveratrol treatment did not significantly affect any of the parameters. SG1002 may reverse oligoasthenozoospermia. It seems to be more potent antioxidant than resveratrol
Martinez-Soto 2010	Parallel, placebo Infertile men N = 50 Conference abstract + manuscript from author	Sperm parameters	Sperm parameters	Y - sperm parameters	No differences were found in traditional sperm parameters or lipid composition of the sperm membrane after DHA treatment, only reduction in the percentage of spermatozoa with DNA damage	+ Positive effect only on DNA fragmentation
Mehni 2014	Multiple arm, placebo, pentoxifylline arms excluded Infertile men with OAT N = 235	Sperm parameters	Sperm parameters	Y - sperm parameters	L-carnitine only improved sperm motility, combined with pentoxifylline it improves all sperm parameters.	+ Positive effect only on sperm motility
Micic 2019	Parallel, placebo	Sperm parameters,	Sperm parameters,	Y - sperm parameters	Proxeed Plus significantly improved sperm volume,	+

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Men with OAT N = 175	DNA fragmentation	DNA fragmentation	Y - DNA fragmentation (median+IQR converted to mean + SD)	motility and DNA fragmentation compared to baseline.	Beneficial effects of carnitine derivatives (Proxeed plus) on progressive motility, vitality and sperm DNA fragmentation
Morgante 2010	Parallel, no treatment Infertile men with idiopathic asthenospermia N = 180	Sperm parameters	Sperm parameters	Y - sperm parameters	Significant improvement in sperm motility.	+ Improvement of sexual satisfaction Significant improvement in sperm motility
Nadjarzadeh 2011	Parallel, placebo Men with Idiopathic OAT N = 60	Sperm parameters	Sperm parameters	Y - sperm parameters	Non-significant changes in semen parameters of CoQ10 group.	- CoQ10 further evidence suggesting that supplementation is associated with alleviating oxidative stress, although it does not show any significant effects on sperm concentration, motility and morphology
Nouri 2019	Parallel, placebo Men with history of infertility N = 44	Sperm parameters	Sperm parameters	Y - sperm parameters	Significant improvement of sperm concentration with lycopene compared to placebo. Increase of total motility in lycopene group compared to baseline.	+ Lycopene improves sperm parameters and oxidative stress biomarkers in infertile men
Nozha 2001	Head-to-head Men with OAT N = unclear, 20?	Sperm parameters	Sperm parameters	N - sperm parameters, no data available	Vitamin E + selenium significantly improves sperm motility	+ Vitamin E + selenium associated with improved sperm motility when compared with vitamin B
Omu 1998	Parallel, no treatment Men with asthenozoopermia N = 100	Sperm parameters	Sperm parameters, pregnancy, live birth	N - sperm parameters, only % increase or decrease, not usable Y - pregnancy rate, clinical Y - live birth	Significant improvement in sperm quality by zinc therapy	+ Zinc has a role in improving sperm parameters. Significant increase in pregnancy, not live birth

Table 2. Outcomes and conclusions from all included studies *(Continued)*

Omu 2008	Multiple arm, no treatment Men with asthenozoospermia N = 100	Sperm parameters	Sperm parameters	Y - sperm parameters	Zinc therapy alone, in combination with vitamin E or with vitamin E+C were associated with comparably improved sperm parameters and less sperm DNA fragmentation	+ Zinc therapy reduces asthenozoospermia
Peivandi 2010	Cross-over, placebo Infertile men N = 30	Sperm parameters	Sperm parameters, pregnancy rate	Y - sperm parameters N - pregnancy rate, not defined as clinical Table 1	Significant improvements in mean sperm concentration and progressive sperm motility upon two months of L-carnitine intake but no significant changes were found in sperm volume or morphology.	+ Sperm outcomes and biochemical pregnancies. L-carnitine intake effectively improved the mean sperm count and progressive sperm motility
Popova 2019	Parallel, no treatment Men planning ART treatment N = 80	Sperm parameters, clinical pregnancy, adverse events	Sperm parameters, clinical pregnancy, adverse events	Y - sperm parameters Y - pregnancy rate, clinical Y - adverse events	No significant change in sperm motility. A pregnancy rate in the combined antioxidants (Androdoz) group was 45% compared to 25% in the control group.	+/- Androdoz contributes to an increase in positive outcomes of ART program. "Androdoz improves the main criteria of sperm analysis and functional tests (HBA-test)". This is based on the improvement of morphology
Pourmand 2014	Parallel, no treatment Men with male factor infertility and varicocele N = 100	Sperm parameters, DNA fragmentation, adverse events	Sperm parameters, DNA fragmentation, adverse events	N - sperm parameters, no SD given N - DNA fragmentation, no SD given Y - adverse events	No statistical difference between the two groups (varicocelectomy with L-carnitine or with no adjuvant therapy).	- Addition of 750 mg of L-carnitine orally daily to standard inguinal varicocelectomy does not add any extra benefit in terms of improvement in semen analysis parameters or DNA damage
Poveda 2013	Multiple arm, placebo Infertile men N = 60 Conference abstract	Sperm parameters	Sperm parameters	N - sperm parameters, data not available	L-carnitine significantly improves sperm concentration, Spermotrend and Maca improve sperm motility.	+ Sperm concentration with L-carnitine and motility with combined antioxidant Spermotrend
Pryor 1978	Cross-over, placebo	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	N - sperm parameters, bar graph of % patients showing	Arginine was no more effective than placebo for sperm parameters and	- There was no difference in the conception rates

