Coenzyme Q10 and Oocyte Quality

Subjects: Reproductive Biology

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Acquiring oocyte competence requires optimal mitochondrial function and adequate ATP levels. In this context, CoQ10 supplementation may improve human oocyte quality and subsequent reproductive performance given its role in ATP synthesis and mitochondrial protection from ROS oxidative damage. In infertility treatments, CoQ10 therapy can be orally supplied to promote a more favorable environment for oocyte development in vivo or by its addition to culture media in an attempt to improve its quality in vitro.

Coenzyme Q10 | oocyte quality | mitochondrial function | antioxidant | ROS | ATP

1. Introduction

Coenzyme Q10 (CoQ10) is a fat-soluble lipophilic molecule ubiquitously situated in the hydrophobic domain of all cell membranes. It particularly acts as an electron and proton carrier of the mitochondrial respiratory chain, being situated in the inner mitochondrial membrane and taking part in ATP synthesis (**Figure 1**)[1].

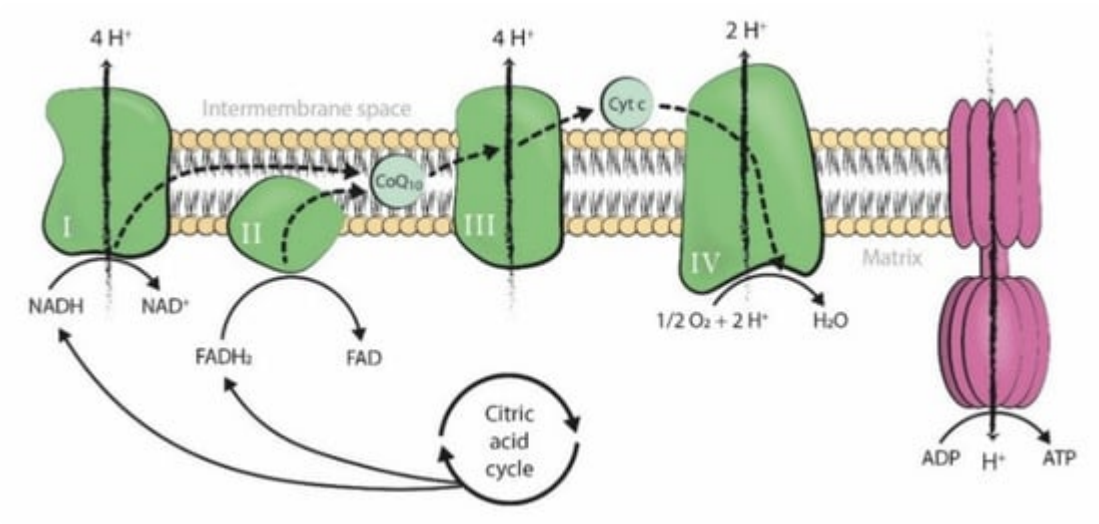

Figure 1. Mitochondrial respiratory chain (Complexes I, II, III, and IV; CoQ10, and cytochrome c) and the F1-F0 ATPase in the inner mitochondrial membrane. The movement of electrons throughout the mitochondrial respiratory chain is coupled with the transfer of protons across the membrane to the intermembrane space, generating an electrochemical proton gradient that is harnessed by F1-F0 ATPase to phosphorylate ADP into ATP (Figure from [2]). ADP: adenosine triphosphate. ATP: adenosine triphosphate. Pi: inorganic phosphate. H+: hydrogen ion (proton). NADH: nicotinamide adenine dinucleotide, reduced form. FADH2: flavin adenine dinucleotide, reduced

form. NAD+: nicotinamide adenine dinucleotide, oxidized form. FAD: flavin adenine dinucleotide, oxidized form. O2: oxygen. H2O: water. Cyt c: cytochrome c. CoQ10: coenzyme Q10.

