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Coenzyme Q10, oxidative stress, and male infertility: A review

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Male infertility has a complex etiopathology, which mostly remains elusive. Although research has claimed that oxidative stress (OS) is the most likely underlying mechanism of idiopathic male infertility, the specific treatment of OS-mediated male infertility requires further investigation. Coenzyme Q10 (CoQ10), a vitamin-like substance, has been found in measurable levels in human semen. It exhibits essential metabolic and antioxidant functions, as well as playing a vital role in mitochondrial bioenergetics. Thus, CoQ10 may be a key player in the maintenance of biological redox balance. CoQ10 concentrations in seminal plasma directly correlate with semen parameters, especially sperm count and sperm motility. Seminal CoQ10 concentrations have been shown to be altered in various male infertility states, such as varicocele, asthenozoospermia, and medical or surgical regimens used to treat male infertility. These observations imply that CoQ10 plays an important physiological role in the maintenance and amelioration of semen quality. The present article thereby aimed to review the possible mechanisms through which CoQ10 plays a role in the regulation of male reproductive function, and to concisely discuss its efficacy as an ameliorative agent in restoring semen parameters in male infertility, as well as its impact on OS markers, sperm DNA fragmentation, pregnancy, and assisted reproductive technology outcomes.

Keywords: Antioxidant; Coenzyme Q10; Male infertility; Oxidative stress

Introduction

Infertility is defined as the failure to successfully achieve pregnancy after 12 months of regular unprotected sexual intercourse [1]. Worldwide, 15% of the world's population is affected by infertility [2]. The factors responsible for infertility have been grouped as male and female factors. Approximate 50% of cases are attributed to combined male and female factors, while 25% are attributed to male factors alone [3]. Infertility in males unambiguously reflects a complex of underlying causes [4,5], and more than 25% of cases of male infertility are idiopathic with no identifiable cause [6]. Oxidative stress (OS) and reactive oxygen species (ROS) are considered damaging to sperm and are responsible for 30%– 80% of cases of subfertility [7]. OS, caused by the disruption of the prooxidant-antioxidant balance [8], affects male fertility and sperm function [9-12].

Although low levels of ROS possess some physiological functions in sperm maturation and capacitation, an imbalance between ROS and seminal antioxidants may disrupt male reproductive function [13]. Similarly, the acrosome reaction and capacitation are boosted by superoxide anion radicals [14]. However, excessive ROS generation leads to OS and diminishes spermatozoa's antioxidant capacity [15-17]. The generation of seminal ROS could be attributed to genital tract infection, genital tract inflammation, varicocele, testicular torsion, and cryptorchidism [18,19]. Other factors include aging and various lifestyle factors, such as exposure to toxic chemicals, cigarette smoking, exposure to radiation, and alcohol abuse [18,20]. Excessive

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ROS generation has been associated with degradation of DNA via the induction of breakage of DNA strands, chromatin cross-linking, and base modifications [21], and lower potential of the mitochondrial membrane [22,23]. The plasma membrane of spermatozoa is composed of lipids, and a high level of polyunsaturated fatty acids and an excessive level of ROS makes the membrane susceptible to damage due to lipid peroxidation [10,24]. In sperm, mobility and decreased membrane fluidity caused by lipid peroxidation have been associated with a lower fertilization capacity [25].

Spermatozoa have a scavenger activity exerted by enzymatic and non-enzymatic antioxidants. The enzymatic antioxidants present in semen include catalase, superoxide dismutase, and glutathione peroxidase, whereas non-enzymatic antioxidants constitute coenzyme Q10 (CoQ10), glutathione peroxidase; vitamins A, B complex, C, and E; carnitines; and minerals (chromium, selenium, zinc, and copper) [21,26]. An imbalance between ROS production and antioxidant capacity results in increased sperm exposure to OS, which plays a critical role in the pathogenesis of male infertility and alters sperm function [9]. Despite the recognition of ROS and OS as a factor contributing to male infertility, antioxidant use for treatment is still debatable. To explore the *in vitro* effective role of different OS in various models, specific differences have been found in the effectiveness exerted by enzymatic and non-enzymatic molecules [27]. Antioxidant therapy has been considered for supplementation and has been introduced into routine clinical practice for the treatment of male infertility [28]. The antioxidants used for male infertility include CoQ10, vitamin A, carnitines, N-acetyl cysteine, vitamin C, vitamin E, pentoxifylline, and micronutrients such as selenium and zinc [28,29]. Antioxidants have been associated with beneficial effects on sperm concentration, motility, morphology, DNA fragmentation, assisted reproductive technology (ART) outcomes (both *in vitro* fertilization [IVF] and intracytoplasmic sperm injection [ICSI]), and seminal plasma antioxidant capacity [30]. However, there is insufficient agreement on the type, dosing, and use of single or combined antioxidants [30,31]. The potential role of CoQ10 in the management of male infertility has been widely investigated. Our attention in this narrative review will be focused on comprehensive and updated evidence on the impact of CoQ10 on the male reproductive system and its efficacy on sperm parameters, sperm DNA fragmentation (SDF), seminal markers of OS, pregnancy, and ART outcomes.