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Men with severe oligozoospermia N = 64			an increase in motility and density N - pregnancy rate, not clear if clinical. Included in biochemical analysis Table 1	biochemical pregnancy rates	of the wives or changes in the quality of the semen during each period of treatment
Raigani 2014	Multiple arm, placebo Men with proven male factor infertility N = 83	Sperm parameters, DNA fragmentation	Sperm parameters, DNA fragmentation	Y - sperm parameters (median+IQR converted to mean+ SD) Y - DNA fragmentation	Sperm concentration, DNA fragmentation not significantly improved in either group	- Zinc sulphate and folic acid supplementation did not ameliorate sperm quality in infertile men with severely compromised sperm parameters, OAT
Rolf 1999	Asthenospermia N = 33	Sperm parameters, pregnancy rates, adverse events	Sperm parameters, pregnancy rate, adverse events	Y - sperm parameters N - pregnancy rate, not stated as clinical pregnancy N - adverse events, not clear which side effects aimed for	No adverse events or pregnancies in either group	- Overall no difference vitamin E + C versus placebo
Saeed Alkumait 2020	Multiple arm, placebo Infertile men N = 151	Sperm parameters	Sperm parameters	N - sperm parameters, data provided as percentage improvement, Analysis 1.16; Analysis 1.22	Significantly higher percentage improvement of progressive sperm motility and concentration with glutathione or CoQ10 compared to placebo	+ Both glutathione and CoQ10 are effective treatment options for improving sperm motility, morphology and concentration
Safarinejad 2009	Multiple arm, placebo Men with idiopathic OAT N = 468	Sperm parameters, adverse events	Sperm parameters, adverse events	Y - sperm parameters N - adverse events, not specified which adverse events aimed for	All semen parameters significantly improved with selenium and N-acetyl-cysteine treatment. Administering selenium plus N-acetyl-cysteine resulted in additive beneficial effects. Zero adverse events	+ Supplemental selenium and N-acetyl-cysteine improve semen quality. Zero adverse events
Safarinejad 2009a	Parallel, placebo Men with idiopathic OAT N = 212	Sperm parameters, adverse events	Sperm parameters, adverse events	Y - sperm parameters N - adverse events, not specified	Significant improvement in sperm density and motility after coenzyme Q10 therapy. Zero adverse events	+ Coenzyme Q10 supplementation resulted in a statistically significant improvement in certain

Table 2. Outcomes and conclusions from all included studies *(Continued)*

				which adverse events aimed for		sperm parameters. Zero adverse events
Safarinejad 2011b	Parallel, placebo Men with idiopathic OAT N = 238	Sperm parameters, adverse events	Sperm parameters, adverse events	Y - sperm parameters N - adverse events, not clear how many patients had gastrointestinal upsets in total	Significant improvement of sperm concentration and progressive motility after omega-3 fatty acids therapy. Significantly more adverse events (gastrointestinal and pruritus) in the omega-3 group	+ These findings suggest a protective effect of omega-3 fatty acid intake in idiopathic infertile men. More adverse events in omega-3 group
Safarinejad 2012	Parallel, placebo Infertile men N = 228	Sperm parameters	Sperm parameters	Y - sperm parameters	Sperm parameters improved significantly after coenzyme Q10	+ Coenzyme Q10 was significantly effective in men with unexplained oligoasthenoteratozoospermia for improving sperm density, sperm motility and sperm morphology
Schisterman 2020	Parallel, placebo Male partner of couples planning infertility treatment. Data from subfertile men used. N = 2370	Sperm parameters, DNA fragmentation, clinical pregnancy, live births, adverse events	Sperm parameters, DNA fragmentation, clinical pregnancy, live births, adverse events	Y - sperm parameters Y - DNA fragmentation N - pregnancy, clinical; N - live births N - adverse events Data not provided for male factor infertility subgroup	No significant difference in sperm parameters between folic acid + zinc and placebo. No results on clinical outcomes in male factor subgroup	- Folic acid and zinc did not significantly improve semen quality. The findings also were similar when restricted to men with known male factor infertility or poor semen quality at baseline
Scott 1998	Multiple arm, placebo Men with subfertility and low sperm motility N = 69	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	Y - sperm parameters N - pregnancy rate, not usable due to pooling of data in the two intervention groups Table 1	Sperm motility increased in both selenium-treated groups, only significant if both treatment groups were combined. Sperm density unaffected	± Selenium supplementation in subfertile men with low selenium status can improve sperm motility and the chance of successful conception. However, not all patients responded; 56% showed a positive response to treatment
Sharifzadeh 2016	Parallel, placebo	Sperm parameters, adverse events	Sperm parameters, adverse events	Y- sperm parameters	Significant increase in concentration in zinc group	+ Normal sperm percentage and total