The role of CoQ10 in oxygen metabolism makes it a source of the superoxide anion radical, one of the main reactive oxygen species (ROS). In contrast, it also acts as an antioxidant by directly scavenging free radicals, protecting cell membranes from lipid peroxidation, and enhancing the activity of antioxidant enzymes, among others [1].

The dual nature of CoQ10 as a pro-oxidant and antioxidant makes it a key regulatory element of the oxidative state balance in the cell. Therefore, insufficient CoQ10 levels could lead to diminished mitochondrial respiration activity, which may result in lower ATP production, less ROS counteraction, increased oxidative stress, mitochondrial damage, and subsequent mitochondrial dysfunction. Indeed, this shapes a positive feedback system, in which lower mitochondrial activity may lead to increased oxidative stress damage, which subsequently induces mitochondrial impairment and, thus, affects the activity of these organelles (**Figure 2**). Therefore, oxidative stress can be caused by, or be the cause of, mitochondrial dysfunction [2], and insufficient CoQ10 levels may contribute to generate them both.

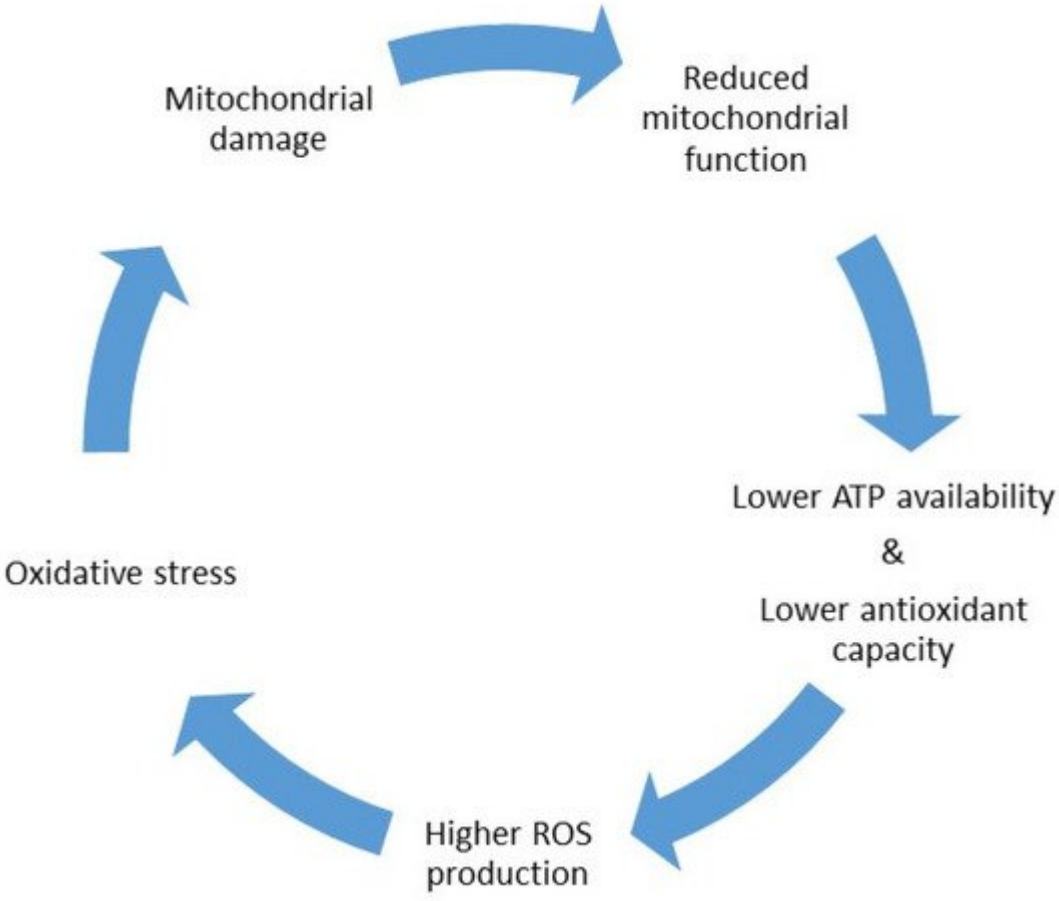

Figure 2. Vicious cycle between mitochondrial dysfunction and oxidative stress damage.

