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REVIEW

The influence of oral antioxidants on men with infertility: A systemic review

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Summary ***Objective: This study aims to investigate the current evidence regarding the impact of oral antioxidant supplementation on semen parameters of infertile men.***

Materials and methods: We conducted a systematic search of PubMed, and Cochrane electronic databases, adhering to modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The focus was on studies exploring the effects of antioxidant therapy on infertile men, with an examination of antioxidants in terms of types, doses, rationale for use, and their impact on semen parameters measures.

Results: A total of 18 studies that met the inclusion criteria were included in this study. Out of these, 14 studies reported a significantly positive influence of antioxidant therapy on basic semen parameters and advanced sperm function. These comprised 11 randomized clinical trials and 7 prospective studies. Commonly utilized antioxidants included Vitamin E, Vitamin C, carnitines, co-enzyme Q10, N-acetyl cysteine, zinc, selenium, folic acid, and lycopene.

Conclusions: Overall, antioxidants generally demonstrate a favorable effect on semen parameters of infertile men. However, further research is necessary to pinpoint the optimal antioxidant regimen that can be applied safely and effectively in clinical practice.

KEY WORDS: Infertility; Antioxidants; Semen parameters.

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INTRODUCTION

Infertility is defined as the inability to conceive after at least 12 months of regular, unprotected intercourse, affecting approximately 15% of couples globally. Notably, male factors contribute to nearly half of the reported cases, often linked to disturbances in testicular function or blockage of reproductive passages (1, 2). Consequently to the efforts to unravel the molecular-level of idiopathic male infertility, the substantial role played by *oxidative stress* (OS) has been underscored. OS refers to the imbalance in the body's redox state, arising from either excessive oxidants or insufficient antioxidants. *Reactive oxygen species* (ROS), commonly known as 'free radicals,' are highly reactive oxygen-derived molecules characterized by unpaired electrons in their outer valence orbital. These include oxygen-centered radicals (hydroxyl radical, nitric oxide radical, and superoxide anion radical) and non-radical derivatives (hydrogen peroxide, peroxynitrite anion, and hypochlorous acid) (3, 4). Various endogenous (e.g., immature spermatozoa, leukocytes, varicocele) and exogenous (e.g., testicular hyperthermia, environmental and habitual exposures) factors have been identified as potential causes of increased ROS production. To counterbalance ROS, antioxidants play a crucial role in maintaining the desired redox equilibrium for optimal sperm function (5). Seminal fluid is rich in antioxidants that nourish and protect sperm, existing in two forms: enzymatic and non-enzymatic antioxidant systems (6). The enzymatic system comprises naturally occurring antioxidants, including glutathione peroxidase, superoxide dismutase, and catalase, believed to originate from the prostate and found in sperm cells or seminal plasma. In contrast, the non-enzymatic system consists of various compounds obtained through diet or supplements. When an excess of ROS is produced or antioxidant activity is insufficient, OS occurs, disrupting the equilibrium between oxidation and reduction. Spermatozoa are particularly susceptible to OS due to their low levels of enzymatic antioxidants, originating from the prostate. Additionally, the high concentration of polyunsaturated fatty acids, notably docosahexaenoic acid, in the sperm cell's plasma membrane makes them attractive targets for ROS-induced oxidation reactions. Recent decades have witnessed significant progress in understanding male infertility, incorporating tests like *sperm DNA fragmentation* (SDF) and measures of OS to enhance clinicians' insights into male fertility potential (7,8). Advances in *assisted reproductive therapy* (ART) have allowed previously infertile men to father biological children. However, OS remains a critical factor influencing reproductive outcomes, both in natural conception and with ART. Approximately 25% of infertile men exhibit significant levels of ROS in their semen compared to fertile counterparts (9). OS negatively impacts semen parameters, fertilization rates, embryonic development, and pregnancy rates (10, 11).

The impact of antioxidants on fertility depends by substantial variations in antioxidant forms, dosages, combinations, and outcome measures across studies. This literature review aims to explore the most commonly used antioxidants in treating male infertility and investigate the effect of their doses that may confer benefits on basic semen parameters, advanced sperm function tests, outcomes of ART, and live-birth rates.

Materials and methods

Research strategy

The research strategy adhered to modified *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (12). A literature search was conducted on PubMed, and Cochrane electronic databases to identify studies exploring the effectiveness of antioxidants in treating male infertility. Keywords and Medical Subject Heading (MeSH) phrases included 'antioxidants,' 'male infertility,' semen parameters'.