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Idiopathic subfertile men N = 114			Y - adverse events		sperm concentration increased after zinc sulphate treatment
Sigman 2006	Parallel, placebo Infertile men with low sperm motility N = 26	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	Y - sperm parameters N - pregnancy rate, biochemical Table 1	No statistically significant or clinically significant increase in motility or total motile sperm counts between baseline, 12 weeks, or 24 weeks in the carnitine or placebo arms.	- Carnitine supplementation demonstrated no clinically or statistically significant effect on sperm motility or total motile sperm counts. No difference in pregnancy rate
Sivkov 2011	Parallel, placebo Men with chronic prostatitis and infertility N = 30	Sperm parameters	Sperm parameters	N - sperm parameters, no SD given Analysis 1.10	One-month course of therapy produced no side effects, had a positive effect on low fertility of ejaculate.	+ Selenium + zinc improve
Sofikitis 2016	Multiple arm, no treatment, Avanafil excluded Oligoasthenospermic infertile men N = 39 Abstract only	Sperm parameters	Sperm parameters	N - sperm parameters, no data available	No significant difference in L-carnitine group regarding sperm parameters	- No direct conclusion made about L-carnitine. From result section concluded: no impact on sperm parameters after use of L-carnitine
Steiner 2020	Parallel, placebo Men with one abnormal semen parameter N = 171	Sperm parameters, DNA fragmentation, clinical pregnancy, live birth	Sperm parameters, DNA fragmentation, clinical pregnancy, live birth	Y - sperm parameters Y - DNA fragmentation (data shared by authors after requested via e-mail) Y - pregnancy, clinical Y - live birth	No difference in sperm motility, DNA fragmentation, pregnancy rate and live birth rate between combined antioxidants and placebo	- No improvement in semen parameters in infertile males. This study suggests that combination antioxidants does not improve pregnancy or live birth rates
Stenqvist 2018	Parallel, placebo Infertile men	Sperm parameters, DNA fragmentation,	Sperm parameters, DNA fragmentation,	Y - sperm parameters Y - DNA frag-	No statistically significant difference between the antioxidant and placebo group was seen for semen	- Six months treatment with combined antioxi-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	fragmentation ≥ 25% N = 79	pregnancy rate, adverse events	pregnancy rate, adverse events	N - pregnancy rate, biochemical Table 1 Y - adverse events	parameters including DNA fragmentation	sperm parameters including DNA fragmentation
Suleiman 1996	Parallel, placebo Asthenospermic men N = 110	Sperm parameters	Sperm parameters, pregnancy rate, live birth, miscarriage	Y - sperm parameters Y - pregnancy rate, clinical Y - live birth Y - adverse events: miscarriage	Vitamin E significantly decreased the MDA concentration in spermatozoa and improved sperm motility. Significant increase pregnancy/live birth rate	+ Vitamin E increases sperm motility, pregnancy rate and live birth rate compared to placebo
Sun 2018	Parallel, head-to-head Infertile men with low acrosin activity N = 232	Sperm parameters	Sperm parameters	Y - sperm parameters	Significant increase of progressive sperm otility in men treated with L-carnitine compared to vitamin E	+ L-carnitine can effectively elevate sperm acrosin activity in male infertility patients, particularly in those with asthenozoospermia
Tremellen 2007	Parallel, placebo Male factor infertility N = 60	Pregnancy rate, adverse events	Pregnancy rate, adverse events, live birth provided by author	Y - pregnancy rate, clinical Y - live birth Y - adverse events	Antioxidant group recorded a statistically significant improvement in viable pregnancy rate. Side-effects on the Menevit antioxidant were rare (8%) and mild in nature.	+ Menevit antioxidant appears to be a useful ancillary treatment that significantly improves pregnancy rates in couples undergoing IVF-ICSI treatment. Side-effects on the Menevit antioxidant were rare (8%) and mild in nature.
Tsounapi 2018	Multiple arm, head-to-head Profertil + avanafil and avafanil only groups not used Idiopathic OAT N = 217	Sperm parameters, DNA fragmentation, pregnancy rate	Sperm parameters, DNA fragmentation, pregnancy rate	N - sperm parameters N - DNA fragmentation Not reported in how many patients sperm outcomes were assessed Y - pregnancy rate, clinical	Significantly higher total and progressive sperm motility in Profertil group compared to L-carnitine and no treatment. No difference in pregnancy rate	+ Profertil or Profertil combined with avanafil or or avanafil alone improves sperm membrane permeability with an improvement in sperm motility
Vinogradov 2019	Parallel, placebo	Sperm parameters,	Sperm parameters,	N - sperm parameters	No statistical differences between results after	+/-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Infertile men with at least one abnormal sperm parameter N = 109	DNA fragmentation	DNA fragmentation	N - DNA fragmenation Only results after cryotolerance test provided	Brudy plus (combined antioxidant) and placebo	No conclusions on outcomes of interest. Brudy Plus increases cryotolerance, promotes the normal formation of the genetic material and reduces the frequency of ultrastructural sperm disorders.
Wang 2010	Head-to-head Infertile men with asthenozoospermia N = 135	Sperm parameters, pregnancy rate, adverse events	Sperm parameters, pregnancy rate, adverse events	Y - sperm parameters N - pregnancy rate, not clear if clinical Table 1 N - adverse events, zero found, however not clear which they aimed for	Significant increase in L-carnitine + vitamin E group for sperm motility, no difference for sperm density and morphology. Pregnancy rate significantly higher in L-carnitine + vitamin E group	+ L-carnitine (+vitamin E) significantly improves sperm motility and pregnancy rate
Wong 2002	Multiple arm, placebo Fertile and subfertile men N = 103	Sperm parameters	Sperm parameters	Y - sperm parameters (median+IQR converted to mean+ SD)	Subfertile men demonstrated a significant 74% increase in total normal sperm count and a minor increase of 4% abnormal spermatozoa	+ Total normal sperm count increases after combined zinc sulphate and folic acid treatment in both subfertile and fertile men
Zalata 1998	Head-to-head, pilot Men attending andrology clinic N = 22 Conference abstract	Sperm parameters	Sperm parameters	N - sperm parameters, only before and after median data given	No significant difference in sperm parameters after treatment (acetyl-cysteine or DHA). DNA damage measured by 8-OHdG (fmol/ug) was significantly decreased after supplementation	- No improvement of sperm parameters
Zavaczki 2003	Parallel, placebo Men with idiopathic infertility N = 20	Sperm parameters, clinical pregnancy, adverse events	Sperm parameters, clinical pregnancy, adverse events	Y - sperm parameters Y - pregnancy rate, clinical Y - adverse events	No significant changes in sperm characteristics were detected	- Magnesium neither leads to a significant improvement of sperm variables nor does it increase the pregnancy rates
Zhou 2016	Parallel, head-to-head	Sperm parameters, pregnancy rate	Sperm parameters, pregnancy rate	Y - sperm parameters N - pregnancy rate, defin-	Significant increase of total and progressive sperm motility in vitamin E and vitamin E + compound amino acids group.	+ Compound amino acid combined with vitamin E can safely and effec-

Table 2. Outcomes and conclusions from all included studies *(Continued)*

	Idiopathic asthenozoospermia N = 120	ition unclear Table 1 Y - adverse events	Greater increase in compound amino acids group. 5.7% pregnancy in combined group, 2% in vitamin E group. No adverse events	tively improve sperm motility in idiopathic asthenospermia patients.