CoQ10 is endogenously synthesized in all human tissues [3]. However, insufficient levels of this molecule are associated with the consumption of some drugs [4], certain diseases in which a mutation in a gene implicated in CoQ10 synthesis is involved [5], and advanced age [6]. In the reproductive field, the decline in human oocyte quality associated with the aging process has been linked with increased oxidative stress and/or mitochondrial dysfunction [7] as mitochondria are necessary for proper meiotic spindle assembly, the segregation of chromosomes, maturation, fertilization, and embryo development [8]. Thus, insufficient CoQ10 levels may constitute a feasible explanation for this age-related oocyte quality deterioration.

Poor oocyte quality is not restricted to the aging process, as many intrinsic and external factors, including environmental pollutants [9][10], may lead to an altered microenvironment surrounding the oocyte and, thus, triggering this condition.

Oocyte maturation is achieved in follicular fluid (FF), where bidirectional communication occurs between cumulus cells and the oocyte. Thus, FF characteristics may influence the final oocyte quality [11]. In 2011, Turi's group analyzed, for the first time, the CoQ10 levels in the FF of women undergoing infertility treatment. Even though they found no direct association between these levels and oocyte/embryo quality [12], in 2017, Akarsu et al. described better embryo morphokinetic parameters, as well as higher pregnancy rates, in women aged under 41 years with higher CoQ10 levels in FF, regardless of their age [13]. Therefore, CoQ10 deficiency, or any other cause that indirectly lowers its levels, may influence oocyte quality and could cause women's infertility.

Finally, an altered ovarian environment with high oxidative stress damage and mitochondrial dysfunction may not be directly related to insufficient CoQ10 levels. Notwithstanding, raising CoQ10 levels may benefit oocyte quality by means of mitochondrial function enhancement and ROS counteraction.

CoQ10 supplementation was shown to be partly effective in treating many human diseases associated with mitochondrial dysfunction [14]. Increasing CoQ10 levels may reduce oxidative stress and enhance mitochondrial function to, thus, improve these patients' symptoms. In reproduction, CoQ10 supplementation may constitute a potential therapeutic option to overcome suboptimal oocyte quality as regards the crucial role of mitochondria in achieving optimal oocyte maturity (**Figure 3**).

