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Citation for final published version:

Brown, Alexandria M. and McCarthy, Helen E. 2023. The Effect of CoQ10 supplementation on ART treatment and oocyte quality in older women. *Human Fertility* 10.1080/14647273.2023.2194554

Publishers page: <http://dx.doi.org/10.1080/14647273.2023.2194554>

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The Effect of CoQ10 Supplementation on ART treatment and Oocyte quality in older women

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Abstract

A significant problem associated with assisted reproductive technologies (ART) is recurrent treatment failure which can be attributed to the age-associated decline in oocyte quality. Co-enzyme Q10 (CoQ10) is an antioxidant and essential component of the mitochondrial electron transport chain. It is reported that de novo CoQ10 production declines with ageing and coincides with age-related decline in fertility, leading to CoQ10 supplementation being advocated to enhance response to ovarian stimulation and improve oocyte quality. CoQ10 supplementation was found to improve fertilisation rates, embryo maturation rates and embryo quality when used before and during in vitro fertilisation (IVF) and in vitro maturation (IVM) treatment in women aged 31 and over. Regarding oocyte quality, CoQ10 was able to reduce high rates of chromosomal abnormalities and oocyte fragmentation, as well as improve mitochondrial function. Proposed mechanisms of CoQ10 function include restoration of reactive oxygen species imbalance, preventing DNA damage and oocyte apoptosis, as well as restoration of Krebs cycle downregulation from ageing. In this literature review we provide an overview of the use of CoQ10 in improving the success of IVF and IVM in older women, and additionally assess the impact of CoQ10 on oocyte quality and discuss potential mechanisms of action by CoQ10 on the oocyte.

Keywords: co-enzyme q10; infertility; ageing; oocyte quality; ivf; ivm

Introduction

An increasing number of women are choosing to delay childbirth until their late 30's or early 40's, particularly in Western societies. This is partially attributable to greater availability of contraceptive options, increased education and employment opportunities, and fewer social incentives for parenthood (Tan et al., 2014; Ubaldi et al., 2019). It is well known that fecundability declines significantly from a woman's early thirties; between the ages of 35 to 39 a third of women have difficulty conceiving (Tan et al., 2014), and after the age of 40 only 16 out 1000 pregnancies result in live births

(Synowiec, 2020).

Several mechanisms are postulated to be responsible for the loss of fertility as women age. Decreased ovarian reserves, lower embryo implantation rates, altered hormonal environments, uterine pathology and poor oocyte quality have all been implicated with age-related fertility loss. Related to oocyte quality with advancing age there are increased incidences of aneuploidies and oocyte fragmentation, as well as decreased mitochondrial activity. Fragmented oocytes lose their developmental potential (Miao et al., 2009), while mitochondrial dysfunction could lead to both oxidative stress and a reduction in ATP synthesis, directly contributing to impairments in meiotic spindle assembly, cell cycle regulation, chromosome segregation, embryo development and implantation (Cimadomo et al., 2018; Hoshino, 2018; Tan et al., 2014; Xu et al., 2018). With the postponement of pregnancy, more couples are now choosing to utilise assisted reproductive technologies (ART), such as in-vitro fertilisation (IVF) and in vitro maturation (IVM), to counteract the age-related decline in fertility (Cimadomo et al., 2018; Tan et al., 2014). However, a significant clinical problem associated with IVF and IVM is recurrent treatment failure, whereby several complete embryo transfer cycles do not result in a live birth. Success is dependent on both the development of the embryo and endometrium, with abnormalities of either potentially resulting in recurrent treatment failure (Tan et al., 2005). Whilst many women choose to undergo ART to counteract age related fertility issues, the highest levels of success with treatment are still seen in women aged 25 to 30, confirming that advancing age is detrimental to success. Previous studies have suggested that poor ART outcome in women over the age of 40 is due to fewer and poorer quality oocytes available for collection; this results in lower fertilisation rates, culminating in fewer treatment cycles reaching the embryo transfer stage for implantation (Tan et al., 2014).