DHA: docosahexaenoic acid; **IUI:** intrauterine insemination; **NAC:** N-acetylcysteine; **OAT:**oligoasthenoteratozoospermia; **ROS:** reactive oxygen species

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Specialised Register search strategy

Searched 15 February 2021

PROCITE platform

Keywords CONTAINS "antioxidants" 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 "ascorbic acid" or "zinc" or "fatty acids" or "oil" or "fish oils" or "plant extracts" or "flavonoids" or "L-arginine" or "pycnogenol" or "folate" or "ubiquinol "or "coenzyme Q10"or "L-carnitin" or "L-carnitine" or "multivitamins" or "beta-caritine" or "N-acetyl cysteine" or "L-acetyl-carnitine" or "acetyl L-carnitine" or "acetylcysteine" or "ethylcysteine" or "alpha tocopherol" or "pentoxifylline" or "omega-3"or "omega-6 fatty acid" or "inositol" or "Myo-inositol" or "d-chiro-inositol" or "melatonin" or "docosahexaenoic acid" or "Magnesium" or "nutritional supplement" or "nutritional supplements" or Title CONTAINS "antioxidants" 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 "nutritional supplement" or "nutritional supplements"

AND

Keywords CONTAINS "idiopathic asthenospermia" or "idiopathic oligozoospermia" or "IVF" or "ICSI" or "Intrauterine Insemination" or "ART" or "Sperm" or "sperm DNA integrity" or "sperm damage" or "sperm quality" or "sperm parameters" or "oligo-asthenozoospermia" or "Oligoasthenospermia" or "oligoasthenoteratozoospermia" or "oligospermia" or "oligozoospermia" or "asthenospermia" or "asthenozoospermia" or "assisted reproduction techniques" or "azoospermia" or "Male" or "male subfertility" or Title CONTAINS "idiopathic asthenospermia" or "idiopathic oligozoospermia" or "Sperm" or "sperm DNA integrity" or "sperm damage" or "sperm quality" or "sperm parameters" or "oligo-asthenozoospermia" or "Oligoasthenospermia" or "oligoasthenoteratozoospermia" or "oligospermia" or "oligozoospermia" or "asthenospermia" or "asthenozoospermia" or "assisted reproduction techniques" or "azoospermia" or "Male"

(462 records)

Appendix 2. CENTRAL via the Cochrane Library search strategy

Searched 15 February 2021, Issue 2

Web platform

#1 MeSH descriptor: [Infertility, Male] explode all trees 751

#2 asthenozoospermia or oligospermia or azoospermia:ti,ab,kw (Word variations have been searched) 698

#3 Asthenospermia or Teratospermia:ti,ab,kw (Word variations have been searched) 133

#4 MeSH descriptor: [Spermatozoa] explode all trees 449

#5 Sperm*:ti,ab,kw (Word variations have been searched) 6224

#6 male subfertility:ti,ab,kw (Word variations have been searched) 343

#7 male infertility:ti,ab,kw (Word variations have been searched) 2554

#8 subfertile men:ti,ab,kw (Word variations have been searched) 185

#9 infertile men:ti,ab,kw (Word variations have been searched) 898

#10 semen:ti,ab,kw (Word variations have been searched) 1943

#11 oligoasthenoteratozoospermia:ti,ab,kw (Word variations have been searched) 49

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 7902

#13 MeSH descriptor: [Antioxidants] explode all trees 4883

#14 antioxidant*:ti,ab,kw (Word variations have been searched) 13362

#15 radical scavenger*:ti,ab,kw (Word variations have been searched) 778

#16 MeSH descriptor: [Vitamins] explode all trees 4741

#17 vitamin*:ti,ab,kw (Word variations have been searched) 31739

#18 MeSH descriptor: [Zinc] explode all trees 1641

#19 zinc:ti,ab,kw (Word variations have been searched) 7834

#20 MeSH descriptor: [Selenium] explode all trees 719

#21 Selenium:ti,ab,kw (Word variations have been searched) 2079

#22 Glutathione or folate:ti,ab,kw (Word variations have been searched) 6182

#23 ubiquin$ or folic acid:ti,ab,kw (Word variations have been searched) 4766

#24 coenzyme q10:ti,ab,kw (Word variations have been searched) 1020

#25 MeSH descriptor: [Carnitine] explode all trees 634

#26 carnitine$ or carotenoid 2539

#27 astaxanthin$ or lycopene 865

#28 menevit 7

#29 multivitamin$ 1254

#30 betacarotene$ or beta carotene$ 1791

#31 ascorbic acid 3909

#32 acetylcysteine 2327

#33 MeSH descriptor: [Acetylcysteine] explode all trees 1116

#34 Acetylcysteine 2327

#35 cysteine or ethylcysteine 1518

#36 alpha-tocopherol$ 2427

#37 fish oil$ 3340

#38 omega$ 7015

#39 MeSH descriptor: [Fatty Acids] explode all trees 22429

#40 fatty acid$ 13252

#41 arginine or flavonoid or carotenoid or riboflavin 6897

#42 pycnogenol$ or lutein$ or lipoic acid$ or Inositol 2391

#43 MeSH descriptor: [Inositol] explode all trees 469

#44 myoinositol or mesoinositol or melatonin 3358

#45 cysteine or docosahexaenoic or magnesium 12626

#46 nutritional supplement$ 3818

#47 nutraceutical$ 651

#48 #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 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 106852