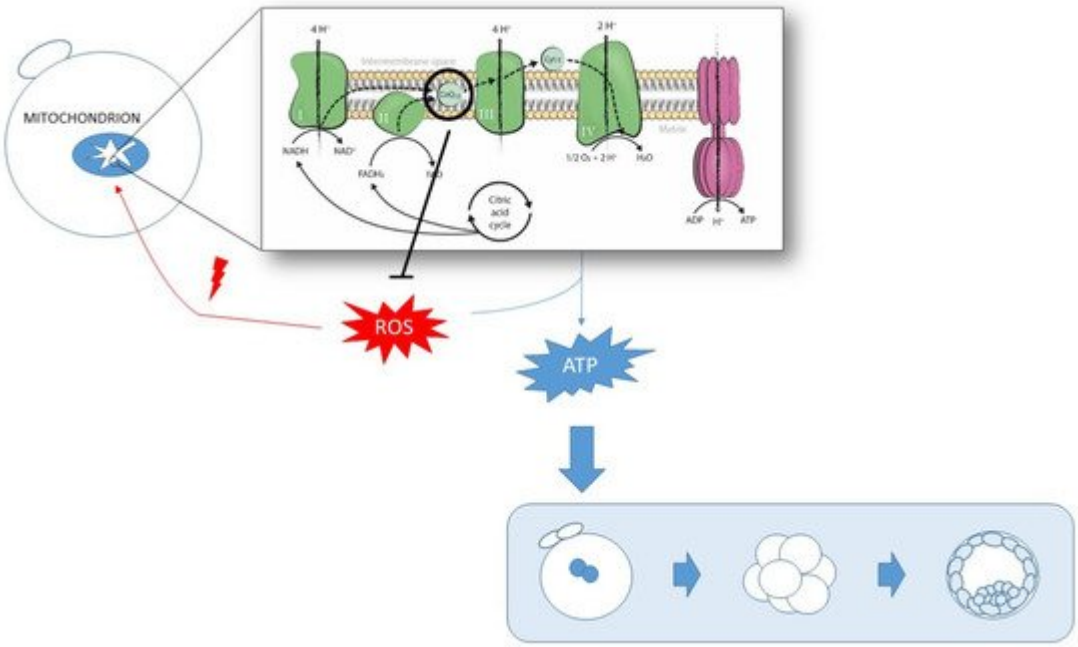

Figure 3. Schematic representation of the role of mitochondria and CoQ10 in acquiring optimal oocyte quality by means of ATP production and ROS counteraction.

This review has been made after an in-depth search in PubMed of all the scientific papers related to this topic. Keywords used for searching the studies were: “human oocyte quality”, “CoQ10”, “antioxidant”, “oxidative stress”, “mitochondrial function”, “pregnancy”, “supplementation”, and “ROS”, among others.

2. CoQ10 Supplementation in IVF Treatments

CoQ10 can be orally supplied prior to any assisted reproduction technique (ART) or as a culture media adjuvant during IVF treatment. Oral treatment attempts to improve oocyte quality in vivo, while culture media supplementation attempts to do so in vitro [2] (**Figure 4**).

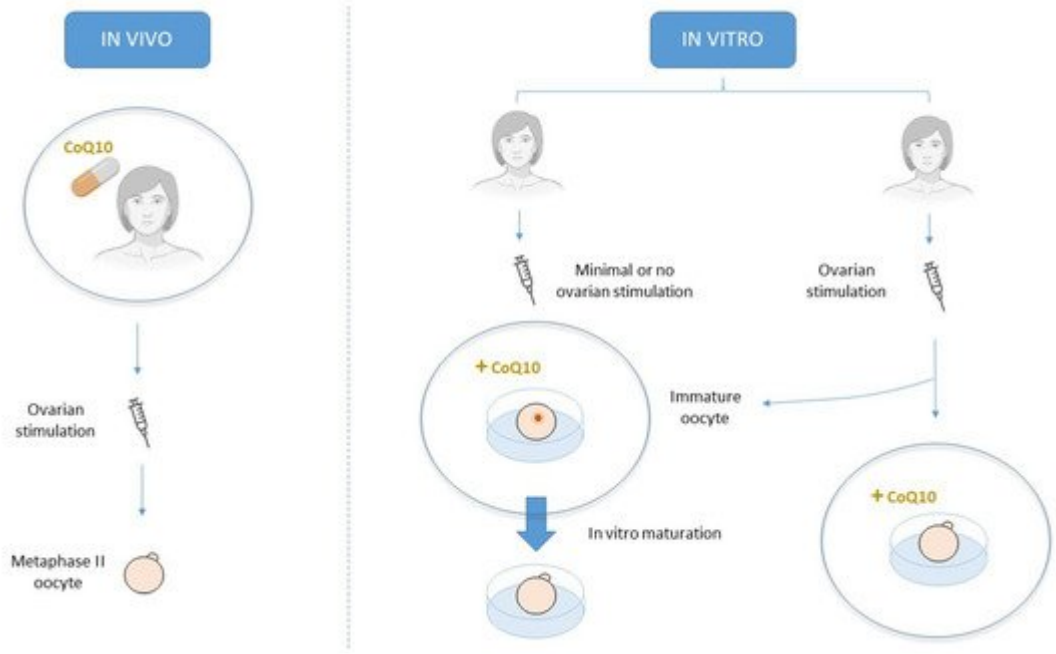

Figure 4. Schematic description of the main three approaches for CoQ10 treatment.