A nutraceutical is any consumable product that provides medical or health benefits, yet there is no internationally accepted definition of these unregulated products and their consumption can represent a risk as they are often administered without medical guidance (T'elessy, 2018). CoQ10, commonly found as a nutraceutical in its oxidised form as ubiquinone, or its reduced form as ubiquinol, is an essential compound found in virtually every cell of the human body (Garrido-Maraver et al., 2014). More recently explored, mitoquinone (MitoQ) is a ubiquinone moiety bound to a lipophilic triphenylphosphonium cation, causing preferential accumulation in the mitochondria at 100-500-fold that of CoQ10 (Al-Zabaidi et al., 2021; Marei et al., 2019). CoQ10 is a lipid-soluble structure, with a primary role as an intermediate of the electron transport system in mitochondria. It is required for oxidative phosphorylation and thus ATP production. Numerous disorders are associated with CoQ10 deficiency, such as male and female infertility. Decreased CoQ10 levels are common in individuals in their late 30's and appear to co-occur with the age-related fertility decline, suggesting a possible causal effect of reduced CoQ10 expression on ovarian ageing. Subsequently, many believe CoQ10 supplementation to be beneficial in those struggling to conceive (Garrido-Maraver et al., 2014; Xu et al., 2018; Y. Zhang et al., 2018). This review aims to evaluate the literature on the use of CoQ10 in improving the success of IVF and IVM in older women, both as an oral supplement and within maturation media, and to assess the impact of CoQ10 on oocyte quality.

Methods

Search Strategy

Searches of databases were conducted in May 2021. Databases searched included PubMed, Scopus and Web of Science in combination, as this allowed the greatest

coverage of content while minimising the number of repeated articles. Search terms included were variations of the term 'CoQ10' (including CoQ10, ubiquinol, ubiquinone, Co-enzyme Q10, mitoquinone and MitoQ) in combination with 'reproduction', 'infertility' and 'fertilisation'. Boolean logic was used, with 'OR' allowing for the many variations in terms for CoQ10, and 'AND' limiting searches to publications mentioning both key terms. Exclusion criteria were applied to remove reviews and book chapters.

Study selection

The initial list of publications was exported to Endnote where any duplicates were removed. Additionally, the decision was made to remove any studies older than 2010, as it was felt this would generate the most up-to-date knowledge. Studies of any design were included on the condition that they investigated the use of CoQ10 as a supplement to improve oocyte quality in older women to improve fertility. Conversely, studies referring to the use of CoQ10 in addressing other causes of infertility (such as PCOS or fibroids), men or young women were not included.

Data Extraction

Titles and abstracts were screened for potentially eligibility, generating a list of 16 publications which were critically analysed. A final shortlist of 6 publications was generated that were felt to be most relevant to the aims of the present study. The selection process of this review was documented with a PRISMA flow chart (Figure 1).

Results

Co-enzyme Q10 and IVF and IVM success

Supplementation of Co-enzyme Q10 during IVF in humans

A double-blind, placebo-controlled, randomised trial was conducted by Bentov et al. (2014) on 39 women aged 35-43 undergoing IVF treatment, to investigate the effects of CoQ10 on oocyte aneuploidy and IVF success. The cohort supplemented with 600 mg CoQ10 daily for 2 months before and during IVF treatment (n=10) resulted in a greater percentage of top-quality embryos at both 48 hours (81.4% vs 66.0%) and 72 hours (64.7% vs 42%) post-retrieval, a lower rate of chromosomal aneuploidy (46.5% vs 62.8%) and a higher clinical pregnancy rate (33.3% vs 26.7%). However, limited sample size reduced the power of the trial, and thus none of the above results reached statistical significance. The decision was made to terminate the study prior the enrolment of target number of participants following evidence that polar body biopsy negatively impacted embryo quality by increasing rate of embryo fragmentation (Levin et al., 2012).

Giannubilo et al. (2018) similarly investigated the effects of CoQ10 on IVF treatment for women aged 31-46 years, focusing on the bioavailability of CoQ10 in the follicular fluid and subsequent consequences for the oocyte. The CoQ10 content of follicular fluid in those supplemented with 200mg CoQ10 for 30 days was higher than in control samples, demonstrating that oral supplementation results in CoQ10 bioavailability in follicular fluid. As high CoQ10 content in follicular fluid is associated with higher pregnancy rates and optimal embryo quality (Akarsu et al., 2017), it indicates the potential of CoQ10 as an oral supplement. Additionally, CoQ10 supplementation resulted in higher fertilisation rates in mature subjects compared to controls (88% vs 74%), and higher rates of Class I embryos (82% vs 60%), and no low-grade embryos which accounted for 15% of embryos in the untreated group.