#49 #12 and #48 800

Appendix 3. MEDLINE search strategy

Searched 1946 to 15 February 2021

Ovid platform

1 exp male infertility/ (28367)
2 (asthenozoospermia or oligospermia or azoospermia).tw. (7892)
3 Asthenospermia.tw. (397)
4 Teratospermia.tw. (186)
5 exp Spermatozoa/ (67917)
6 Sperm$.tw. (140359)
7 (male$ adj2 subfertil$).tw. (847)
8 (male$ adj2 infertil$).tw. (12565)
9 (subfertil$ adj2 men).tw. (541)
10 (infertil$ adj2 men).tw. (4777)
11 (male$ adj2 fertility).tw. (6841)
12 semen.tw. (31400)
13 oligoasthenoteratozoospermi$.tw. (436)
14 or/1-13 (173982)
15 exp antioxidants/ or free radical scavengers/ (475410)
16 (antioxidant$ or radical scavengers).tw. (216213)
17 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/ (346760)
18 vitamin$.tw. (216170)
19 exp Zinc/ (61038)
20 exp Selenium/ (21146)
21 (Glutathione$ or folate).tw. (157585)
22 exp Glutathione Peroxidase/ or exp folic acid/ (58107)
23 exp Ubiquinone/ (9520)
24 (ubiquin$ or folic acid).tw. (30120)
25 coenzyme q10.tw. (3669)
26 exp Carnitine/ (9862)
27 (carnitine$ or carotenoid$).tw. (37347)
28 (astaxanthin$ or lycopene$).tw. (7417)
29 menevit.tw. (4)
30 multivitamin$.tw. (3884)
31 (betacarotene$ or beta carotene$).tw. (14351)
32 ascorbic acid.tw. (32509)
33 n-acetylcysteine.tw. (11805)
34 exp Acetylcysteine/ (13416)
35 Acetylcysteine.tw. (12668)
36 Acetyl cysteine.tw. (3852)
37 Acetyl-carnitine.tw. (193)
38 ethylcysteine.tw. (63)
39 alpha-tocopherol$.tw. (15935)
40 (fish adj2 oil$).tw. (11110)
41 omega$.tw. (54443)
42 exp fatty acids/ or exp fish oils/ or exp cod liver oil/ or exp fatty acids, omega-3/ or exp plant oils/ (491790)
43 fatty acid$.tw. (223751)
44 (plant adj4 oil$).tw. (3347)

45 arginine.tw. (97456)
46 flavonoid$.tw. (45757)
47 carotenoid$.tw. (21782)
48 riboflavin$.tw. (10588)
49 pycnogenol$.tw. (422)
50 lutein$.tw. (39856)
51 lipoic acid$.tw. (4801)
52 exp Inositol/ (23338)
53 (Inositol or myoinositol).tw. (38341)
54 mesoinositol.tw. (37)
55 melatonin.tw. (25393)
56 n acetyl cysteine.tw. (3799)
57 docosahexaenoic acid.tw. (12475)
58 magnesium.tw. (59507)
59 nutritional supplement$.tw. (6734)
60 (diet$ adj3 supplement$).tw. (46060)
61 nutraceutical$.tw. (7918)
62 or/15-61 (1870788)
63 randomized controlled trial.pt. (522865)
64 controlled clinical trial.pt. (94063)
65 randomized.ab. (511964)
66 placebo.tw. (221812)
67 clinical trials as topic.sh. (194655)
68 randomly.ab. (352424)
69 trial.ti. (236140)
70 (crossover or cross-over or cross over).tw. (88258)
71 or/63-70 (1382956)
72 (animals not (humans and animals)).sh. (4754307)
73 71 not 72 (1272491)
74 14 and 62 and 73 (818)

Appendix 4. Embase search strategy

Searched 1980 to 1 February 2018

Ovid platform

1 exp male infertility/ (41498)
2 (asthenozoospermia or oligospermia or azoospermia).tw. (10447)
3 Asthenospermia.tw. (491)
4 Teratospermia.tw. (231)
5 exp Spermatozoa/ (38581)
6 Sperm$.tw. (152175)
7 (male$ adj2 subfertil$).tw. (1093)
8 (male$ adj2 infertil$).tw. (17498)
9 (subfertil$ adj2 men).tw. (697)
10 (infertil$ adj2 men).tw. (6809)
11 (male$ adj2 fertility).tw. (8382)
12 semen.tw. (37677)
13 oligoasthenoteratozoospermi$.tw. (613)
14 or/1-13 (186476)
15 vitamin$.tw. (260836)
16 exp Zinc/ (111983)
17 exp Selenium/ (38394)
18 (zinc or selenium).tw. (162319)
19 (Glutathione$ or folate).tw. (182859)
20 exp Ubiquinone/ (7619)
21 ubiquin$.tw. (9386)
22 coenzyme q10.tw. (5111)
23 exp Carnitine/ (15817)
24 (carnitine$ or carotenoid$).tw. (41967)
25 (astaxanthin$ or lycopene$).tw. (8652)
26 menevit.tw. (13)