Oral preovulatory CoQ10 treatment exerts positive effects on the ovaries of aged mice. On the one hand, it improves the ovarian reserve, ovarian response, and oocyte quality while taking oocyte mitochondrial parameters back to normal levels of young controls [15]. On the other hand, it increases the number of cumulus cells surrounding the oocyte, as well as their mitochondrial activity, which favors oocyte competence acquisition and subsequent reproductive performance [16]. Furthermore, CoQ10 addition to culture media has successfully reverted the age-induced effects observed in aged oocytes from mice [17] and pigs [18].

Increased oxidative stress damage is not only restricted to the aging process. Along these lines, CoQ10 has also proven to partially revert oxidative stress damage in the oocytes of young mice [19] and other animal models [20][21].

Finally, CoQ10 supplementation has been tested in in vitro maturation (IVM) culture. Maside et al. did not find any benefits in a porcine model [22]; however, Abdulhasan et al. reported higher maturation rates and greater mitochondrial mass and function in immature bovine oocytes after 24 h in IVM medium supplemented with 40 µM of CoQ10 [23]. Moreover, immature mouse oocytes matured in vitro and co-cultured with FF from infertile women with endometriosis demonstrated a trend toward higher maturation rates after CoQ10 supplementation compared to the very low maturity reported in the control group as a result of the endometriotic environment [24].

3. CoQ10 supplementation in human clinical trials

CoQ10 has been shown as a safe and well tolerated antioxidant treatment in humans [1]. Some adverse effects, such as nausea, diarrhea and abdominal pain, have been described after CoQ10 intake in the treatment of other diseases [25][26]. However, they are mild and occasionally-occurring side effects [27].

It is also a versatile therapy because it can be administered following a wide variety of protocols and at different ART treatment time points. Oral CoQ10 may benefit women with poor ovarian reserve, poor response to ovarian stimulation, advanced age or PCOS. What they all have in common are fewer and, usually less competent, mature oocytes [28][29]. However, promising results have been found mostly in follicular terms [30][31][32], and an enhancement at the oocyte level has been achieved only in a population of young poor responders [33]. This finding suggests that the lower age-related CoQ10 levels might be too low to be rescued after this antioxidant treatment. These patients may need higher doses or a different administration protocol, which have not yet been defined.

Regarding the beneficial effects of CoQ10 supplementation at the follicular level, higher levels of this molecule may create a more favorable environment for developing competent follicles. It has been proven that oxidative stress leads to higher apoptotic processes in granulosa cells [34]. CoQ10, by means of counteracting oxidative stress, can reduce this programmed granulosa cell death and, thus, reduce follicular atresia. This is evidenced by the higher antral follicle counts and larger number of mature follicles recorded in some reviewed studies [30][31]. However, this improvement did not suffice to significantly enhance oocyte quality, which has been directly evaluated in only a few studies [35][36][30], but is indirectly evidenced by similar pregnancy outcomes in others [36][30][33]. It is important to bear in mind that, although CoQ10 can have an impact at the follicular level, the ultimate objective of every ART treatment is to achieve successful pregnancy, which means that clear upgrades in pregnancy rates are needed to introduce this treatment into our routine clinical practice. A recent systematic review and meta-analysis of five randomized controlled trials (RCTs) concluded that CoQ10 oral supplementation increased clinical pregnancy rates (CPR) compared to a placebo or no treatment [28.8% vs. 14.1%; odds ratio (OR) 2.44, 95% confidence interval (CI) 1.30–4.59, p = 0.006] [37]. However, these results lose relevance given the high heterogeneity in the analyzed RCTs.