CoQ10: biochemical properties and physiological functions

In humans, CoQ10 is synthesized from tyrosine. CoQ10 is a vital constituent of the inner mitochondrial membrane. It is involved in the inhibition of lipid peroxidation and DNA oxidation [7]. CoQ10 also plays an essential role in electron transport in the mitochondrial respiratory chain and oxidative phosphorylation, and functions as a lipid-soluble antioxidant in cell membranes and lipoproteins [32,33]. CoQ10 also participates in adenosine triphosphate production in aerobic respiration [21]. Moreover, CoQ10 therapy has been applied as a prospective intervention in the management of various pathological dysfunctions such as diabetes, cancer, Parkinson disease, Huntington disease, heart disorders, and infertility [34].

The introduction of CoQ10 therapy started in patients with heart failure; subsequently, it has been more widely recognized as a way to slow down age-related pathologies, improve bioenergetics in the cell, and counteract OS. Various studies have proven the effectiveness of CoQ10 supplementation in enhancing male fertility and cardiovascular function [9,34,35]. CoQ10 functions as an antioxidant by inhibiting lipid peroxidation of the sperm membrane [35]. There are three redox states of CoQ10 in the Q-cycle in organisms. These are ubiquinol (CoQ10-H2-reduced form), ubiquinone (oxidized form), and semiquinone (a radical) [36]. CoQ10 is concentrated in the mitochondria-containing midpiece of the sperm, where it takes part in all energy-regulated processes [35].

Effects of CoQ10 on sperm parameters

Several clinical studies have reported beneficial effects of CoQ10 supplementation on sperm parameters of infertile patients [21,37,38]. In 287 patients with idiopathic oligoasthenoteratozoospermia (OAT), CoQ10 supplementation (600 mg/day) for 12 months significantly increased sperm concentration (+113.7%), sperm progressive motility (+104.8%) and normal sperm morphology (+78.9%) [39]. A systematic review and meta-analysis evaluating the effects of CoQ10 oral administration on CoQ10 seminal concentration, sperm concentration, and sperm motility was conducted on three trials with a total of 149 patients receiving CoQ10 and 147 control men. The results showed that CoQ10 supplementation led to a significant increase in all three endpoints taken into consideration (namely seminal concentration of CoQ10, sperm concentration, and sperm motility) [40]. Furthermore, our recent meta-analysis of three placebo-controlled randomized clinical trials (RCTs) involving 296 participants demonstrated a significant impact of CoQ10 on improving sperm total and progressive motility [32].

Gvozdjakova et al. [36] showed that the administration of CoQ10 (30 mg/day), L-carnitine fumarate (440 mg/day), vitamin E (75 IU/day), and vitamin C (12 mg/day) to infertile male patients improved sperm concentration and pregnancy rates. In one of our RCTs, 35 men with idiopathic OAT were treated for 3 months with CoQ10 at the dose of 200 mg/day and 30 patients with 400 mg/day. The results showed greater improvement in semen parameters in men

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who took 400 mg/day [38]. In another study of 70 men with idiopathic OAT, we also demonstrated that CoQ10 therapy (200 mg/day) was associated with improved sperm concentration and motility, as well as a reduction in OS markers [38].

In another study, patients with idiopathic infertility were supplemented with CoQ10 (200 mg/day) and D-Asp (2,660 mg/day) for 12 weeks. The concentrations of CoQ10 and D-Asp increased significantly in the spermatozoa and seminal plasma. In addition, sperm motility improved, whereas no effect was found on sperm concentration and morphology [36]. Similarly, the efficacy of CoQ10 supplementation has also been evaluated in infertile patients with varicocele. A significant improvement of sperm parameters and total antioxidant capacity (TAC) was reported in men treated with CoQ10 at a dose of 100 mg/day for 3 months [41]. Furthermore, in a study comparing the effects of two doses of CoQ10 on sperm parameters and TAC in patients with idiopathic OAT for 3 months, it was found that CoQ10 significantly increased sperm concentration, total motility, and progressive motility [3]. CoQ10 also increased TAC, superoxide dismutase, and catalase activities, with a stronger improvement found in patients taking the highest dose [21].