27 multivitamin$.tw. (5410)
28 (betacarotene$ or beta carotene$).tw. (16302)
29 ascorbic acid.tw. (34271)
30 n-acetylcysteine.tw. (15260)
31 exp acetylcysteine/ (36882)
32 acetylcysteine.tw. (16482)
33 Acetyl cysteine.tw. (5195)
34 ethylcysteine.tw. (61)
35 alpha-tocopherol$.tw. (16965)
36 (fish adj2 oil$).tw. (14085)
37 omega$.tw. (58096)
38 fatty acid$.tw. (249621)
39 (plant adj4 oil$).tw. (4475)
40 arginine.tw. (106421)
41 flavonoid$.tw. (64656)
42 carotenoid$.tw. (22714)
43 riboflavin$.tw. (10370)
44 pycnogenol$.tw. (530)
45 lutein$.tw. (39919)
46 lipoic acid$.tw. (5877)
47 exp antioxidant/ (230945)
48 free radical scavengers/ (22672)
49 (antioxidant$ or radical scavengers).tw. (277325)
50 exp vitamin/ or exp ascorbic acid/ or exp carotenoid/ or exp multivitamin/ or vitamin b group/ (621591)
51 exp edible oil/ or exp castor oil/ or exp lyprinol/ or exp olive oil/ or exp safflower oil/ 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 6 fatty acid/ or exp polyunsaturated fatty acid/ (204908)
52 exp fatty acid/ (559218)
53 exp vegetable oil/ (94438)
54 exp fish oil/ (17335)
55 exp cod liver oil/ (1166)
56 exp omega 3 fatty acid/ (33182)
57 exp inositol/ (11798)
58 docosahexaenoic acid.tw. (15376)
59 magnesium.tw. (65749)
60 (Inositol or myoinositol).tw. (41786)
61 mesoinositol.tw. (6)
62 melatonin.tw. (31022)
63 nutritional supplement$.tw. (9377)
64 nutraceutical$.tw. (9596)
65 or/15-64 (2223822)
66 Clinical Trial/ (997470)
67 Randomized Controlled Trial/ (645082)
68 exp randomization/ (90499)
69 Single Blind Procedure/ (41994)
70 Double Blind Procedure/ (179653)
71 Crossover Procedure/ (66262)
72 Placebo/ (351139)
73 Randomi?ed controlled trial$.tw. (251370)
74 Rct.tw. (40792)
75 random allocation.tw. (2167)
76 randomly allocated.tw. (37793)
77 allocated randomly.tw. (2631)
78 (allocated adj2 random).tw. (844)
79 Single blind$.tw. (26258)
80 Double blind$.tw. (211910)
81 ((treble or triple) adj blind$).tw. (1277)
82 placebo$.tw. (317458)
83 prospective study/ (662988)
84 or/66-83 (2319854)
85 case study/ (76027)
86 case report.tw. (429175)

87 abstract report/ or letter/ (1157989)
88 or/85-87 (1651677)
89 84 not 88 (2262250)
90 14 and 65 and 89 (1858)

Appendix 5. PsycINFO search strategy

Searched from 1806 to 15 February 2021

Ovid platform

1 exp Infertility/ (2254)
2 (asthenozoospermia or oligospermia or azoospermia).tw. (43)
3 exp Sperm/ (939)
4 Sperm$.tw. (3309)
5 (male$ adj2 subfertil$).tw. (10)
6 (male$ adj2 infertil$).tw. (233)
7 (subfertil$ adj2 men).tw. (3)
8 (infertil$ adj2 men).tw. (110)
9 (male$ adj2 fertility).tw. (176)
10 semen.tw. (489)
11 oligoasthenoteratozoospermi$.tw. (2)
12 Asthenospermia.tw. (2)
13 Teratospermia.tw. (0)
14 or/1-13 (5900)
15 vitamin$.tw. (7518)
16 exp Zinc/ (857)
17 exp Antioxidants/ (2813)
18 (zinc or selenium).tw. (2535)
19 (Glutathione$ or folate).tw. (3992)
20 ubiquin$.tw. (109)
21 coenzyme q10.tw. (224)
22 (carnitine$ or carotenoid$).tw. (837)
23 (astaxanthin$ or lycopene$).tw. (99)
24 menevit.tw. (0)
25 multivitamin$.tw. (253)
26 (betacarotene$ or beta carotene$).tw. (152)
27 ascorbic acid.tw. (443)
28 n-acetylcysteine.tw. (470)
29 exp Cysteine/ (671)
30 acetylcysteine.tw. (481)
31 alpha-tocopherol$.tw. (230)
32 (fish adj2 oil$).tw. (329)
33 omega$.tw. (3111)
34 fatty acid$.tw. (4836)
35 (plant adj4 oil$).tw. (45)
36 l-arginine$.tw. (1138)
37 arginine$.tw. (3108)
38 flavonoid$.tw. (470)
39 carotenoid$.tw. (397)
40 riboflavin$.tw. (222)
41 pycnogenol$.tw. (15)
42 lutein$.tw. (1662)
43 lipoic acid$.tw. (196)
44 (antioxidant$ or radical scavengers).tw. (5764)
45 Inositol.tw. (1568)
46 myoinositol.tw. (143)
47 mesoinositol.tw. (0)
48 acetyl cysteine.tw. (174)
49 melatonin.tw. (4918)
50 or/15-49 (35448)
51 random.tw. (60657)
52 control.tw. (458650)

53 double-blind.tw. (23452)
54 clinical trials/ (11854)
55 placebo/ (5907)
56 exp Treatment/ (1080498)
57 or/51-56 (1489038)
58 14 and 50 and 57 (40)