Study selection

Screening of articles was performed based on title and abstract by all authors followed by examination of relevant full papers. Additionally, review articles were scrutinized for potential inclusion (male patients, human studies). Exclusion criteria were based on study methods (retrospective, case report, editorial, or commentary). Data extraction was cross-checked and verified.

Outcome measures

The outcomes of interest included the type and dosage of antioxidants, their mechanism of action, impact on basic semen parameters and advanced sperm function tests.

Results

The search strategy identified 380 articles, with 315 excluded based on title and/or abstract. The remaining 65 articles underwent screening, leading to the identification of 18 studies that met the inclusion and exclusion criteria. These comprised 11 randomized clinical trials (13-23) and 7 prospective studies (24-30). Out of these, 14 studies (13-19, 24-30) reported a significant positive effect of antioxidant therapy on various parameters such as basic semen parameters, advanced sperm function tests. Commonly investigated antioxidants included vitamin E, vitamin C, carnitines, *N-acetyl cysteine* (NAC), *coenzyme Q10* (CoQ10), zinc, selenium, folic acid, and lycopene. The doses and mechanisms of action for each antioxidant are presented in Table 1. Additionally, Table 2 outlines the outcomes of antioxidant treatment that were assessed across studies (13-30).

Table 1.
The mode of action of commonly used antioxidants.

Antioxidant compound	Mechanism of action
Ascorbic acid (vitamin C)	Neutralises free radicals
Tocopherol (vitamin E)	Neutralises free radicals
Folate (vitamin B9) Selenium	Scavenges free radicals
Selenium	Enhancement of enzymatic antioxidant activity
Zinc	Inhibition of NADPH oxidase
Carnitines	Neutralizes free radicals and acts as an energy source
CoQ10	In its reduced form, scavenges free radicals intermediate in mitochondrial electron transport system
NAC	Enhances enzymatic antioxidant activity
Lycopene	Quenches free radicals

NADPH: Nicotinamide Adenine Dinucleotide Phosphate.

Table 2.
Studied antioxidants effect on semen parameters.

Clinical circumstance	Antioxidant	Reference
Basic semen parameters		
Oligozoospermia	Vitamin E, vitamin C, NAC, carnitines, CoQ10, lycopene, selenium and zinc	
	Vitamin E (300 mg)	(12)
	Vitamin E (180 mg), vitamin A (30 mg) and essential fatty acids or NAC (600 mg)	(25)
	NAC (600 mg) + other vitamins/minerals	(13)
	LC (2 g)	(14)
	CoQ10 (300 mg)	(15)
	NAC (600 mg) and selenium (200 mg)	(16)
	Folic acid (5 mg) + zinc (66 mg)	(17)
	Lycopene (2 mg)	(26)
Asthenozoospermia	Vitamin E, vitamin C, NAC, carnitines, CoQ10, lycopene, selenium and zinc	
	Vitamin E (400 mg) + selenium (200 lg)	(27)
	CoQ10 (300 mg)	(15)
	Lycopene (2 mg)	(26)
	LC (2 g) and LAC (1 g)	(19)
	NAC (600 mg)	(20)
	NAC (600 mg) and selenium (200 mg)	(16)
	Zinc (400 mg), vitamin E (20 mg) and vitamin C (10 mg)	(18)
Teratozoospermia	Vitamin E, NAC, lycopene, selenium and zinc	
	Vitamin E (400 mg) + selenium (200 lg)	(27)
	Lycopene (8 mg)	(28)
	NAC (600 mg) and selenium (200 mg)	(16)
	Zinc (400 mg), vitamin E (20 mg) and vitamin C (10 mg)	(18)
Advanced sperm function		
OS (oxidative stress)	Vitamin E, vitamin C, NAC, selenium and zinc	
	Vitamin E (300 mg)	(22)
	Vitamin E (180 mg) and b-carotene (30 mg)	(25)
	Vitamin E (20 mg), vitamin C (10 mg) and zinc (400 mg)	(18)
	Vitamin E (400 mg) and selenium (225 g)	(23)
	NAC (600 mg)	(20)
High SDF (sperm DNA fragmentation)	Vitamin E, vitamin C, zinc, selenium and folic acid	
	Vitamin E (1 g) + vitamin C (1 g)	(21)
	Vitamin C (400 mg), vitamin E (400 mg), b-carotene (18 mg), zinc (500 mmol) and selenium (1 mmol)	(29)
	LC (1500 mg); vitamin C (60 mg); CoQ10 (20 mg); vitamin E (10 mg); zinc (10 mg); folic acid (200 lg)	(30)
	selenium (50 lg); vitamin B12 (1 lg)	(31)