Overall, these studies show that supplementation with CoQ10 enhances sperm parameters such as sperm concentration, motility, and morphology, and improves OS markers in men with idiopathic infertility. However, there is no consensus on the dosage to prescribe. In an attempt to answer this question, evidence from clinical trials and meta-analyses on the impact of CoQ10 treatment in male infertility revealed that oral supplementation with CoQ10 raised seminal CoQ10 levels, sperm motility, and spermatozoa concentration [32,42].

CoQ10 effects on OS markers

As previously discussed, ROS affect sperm quality, leading to DNA, protein, and lipid oxidation, and are involved in the pathogenesis of male infertility [43]. However, there is no general agreement on the validation, reproducibility, and standardization for the measurement of ROS-induced changes in DNA, lipids, and proteins; TAC in human body fluids; or enzymatic players involved in redox status [44,45].

There is evidence supporting the protective role of CoQ10 against ROS-induced sperm damage [37,38]. CoQ10 is known to inhibit superoxide production [46], and a strong negative association has been observed between CoQ10 levels and hydrogen peroxide [46]. In patients with idiopathic OAT, a significant increase in superoxide dismutase, TAC, and catalase activity after CoQ10 treatment has been reported [30]. We demonstrated that CoQ10 treatment (200 mg/day) could reduce or ameliorate OS markers such as ROS, TAC, catalase, superoxide dismutase, and glutathione peroxidase in infertile men with idiopathic OAT [21,38] and idiopathic oligoasthenozoospermia (OA) [30,37]. Overall, these studies have demonstrated beneficial effects of CoQ10 on improving both enzymatic and non-enzymatic antioxidant capacity among men with idiopathic infertility (Table 1).

CoQ10 and SDF

SDF is one of the main underlying molecular-level disruptions that may explain idiopathic male infertility. OS is considered to be the key mechanism causing SDF [47]. An excess of ROS causes nicks and breaks in DNA, which need to be repaired [48]. Most DNA in human spermatozoa is transported in a condensed form of chromatin in the sperm head, making sperm DNA more resistant to injury during transit in both the male and female reproductive tracts; however, SDF may result from exposure to seminal OS in the epididymis or abnormal chromatin packaging [49]. Spermatozoa are susceptible to ROS due to their composition of high levels of polyunsaturated fatty acids in their cytoplasm and plasma membrane. DNA damage can be the result of decreased protamination, replication errors, environmental toxins, ultraviolet rays, endogenous endonuclease activation, and ionizing rays [47]. DNA fragmentation can lead to infertility by altering sperm function [50]. Males with a high SDF rate have a substantially lower likelihood of conceiving naturally or via ART procedures [51]. Accordingly, patients with a high percentage of spermatozoa affected by DNA fragmentation have high levels of seminal ROS and decreased antioxidant capacity [26].

Both *in vivo* and *in vitro* studies have shown that increased SDF could impair male reproductive functions via its impacts on fertilization, implantation, early embryo development, and pregnancy [49]. Studies have reported that deficiency of CoQ10 is associated with high sperm DNA damage and low sperm count and motility [32,40,52,53]. This may be explained by the fact that seminal CoQ10, with antioxidant and metabolic properties, plays a major role in mitochondrial bioenergetics and maintenance of seminal redox status [33].

Evidence has shown that antioxidant treatment reduces the prevalence of SDF in semen samples and seems to improve the outcomes of ICSI in patients with elevated SDF levels [49]. Gual-Frau et al. [54] administered antioxidants containing CoQ10 to 20 infertile patients with low-grade varicocele and high SDF levels. A significant decrease in SDF levels and a substantial rise in sperm concentration were observed following treatment . These findings are consistent with our recent randomized controlled study on 65 infertile men with idiopathic OA and 40 fertile men, which illustrated an improvement in semen parameters and a reduction in OS markers and SDF in infertile patients following CoQ10 therapy (200 mg/day for 3 months) (Table 1) [37].