Appendix 6. AMED search strategy

Searched from 1961 to 15 February 2021

Ovid platform

1 exp Infertility male/ (167)
2 (asthenozoospermia or oligospermia or azoospermia).mp. [mp=abstract, heading words, title] (19)
3 exp Spermatozoa/ (83)
4 Sperm$.tw. (267)
5 (male$ adj2 subfertil$).tw. (4)
6 (male$ adj2 infertil$).tw. (178)
7 (subfertil$ adj2 men).tw. (2)
8 (infertil$ adj2 men).tw. (11)
9 (male$ adj2 fertility).tw. (34)
10 semen.tw. (164)
11 oligoasthenoteratozoospermi$.tw. (0)
12 Asthenospermia.tw. (2)
13 Teratospermia.tw. (0)
14 or/1-13 (500)
15 exp Antioxidants/ (2520)
16 exp Free radicals/ (616)
17 (antioxidant$ or radical scavengers).tw. (4038)
18 exp Vitamins/ (3403)
19 exp Dietary supplements/ (1749)
20 exp Ascorbic acid/ (318)
21 vitamin$.tw. (2742)
22 exp Zinc/ (136)
23 (zinc or selenium).tw. (533)
24 (Glutathione$ or folate).tw. (1006)
25 exp Selenium/ (110)
26 (ubiquin$ or folic acid).tw. (202)
27 coenzyme q10.tw. (93)
28 exp Carnitine/ (22)
29 (carnitine$ or carotenoid$).tw. (261)
30 multivitamin$.tw. (76)
31 ascorbic acid.tw. (541)
32 n-acetylcysteine.tw. (39)
33 Acetylcysteine.tw. (42)
34 alpha-tocopherol$.tw. (95)
35 (fish adj2 oil$).tw. (201)
36 omega$.tw. (308)
37 exp Fatty acids/ (701)
38 exp Fish oils/ (126)
39 fatty acid$.tw. (1095)
40 (plant adj4 oil$).tw. (1187)
41 l-arginine$.tw. (157)
42 flavonoid$.tw. (1930)
43 riboflavin$.tw. (26)
44 (Inositol or myoinositol).tw. (74)
45 pycnogenol$.tw. (18)
46 nutritional supplement$.tw. (256)
47 or/15-46 (12721)
48 14 and 47 (64)

Appendix 7. Epistemonikos search strategy

Searched from inception to 18 February 2021

(title:((title:(male* OR men) OR abstract:(male* OR men)) AND (title:(infertility OR subfertility) OR abstract:(infertility OR subfertility)) AND (title:(vitamin* OR antioxidant* OR mineral*) OR abstract:(vitamin* OR antioxidant* OR mineral*))) OR abstract:((title:(male* OR men) OR abstract:(male* OR men)) AND (title:(infertility OR subfertility) OR abstract:(infertility OR subfertility)) AND (title:(vitamin* OR antioxidant* OR mineral*) OR abstract:(vitamin* OR antioxidant* OR mineral*))))

(58 records)

Appendix 8. 'The World Health Organization International Clinical Trials Registry Platform' search portal

Searched 15 February 2021

Web platform

1) Antioxidant* AND men

2) Vitamins* AND men

3) Antioxidant* AND male

4) Vitamin* AND male

5) Infertility AND men

6) Infertility AND male

Appendix 9. 'ClinicalTrials.gov' trials register

Searched 15 February 2021

Web platform

1) Antioxidants (clinical condition: infertility)

2) Vitamins (clinical condition: infertility)

Appendix 10. OpenGrey

Searched 15 February 2021

Web platform

1) Antioxidant*

2) Vitamin*

3) Infertility AND Men

4) Antoxidant AND fertility

Appendix 11. ProQuest Dissertations & Theses database

Searched 15 February 2021

Web platform

1) Antioxidants AND sperm AND (men OR male) AND (fertility or infertility) AND random*

2) Antoxidants AND sperm AND (men OR male) AND (fertility or infertility)

Appendix 12. Web of Science

Searched 15 February 2021

Web platform

1) Antioxidants AND sperm AND male AND (fertility OR infertil*) *limited by 'clinical trial'*

WHAT'S NEW

Date	Event	Description
6 September 2021	New search has been performed	Twenty-nine new studies were added in this update (Abbasi 2020; Alahmar 2019; Alahmar 2020; Amini 2020; Ardestani 2019; Bahmyari 2021; Cheng 2018; Eslamian 2020; Gamidov 2019; Gonzalez-Ravina 2018; Goswami 2015; Huang 2020; Joseph 2020; Kizilay 2019; Kopets 2020; Korshunov 2018; Kumalic 2020; Lu 2018; Nouri 2019; Popova 2019; Saeed Alkumait 2020; Safarinejad 2011b; Schisterman 2020; Steiner 2020; Stenqvist 2018; Sun 2018; Tsounapi 2018; Vinogradov 2019; Zhou 2016). There is one new study placed in studies awaiting classification (Kuzmenko 2018). One previously excluded study was included as a substudy of another included study (Raigani 2014).
6 September 2021	New citation required and conclusions have changed	Outcome definitions were adjusted based on the core outcome set for infertility treatments developed and published by Duffy 2021.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 1, 2011

Date	Event	Description
4 December 2018	New citation required and conclusions have changed	Pentoxifylline was removed from the review due to the fact that it is a prescription drug and not an 'over-the-counter' supplement. Progressive sperm motility was added as a secondary outcome; this is an outcome with more clinical importance than total sperm motility.
4 December 2018	New search has been performed	Nineteen new studies were added in this update (Barekat 2016; Blomberg Jensen 2018; Boonyarangkul 2015; Busetto 2018; Cyrus 2015; Deng 2014; Ener 2016; Exposito 2016; Gamidov 2017; Gopinath 2013; Haghighian 2015; Haje 2015; Martinez 2015; Mehni 2014; Micic 2019; Pourmand 2014; Raigani 2014; Sharifzadeh 2016; Sofikitis 2016). There is one study placed in awaiting classification (Goswami 2015). All pentoxifylline studies were excluded. Two previously included studies were excluded for containing an ineligible study population.
10 February 2015	Amended	Correction of some analysis graph labels.
28 November 2014	New search has been performed	14 new studies were added in this update (Attallah 2013, Azizollahi 2013, Dimitriadis 2010, Eslamian 2013, Kumamoto 1988, Martinez-Soto 2010, Morgante 2010, Nadjarzadeh 2011, Poveda 2013, Pryor 1978, Safarinejad 2011b, Safarinejad 2012, Sivkov 2011, Wang 2010). The search was updated in August 2014 and six studies were placed in awaiting classification (Anarte 2013a;