Discussion

Antioxidants, whether biological or chemical compounds, act scavenging free radicals, neutralizing their

effects, and disrupting the chain reaction leading to OS in body tissues. In the context of male fertility, antioxidants are commonly prescribed for their accessibility and relatively low cost. However, conflicting results have been observed in studies assessing the impact of antioxidant therapy on male fertility. While some studies reported positive effects on semen parameters, sperm function, and pregnancy rates, others failed to confirm such benefits or even indicated a negative influence on male fertility. The heterogeneity across studies and the unknown optimal balance of the redox system for sperm function contribute to these discrepancies. Overconsumption of antioxidants may lead to reductive stress with potential detrimental effects on human health, including impairment of mitochondrial activity (31-33).

Antioxidants: Mechanism of action and rationale for use

Numerous compounds with antioxidant properties have been explored for treating male infertility (Table 1). Understanding the mechanisms of action of commonly used compounds is crucial before delving into the associated evidence in clinical practice.

Vitamin E (α-tocopherol): This potent chain-breaking antioxidant is a fat-soluble compound predominantly located in cell membranes. It quenches free hydroxyl radicals and superoxide anions, reducing lipid peroxidation initiated by ROS at the plasma membrane level. Vitamin E levels found to be correlated to the percentage of motile spermatozoa in semen. Lower vitamin E levels were observed in the semen of infertile men (34).

Vitamin C (ascorbic acid): A water-soluble compound that is found in high concentrations in seminal plasma more than in blood serum. It neutralizes hydroxyl, superoxide, and hydrogen peroxide radicals, offering protection against endogenous oxidative damage. Seminal fluid analyses from infertile men with asthenozoospermia revealed lower vitamin C levels and higher ROS levels compared to fertile controls (35).

Carnitines (L-carnitine and L-acetyl carnitine): These water-soluble antioxidants are involved in sperm metabolism, fueling essential activities like sperm motility. Carnitines exhibit antioxidant activities by scavenging superoxide anions and hydrogen peroxide radicals, inhibiting lipid peroxidation. Semen samples from infertile men with oligoasthenoteratozoospermia showed significantly lower carnitine levels (36).

CoQ10: This vital antioxidant is present in almost all body tissues, particularly in sperm mitochondria involved in cellular respiration and energy production. CoQ10's role in promoting motility and acting as an antioxidant is rationalized by its inhibitory effect on superoxide formation (37).

NAC (N-acetyl cysteine): This amino acid, converted to cysteine in body tissues, acts as a precursor of glutathione, a crucial naturally occurring antioxidant that neutralizes various ROS. NAC directly reduces OS by scavenging hypochlorous acid and hydroxyl radicals. Studies have documented its positive influence on germ cell survival, showcasing reductions in ROS levels and improvements in sperm motility after incubation with *NAC (38)*.

Selenium: An essential trace element, selenium's role in spermatogenesis is linked to its ability to protect sperm DNA against OS damage. Selenium's antioxidant properties are associated with its augmentation of glutathione function. Selenoenzymes, including *phospholipid hydroperoxide glutathione peroxidase* (PHGPX) and sperm capsular selenoprotein glutathione peroxidase, contribute to maintaining sperm structural integrity. Selenium deficiency is often correlated with morphological sperm abnormalities and impaired motility (39).

Zinc: Another essential trace element, zinc, plays vital roles in RNA and DNA metabolism, signal transduction, gene expression, and apoptosis regulation. Its antioxidant properties stem from its ability to decrease the production of hydrogen peroxide and hydroxyl radicals by antagonizing redox-active transition metals like iron and copper. Higher zinc concentrations in seminal plasma are observed in fertile men compared to subfertile men, and zinc deficiency is associated with various sperm structural abnormalities (40).

Folic Acid (Vitamin B9): Involved in nucleic acid synthesis and amino acid metabolism, folic acid is used in male infertility treatment for its free radical scavenging abilities. Folic acid intake is linked to an increased reduced-to-oxidized glutathione ratio (41).

Lycopene: A naturally synthesized carotenoid found in fruits and vegetables, lycopene contributes significantly to the human redox defense system due to its potent ROS quenching abilities (42).

Antioxidant effect on basic semen parameters

Semen analysis remains a fundamental test for assessing male fertility due to its simplicity and wide availability. However, continuous updates in reference values pose challenges in interpreting the evidence surrounding the potential impact of antioxidants, as changes in criteria may label patients differently. Despite these challenges, studies have reported improvements in basic semen parameters following oral antioxidant intake, either alone or in combination.