Table 1. Effects of CoQ10 on male infertility, pregnancy outcomes, and assisted reproductive techniques

Study	Participan	RCT	Intervention	Intervention period	Outcome
Alahmar et al. (2021) [37]	Infertile patients with idiopathic oligoasthenozoospermia; 65 patients	Yes	CoQ10 200 mg/day orally	3 mo	Improved sperm concentration, progressive motility, total motility, seminal fluid CoQ10 concentration, TAC, ROS levels and SDF percentage, and glutathione peroxidase levels.
Alahmar and Sengupta (2021) [38]	Men with OAT; 70 patients	Yes	CoQ10 200 mg/day	3 mo	Improved sperm concentration, motility, and antioxidant status.
Alahmar (2019) [21]	Men with idiopathic OAT 35 subjects treated with CoQ10 at the dose of 200 mg/day and 30 patients with 400 mg/day	Yes	CoQ10 200 mg/day, 400 mg/day	3 mo	Idiopathic OAT with a greater improvement shown in men who took 400 mg/day than in those who took 200 mg/day
Cheng et al. (2018) [55]	Idiopathic oligoasthenozoospermia; 262 patients	Yes	L-carnitine 10 mg twice daily and CoQ10 20 mg thrice daily	3 mo	Combination of L-carnitine and CoQ10 can improve the sperm motility and outcome of clinical pregnancy in idiopathic OAT patients. Pretreatment with CoQ10 improves ovarian response to stimulation and embryological parameters in young women with poor ovarian reserve in IVF-ICSI cycles.
Tiseo et al. (2017) [35]	Subfertile couples; 211 subjects	No	CoQ10 19.2 mg/day (2.4–247.2 mg/day)	Not specified	Mean dietary intake of CoQ10 in this study was 10-fold lower than the supplemental dose used in clinical trials, showing improved sperm motility.
Giacone et al. (2017) [56]	12 Normozoospermic men and 12 asthenozoospermic patients	No	Zinc, D-aspartic acid, CoQ10 12 mg	Not specified	Improved sperm motility and increased fertilization rate in IVF/ICSI.
Nadjarzadeh et al. (2014) [51]	Idiopathic OAT; 60 patients	Yes	CoQ10 200 mg/day or placebo	3 mo	Enhanced semen quality and motility.
Gaby et al. (2013) [57]	Idiopathic OAT; 228 patients	Yes	CoQ10/200 mg/day	26 wk	Increased sperm concentration and morphology. Decreased motility and follicle stimulating hormone activity.
Abad et al. (2013) [58]	Asthenteratozoospermic patients; 20 subjects	No	L-carnitine 1,500 mg, CoQ10 20 mg, vitamin C 60 mg, vitamin E 10 mg, vitamin B 9200 µg, vitamin B12 1 µg, zinc 10 mg, selenium 50 µg	3 mo	DNA damage reduced from 28.5% to 20.12%.
Safarinejad (2012) [39]	Idiopathic OAT; 287 patients	No	CoQ10 300 mg twice daily	12 mo	Increased sperm concentration, progressive motility, and normal morphology.
Nadjarzadeh et al. (2011) [49]	Infertile men with idiopathic OAT; 60 patients	Yes	CoQ10 200 mg once daily	19 mo	Improved seminal parameters, lipid peroxidation.
Safarinejad et al. (2009) [59,60]	Infertile men with idiopathic OAT; 212 patients	Yes	CoQ10 300 mg once daily	26 wk	Improved seminal parameters and testicular volume.
Balercia et al. (2009) [61]	Idiopathic asthenozoospermia; 60 patients	No	CoQ10 200 mg/day	3 mo	Administration of CoQ10 increased CoQ10 levels in semen. It could be effective in enhancing sperm kinetic features in idiopathic asthenozoospermic patients.

CoQ10, coenzyme Q10; RCT, randomized clinical trial; TAC, total antioxidant capacity; ROS, reactive oxygen species; SDF, sperm DNA fragmentation; OAT, oligoasthenoteratozoospermia; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection.

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In a study of 29 known asthenozoospermic males, a substantial decrease of SDF from 28.5% to 20.12% was reported after 3 months of CoQ10 plus L-carnitine administration [62]. In another study, Ghanbarzadeh et al. [33] showed that pretreatment with CoQ10 and L-carnitine significantly improved sperm parameters, sperm function, and reproductive hormone profile in male Wistar rats with high low-density lipoprotein (LDL) and oxidized LDL serum levels. In a recent study, our research group also observed that when idiopathic OA patients were received 3 months of CoQ10 supplementation, their semen parameters significantly improved, along with a significant reduction in seminal OS markers and SDF compared to the baseline [37]. These data suggest that CoQ10 plays a positive role in the amelioration of SDF, although limited studies are available so far. More unbiased and well-performed RCTs are needed to better clarify this issue.