Date	Event	Description
		Gopinath 2013; Iacono 2014; Nadjarzadeh 2014; Nashivochnikova 2014a; Nematollahi-Mahani 2014).
28 November 2014	New citation required and conclusions have changed	Comparisions were restructured into a more logical framework. Clinical pregnancy rate data were used in this update rather than the undefined pregnancy rate data of the original review as this is more clinically meaningful when considering the evidence for use of antioxidants.
7 December 2011	Feedback has been incorporated	Change of emphasis to conclusions, additional sensitivity analysis performed, Risk of Bias, Summary of Findings Table and Discussion sections edited to increase this review's focus on clinical outcomes of pregnancy and live birth.
3 May 2011	Amended	2.1 Analysis edited to fixed effect Peto. The conclusions remain the same.
8 March 2011	Amended	Changed summary of findings table to reflect quality of studies
21 December 2010	Amended	Minor edits made - no changes to conclusions
4 May 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

WL: starting from the 2021 update: selected studies for inclusion, assessed quality, performed data extraction, entered data, updated the background text, and wrote the final 2021 review pdate.
RS: selected studies for inclusion in the 2018 and 2021 update, commented on the 2021 update. In the 2018 update also updated and renewed the whole background text, and wrote the final review update in 2018.
RM-P: selected studies for inclusion in the 2014, 2018 and 2021 update and commented on the final version of the update. In the 2014 update also assisted with background text updating and entered text into tables of characteristics.
VJ: provided technical advice and commented on the final version of the update in 2018 and 2021.
KF: starting from the 2021 update: assessed quality and performed data extraction. Also provided clinical expertise.
JdB: starting from the 2021 update: assessed quality and performed data extraction. Also provided clinical expertise.
MGS: initiated, conceptualised and wrote the protocol, performed the searches in all versions. Up to and including the 2014 update: selected studies for inclusion, assessed quality, performed data extraction, entered data and wrote the first review and the 2014 update. Commented on the final versions of the 2018 and 2021 update.

DECLARATIONS OF INTEREST

The institution of first author Wiep R de Ligny and Roos M Smits received an unrestricted grant for conducting the trial NCT03337360, to cover the salary of the trial co-ordinators Wiep R de Ligny and Roos M Smits. This trial (NCT03337360) started in April 2018. No data have been extracted from this study. The trial NCT03337360 is submitted to 'Ongoing studies'. This matter was referred to Cochrane's Funding Arbiters who have confirmed that Dr de Ligny's and Dr Smits' declared interest does not constitute a COI under the current policy.

The following author has reported financial activities outside the submitted work: KF has received travel and conference support from Ferring.

JdB, VJ, MGS and RM-P have no conflicts to declare.

SOURCES OF SUPPORT

Internal sources

- Cochrane Gynaecology and Fertility Group, New Zealand

  Advice and support

External sources

- None, Other

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2011 full review, sperm outcomes of concentration and motility were added as these two sperm outcomes are thought to reflect the oxidative process. A study by El-Taieb (El-Taieb 2009) states that "increased ROS generation and reduced antioxidant capacity is negatively correlated with sperm concentration and motility in infertile men".

The comparisons 'antioxidant versus placebo' and 'antioxidants versus no treatment' were combined as the one comparison 'antioxidants versus control', and then it was stated in the sensitivity analysis whether exclusion of those that failed to use placebo would have altered the conclusions - as per statistical advice in the editorial comments.

Subgrouping and sensitivity analysis were performed on the outcomes of live birth and pregnancy in order to assess the potential of overestimation of benefit and reporting bias.

Subgroup analysis was performed on studies that enrolled couples undergoing IVF/ICSI and a sensitivity analysis was performed on those studies enrolling men undergoing IUI.

Sensitivity analysis was performed to consider whether conclusions were any different if eligibility was restricted to those studies without risk of bias.

A post hoc sensitivity analysis was conducted to examine the effect of excluding from the analysis those studies which reported remarkably low standard deviations as the review authors considered that these data were potentially erroneous.

In the 2014 update of the review 'pregnancy rate per couple' was redefined to be 'clinical pregnancy rate'. Stillbirth as an outcome was removed; this will be reported as an adverse event, as reported by the studies. The outcome 'level of sperm DNA damage after treatment' was reworded as 'level of sperm DNA fragmentation'.

In the 2018 update, we decided to remove pentoxifylline due to the fact that it is a prescription drug and not an 'over-the-counter' or overall free available supplement. In the future, there will be a new Cochrane Review solely on this item. We added a new secondary outcome: progressive sperm motility. In past versions of this review we already noticed that four studies only reported on progressive sperm motility and not on total sperm motility. In this 2018 update, we noticed that eight more studies (out of the 17 new included) report only on progressive sperm motility. We came to the conclusion that progressive sperm motility is the motility outcome with more clinical importance.

Furthermore, in the 2018 update we clarified that this review is (as the title implies) solely for subfertile men; men with abnormal semen parameters. In the previous updates it was said to include "men of a couple with male factor infertility or unexplained infertility". However, male factor infertility has always been the main focus of the search and the review. Broadening the focus of the review to also unexplained infertility would change the scope of the review. Therefore we changed the inclusion and exclusion criteria, which are now also more like those in the review '*Antioxidants for female subfertility*' (Showell 2017).
Other changes were made in regard with the risk of bias assessments of blinding: we decided to assess 'performance bias' and 'detection bias' separately.

In the 2021 review update, outcome measures were redefined based on the core outcome set for infertility treatments developed and published in 2020 (Duffy 2020, Duffy 2021).

INDEX TERMS

Medical Subject Headings (MeSH)

*Abortion, Spontaneous [epidemiology]; Antioxidants [adverse effects]; *Infertility, Female [drug therapy]; *Infertility, Male [drug therapy] [etiology]; Live Birth [epidemiology]; Pregnancy Rate

MeSH check words

Adolescent; Adult; Aged; Child; Female; Humans; Male; Middle Aged; Pregnancy; Young Adult