Vitamin E: Used in combination with other vitamins and minerals, vitamin E alone (300 mg daily) showed a significant improvement in sperm motility in infertile men (23). A study comparing vitamin E, clomiphene citrate, and a combination of both treatments in patients with idiopathic oligoasthenozoospermia reported a significant improvement in sperm concentration and motility with the combined regimen (13). Another study using vitamin E (400 mg) + selenium (200 µg) for 100 days showed a significant improvement in sperm motility, morphology, or both in infertile men (34). However, some studies failed to reproduce significant effects on semen parameters using vitamin E alone or in combination with other antioxidants (28, 30).

Vitamin C: Studies demonstrated the positive effects of vitamin C, particularly in heavy smokers, showing dose-dependent improvements in sperm quality (43). Vitamin C as an adjunct therapy post-varicocelectomy resulted in a statistically significant improvement in sperm motility and morphology compared to a placebo group (44). Several antioxidant supplements containing vitamin C have been investigated, showing significant improvement in sperm motility with combinations including zinc and vitamin E (19).

Carnitines: Studies confirmed the significant influence of carnitines, especially on sperm motility (45). A placebo-controlled trial demonstrated significant improvement in all semen parameters, with the most significant increase in sperm motility, using a combined treatment of L-carnitine (2 g) and L-acetyl carnitine (1 g) (20). LC and LAC treatment showed significant improvement in semen parameters, particularly in patients with lower baseline values of motility (46).
CoQ10: CoQ10 significantly improved sperm concentration and motility compared to placebo in men with idiopathic oligoasthenozoospermia (16). A clinical trial demonstrated improvements in sperm morphology, catalase, and superoxide dismutase with CoQ10 treatment (47). These findings highlight the potential benefits of antioxidant supplementation in improving sperm parameters, but variations in study outcomes emphasize the need for further research and standardization. A systematic review of three randomized controlled clinical trials involving 332 infertile men indicated that CoQ10 treatment (200-300 mg daily) led to a significant increase in sperm concentration (MD 5.33 x 10^6 sperm/mL, $p < 0.001$) and motility (MD 4.5%, $p < 0.001$) (48).
NAC (N-acetyl cysteine): In a randomized placebo-controlled study of 120 patients with idiopathic infertility, daily treatment with 600 mg NAC for 3 months resulted in a significant improvement in volume, motility, and viscosity of semen compared to placebo (21). Combining 600 mg NAC with 200 mg selenium showed a significant improvement in all semen parameters, with a dose-dependent positive correlation between the sum of selenium and NAC concentrations and mean sperm concentration, motility, and normal morphology (17).
Folic Acid: In a double-blind, placebo-controlled interventional study, subfertile men receiving combined therapy of folic acid and zinc showed a statistically significant 74% increase in total normal sperm concentration after 26 weeks of treatment (18).
Selenium: A randomized placebo-controlled clinical trial involving 468 infertile men with idiopathic oligoasthenozoospermia demonstrated significant improvements in all semen parameters with selenium (200 mg) alone, NAC (600 mg) alone, or a combination of both supplements compared to placebo (17). The combination of selenium with vitamin E resulted in increased sperm motility (24). However, a study with normozoospermic men using selenium (300 mg) daily for 48 weeks did not show a significant influence on semen parameters (29).
Zinc: In a prospective trial with asthenozoospermic men, zinc supplementation for 3 months led to a significant improvement in sperm concentration, progressive motility, fertilizing capacity, and a reduction in the incidence of anti-sperm antibodies (19). Oral zinc supplementation restored seminal catalase-like activity and improved sperm concentration and progressive motility in asthenozoospermic men (49).
Lycopene: In a study involving 30 men with idiopathic oligoasthenozoospermia, treatment with 2 mg lycopene twice daily for 3 months resulted in statistically significant improvements in sperm concentration and motility in 66% and 53% of patients, respectively (33). A similar dose of lycopene was used in the treatment of 50 patients with idiopathic oligoasthenozoospermia, and after a 1-year follow-up, sperm concentration, motility, and morphology improved in 70%, 54%, and 38% of patients, respectively (35).