CoQ10 and pregnancy outcomes

Several studies have demonstrated improved pregnancy rates after CoQ10 administration [63,64]. Some studies suggested that the increased pregnancy rate is due to the beneficial effects of CoQ10 on sperm concentration and motility. In line with such findings, Gvozdjakova et al. [36] showed a significant improvement in the pregnancy rate after the administration of CoQ10 at a daily dose of 90 mg for 3 to 9 months in 40 infertile men with OA. The administration of Carni-Q-Nol (each soft gel containing 440 mg L-carnitine fumarate, 30 mg CoQ10, 75 IU vitamin E, and 12 mg vitamin C) was effective for improving the pregnancy rate, as 45% of the female partners of these patients achieved pregnancy. In the same group, three males (7.5%) achieved fatherhood after undergoing ART, and the other 12 women (30%) became pregnant 5–6 months after their partners began therapy [36].

Safarinejad [39] also reported an increase in the pregnancy rate after treatment with CoQ10 in 287 patients with idiopathic OAT who received supplementation of 300 mg of CoQ10 twice daily for 12 months. After treatment, the participants showed improved sperm quality. A positive impact was found on pregnancy rates, as 34.1% of couples achieved spontaneous clinical pregnancy after 9–12 months of treatment [40]. In a study aiming to assess the effects of CoQ10 administered in combination with L-carnitine in idiopathic OAT patients, sperm parameters were found to be improved, with a lower percentage of SDF and consequently a higher clinical pregnancy rate [45], showing that the combination of CoQ10 and L-carnitine improved pregnancy outcomes in patients with idiopathic male infertility.

CoQ10 and ART outcomes

OS significantly impacts the success rate of ART. Spermatozoa and oocytes, once removed from their microenvironments, can be exposed to excessive levels of ROS as a consequence of the lack of scavenger system systems present in the reproductive tract. For this reason, pretreatment with antioxidants could be useful to improve the quality of gametes [30]. According to Arhin et al. [65], evidence from many RCTs has shown that oral antioxidant supplementation leads to a significant increase in the pregnancy rate in couples undergoing ART cycles by enhancing male fertility. However, the results of some of these studies must be interpreted with the utmost care due to discrepancies in the treatment regimens. Thanks to its ability to improve sperm quality, CoQ10 could play a role in improving ART outcomes. An *in vitro* study showed that incubation of spermatozoa for 3 hours with an antioxidant formula containing zinc, D-Asp, and Co-Q10 had a beneficial effect on sperm motility, recovery of spermatozoa by swim-up, and lipid peroxidation. This suggests that these molecules may have a place in sperm preparation before ART [63]. In another study carried by Lewin and Lavon [66], the effects of oral CoQ10 administration on the outcomes of ICSI were investigated in seven patients with low fertilization rates after ICSI at a dose of 60 mg/day for an average of 103 days before undergoing subsequent ICSI cycles. The treatment significantly increased the fertilization rate, from 10.3% ± 10.5% in ICSI cycles without treatment to 26.3% ± 22.8% after CoQ10 intake. Lewin and Lavon [66] also examined the seminal fluid of 38 subjects (normozoospermic and asthenozoospermic) and noted that in patients with asthenozoospermia, there was an increase in motility after incubation with 50 μM CoQ10 for 24 hours. However, they did not test the increase in the fertility rate in ICSI.

In another retrospective study of 797 intrauterine insemination and 253 IVF cycles, women who received supplementation with 600 mg of CoQ10 along with dehydroepiandrosterone (DHEA) for over a month were found to have reduced levels of gonadotropins upon stimulation and a higher number of mature follicles than women taking DHEA alone [50]. In a recent meta-analysis of 61 RCTs including 6,264 infertile patients, antioxidant treatment was found to be correlated with an increase in clinical pregnancy rate and live birth rate [67].

Conclusion

The present review shows that the antioxidant properties of CoQ10 and its vital role in mitochondrial bioenergetics form the basis of the ameliorative role of seminal CoQ10 in male fertility parameters. Evidence reveals that CoQ10 mainly improves sperm count and motility in infertile men, with most studies emphasizing its role in as-

thenozoospermia. It appears that CoQ10 also protects sperm from oxidative damage, thereby improving OS markers and SDF. Moreover, CoQ10 administration in couples resulted in improved ART outcomes, such as increased fertilization rates in IVF/ICSI. Further in-depth interventions are needed to reveal the exact mode of action of CoQ10 and to determine the appropriate standardized dose and duration of CoQ10 supplementation in the treatment of specific male infertility cases.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization, Data curation, & Formal analysis: ATA. Methodology: ATA, AEC, RS, PS. Project administration: ATA, REC, RS, PS. Visualization: ATA, RS, RC, SD. Writing–original draft: ATA. Writing–review & editing: AEC, RS, RC, PS, SD.

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