Another approach is to supplement CoQ10 directly *in vitro* during IVF treatment. High levels of this antioxidant come into close contact with the oocyte, although its apparent positive action at the follicular level is absent. In this context, CoQ10 supplementation does not offer any advantage over the standard culture of fertilized oocytes from women of advanced age [38], which seems logical if we consider that these oocytes had already undergone two consecutive meiotic divisions with age-related damaged cell machinery. For this reason, CoQ10 supplementation during the IVM of immature aged oocytes, which are arrested in the prophase of the first meiosis, seems more plausible. Indeed promising results have been shown in this line [39], which suggest that CoQ10 might help these aged oocytes to properly resume meiosis, as evidenced by lower aneuploidy rates. CoQ10 might achieve this by improving the mitochondrial function [40], as evidenced by the increased mitochondrial mass in treated oocytes [41] and, thus, provides the energy they lacked due to the aging process, which is essential for acquiring final maturation. In any case, the improvement was not fully achieved as more age-related factors contribute to this poor oocyte quality [42] and CoQ10 treatment itself may not be enough to overcome them. In contrast, CoQ10 addition during IVM of oocytes from young women did not show any advantage [39], which suggests that these oocytes already had the sufficient energy needed to resume meiosis, and higher CoQ10 levels did not lead to any advantage. Thus other strategies to improve maturation rates in such patients should be investigated.

Nevertheless, MitoQ supplementation during IVM culture showed significant improved oocyte quality regardless of patients' age [43]. We hypothesize that the advantageous location of this targeted molecule and its ability to concentrate at higher rates in mitochondria may favor its mechanism of action and, thus, exert significant changes on young oocytes. MitoQ, or any other mitochondria-targeted antioxidant, supplementation deserves further research in human clinical trials.

In any case, the majority of the studies herein discussed focused on clinical outcomes, and did not evaluate the effects of CoQ10 on the oxidative stress status or at the mitochondrial level in oocytes. Ma *et al*. in 2018 and Al-Zubaidi *et al*. in 2021 were the only ones to analyze such parameters, and proved higher mitochondrial mass and mitochondrial membrane potential, respectively, after CoQ10/MitoQ addition to IVM medium [39][41][43]. However, they did not evaluate oxidative stress markers or any other indicator of oocyte energy status as many animal studies have previously done [15][18][19][23].

Therefore, further research is needed in this field, and should focus mainly on the molecular level to understand the exact mechanism by which CoQ10 enhances mitochondrial function. By solving this research question, we would be able to establish the best protocol, dose, molecular form and approach for its administration. Presently, our recommendation is to continue investigating this antioxidant in the reproductive field, but mostly as oral treatment or during IVM. Its addition to fertilized oocytes during standard culture seems worthless as its main role in improving oocyte competence should be performed prior to completing the second meiosis, and probably even earlier. In addition, more attention should be paid to mitochondria-targeted antioxidants, which have been poorly studied in human clinical trials and seem more efficient than the isolated CoQ10 form.

4. Conclusions

CoQ10 constitutes a safe well tolerated therapy capable of improving oocyte quality through oxidative stress counteraction and mitochondrial function enhancement. In humans, oral CoQ10 supplementation seems to exert positive effects, especially at the follicular level, by creating a more favorable environment for competent follicle development. However, these benefits are not necessarily translated to substantial oocyte improvements and subsequent gestational results. Indeed, no improvement has been reported regarding finally pregnancy outcome using this therapy. CoQ10 addition to culture media appears effective if performed in immature stages. In this scenario, mitochondria-targeted molecules may confer a certain advantage and offer a better prognosis.

Hence, the available data reviewed in this work do not clearly prove the advantage of CoQ10 supplementation in improving human oocyte quality. It seems promising, thus it deserves further research, specially using these modified CoQ10 forms, as well as molecular studies evaluating the impact of this therapy on oxidative stress status and mitochondrial function in human gametes.

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