Antioxidant influence on advanced sperm function tests
The conventional semen analysis has faced criticism for its limited ability to predict fertility accurately. While it offers valuable information on sperm production, accessory organ secretions, ejaculation, and emission, it falls short in predicting fertility (50). It does not provide insights into the functional potential of sperm to successfully fertilize an ovum or undergo the necessary maturation processes for fertilization. To address this limitation, advanced tests of sperm function were developed to enhance the predictive power of semen studies. Among these advanced tests, SDF and OS measures have been the most widely studied. Recent research has expanded our understanding of the implications of SDF on male fertility (8). Human sperm DNA, mostly bound to protamine, forms a condensed chromatin that is easily transportable through the sperm head and more resistant to damage during transit through the reproductive tracts (51). However, SDF can occur due to errors in chromatin packaging during spermatogenesis or exposure to seminal OS during epididymal transit (52). Both in vitro and in vivo studies confirm that elevated SDF can negatively impact fertility at various stages, including fertilization, early embryo development, implantation, and pregnancy (53,54). Therefore, addressing OS appears to be a justifiable approach to minimize SDF incidence in semen samples. Several studies have investigated the impact of dietary antioxidant supplementation on sperm DNA integrity (22, 25, 36, 55). While these studies generally assessed small-sized samples and had short treatment durations, they consistently reported a positive effect on SDF measures. For instance, *Greco et al.* (20) found a significant reduction in SDF percentage ($p < 0.001$) in patients with unexplained infertility and elevated SDF levels treated with vitamin C and vitamin E. Another study reported a 19% decrease in SDF ($p < 0.001$) with a combination of antioxidants containing zinc and selenium (36). *Abad et al.* (29) examined the effects of oral antioxidant therapy on SDF dynamics, revealing significant reductions at each experimental time-point ($p < 0.05$). Studies also explored antioxidant therapy in patients with high SDF due to varicocele. In one study, a combined antioxidant regimen led to a significant decrease in SDF levels (22.1%, $p = 0.02$) and an increase in sperm concentration ($p = 0.04$) (38). Assessing seminal OS levels has become integral in evaluating infertile men, considering its utility in various clinical scenarios (56). However, routine clinical use is hindered by factors such as test availability, complexity, cost-effectiveness, and a lack of universally accepted analysis methods. Various assays, classified as direct (e.g., chemiluminescence and flow cytometry assays) and indirect (e.g., myeloperoxidase test, lipid peroxidation levels), are available to measure OS. Each type has its advantages and disadvantages, with direct assays providing accurate measures but being expensive and requiring expertise, while indirect assays are simpler and more cost-effective but

assess an end state influenced by various unknown pathological processes (57-59). Numerous studies investigating the impact of antioxidant therapy on male fertility have evaluated its effects on OS as a key outcome measure. For instance, a 6-month regimen of vitamin E (300 mg daily) significantly reduced lipid peroxidation in semen samples from 110 asthenozoospermic men (23). Similarly, *Comhaire et al.* (24) reported a significant decrease in seminal ROS levels with a combination of 180 mg vitamin E and 30 mg β-carotene in 27 infertile men. *Omu et al.* (17) examined the effectiveness of daily supplementation with vitamin E (20 mg), vitamin C (10 mg), and zinc (400 mg) over 3 months in 45 asthenozoospermic men, observing a twofold reduction in malondialdehyde (an indicator of lipid peroxidation) ($p < 0.01$), a significant decrease in pro-apoptosis markers ($p < 0.05$), and a substantial increase in total antioxidant capacity ($P < 0.01$). Another study revealed that vitamin E (400 mg) and selenium (225 mg) intake for 3 months led to significant reductions in malondialdehyde levels, coupled with improvements in sperm motility and viability (24). Furthermore, *Oeda et al*. (60) observed a direct dose- and time-dependent reduction in seminal ROS when semen samples were incubated with N-acetylcysteine (NAC), suggesting the potential usefulness of NAC in reducing OS. In a randomized placebo-controlled study involving 120 patients with idiopathic infertility, those receiving 600 mg of NAC daily showed significant improvements in sperm motility compared to the placebo group (61). Additionally, *Gharagozloo and Aitken* (62) conducted a systematic review of 20 trials, indicating a significant reduction in OS or sperm DNA damage after antioxidant treatment in 19 of them.

Conclusions

Numerous research has investigated the impact of antioxidant therapy on male fertility, demonstrating its potential in reversing OS-induced sperm dysfunction. Commonly used compounds include vitamin E, vitamin C, carnitines, zinc, selenium, NAC, CoQ10, folic acid, and lycopene. However, the identification of an ideal antioxidant treatment method is hindered by study design heterogeneity and the unknown normal physiological level of the fine redox balance. Further studies are necessary to determine the optimal and safe antioxidant preparation for managing male infertility.

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