Exogenous treatment of Co-enzyme Q10 during IVM in humans

Ma et al. (2020) conducted clinical laboratory observations on IVF patients to determine post-meiotic aneuploidy rates and oocyte maturation rates of metaphase II oocytes during IVM. For women aged 38 years and older, rates of oocyte maturation were significantly higher when cultured with 50 μ mol/L CoQ10 than that of the control group (82.6% vs 63.0%, $p=0.035$). CoQ10 also significantly reduced the post-meiotic aneuploidy rate from 65.5% to 36.8% ($p=0.020$). In women aged less than 30 years, oocyte maturation rates were similar in the control and treated group (76.9% vs 80%), as were the oocyte aneuploidy rates (30% vs 28.6%). This study demonstrated for the first time that supplementation of human oocyte culture media with CoQ10 resulted in significantly increased maturation rates and decreased aneuploidy rates in older women.

Al-Zubaidi et al. (2021) investigated oocyte maturation rates in 89 germinal-vesicle stage human oocytes collected from patients aged 36.0 ± 4.8 years in the control group and 35.7 ± 4.4 years in the group with oocytes matured with 50 nM MitoQ. Following IVM for 30 hours, 51% of oocytes extruded a first polar body (as a marker of oocyte maturation), while in the MitoQ treated group this rate of maturation was greatly improved to 77% of oocytes. Additionally, the percentage of oocytes with misaligned chromosomes was calculated in each group via laser scanning confocal microscopy and fluorescence staining. MitoQ treatment significantly decreased the percentage of oocytes with misaligned chromosomes compared to control groups (25% vs 61%).

Exogenous treatment of Co-enzyme Q10 during IVM in mice

M. Zhang et al. (2019) similarly investigated the effects of CoQ10 as a media supplement during IVM of artificially aged metaphase II mouse oocytes. While most young oocytes could be fertilised, aged oocytes had a significantly lower fertilisation rate (88.1 vs 42.3%, $p<0.001$). With supplementation of 50 μ m of CoQ10, the rate of

fertilisation was significantly increased to 52.2% ($p < 0.05$), which indicates the potential of CoQ10 in improving fertilisation rates.

Co-enzyme Q10 and oocyte quality in aged individuals

Effect of Co-enzyme Q10 on chromosomes

A normal spindle assembly with aligned chromosomes is regarded as a key marker of high-quality oocytes. M. Zhang et al. (2019) performed immunofluorescence staining on artificially aged mouse oocytes and young controls, finding that young control oocytes in metaphase II, displayed a typical barrel-shaped spindle apparatus along with well-aligned chromosomes. In contrast, aged oocytes displayed an increased frequency of disorganised spindle morphologies and misaligned chromosomes. However, in vitro supplementation with 50 μ m CoQ10 significantly reduced abnormalities compared to aged controls (35.3 vs 10.5%, $p < 0.01$), demonstrating the potential of CoQ10 to improve oocyte quality. These findings were further supported by human studies by Ben-Meir et al. (2015), Bentov et al. (2014) and Ma et al. (2020) evaluating aneuploidy rates.

Additionally, Ma et al. (2020) observed that the majority of aneuploidies (86.9%) observed were trisomies and monosomies, occurring from the premature separation of sister chromatids, which is believed to be the origin of the age-related increases in aneuploidies. Premature separation of chromatids is believed to be attributed to the dysfunction of cohesion complex and shugoshins, which maintain sister chromatid cohesion during meiosis. Both these nuclear proteins have been shown to lose function after prolonged exposure to reactive oxygen species (ROS) (Handyside et al., 2012), which are known to increase with ageing, as demonstrated by M. Zhang et al. (2019) and later discussed.

Effect of Co-enzyme Q10 on oocyte fragmentation

It is documented that oocytes exhibiting fragmentation are both less likely to fertilise and less likely to develop into competent embryos (Rose & Laky, 2013), demonstrating its proficiency as a marker of oocyte quality. M. Zhang et al. (2019) evaluated oocyte morphology and fragmentation rates in mice and found a large majority of young control oocytes were morphologically normal and developed to metaphase II with a first polar body and relatively low rates of fragmentation. In the aged group, a significantly higher frequency of fragmented oocytes were present (6.2% vs 48.9%, $p < 0.001$), however, the addition of 50 μ M CoQ10 significantly reduced the fragmentation rate (48.9% vs 25.3%, $p < 0.05$).

The impact of Co-enzyme Q10 on mitochondrial quality and function

Mitochondrial dysfunction is frequently implicated in oocyte ageing, as well as directly contributing to oocyte competency. Ben-Meir et al. (2015) investigated oocyte mitochondrial function in mice using 9-month-old, retired breeding dams as an aged model paired with 7-week-old male studs of proven fertility. Not only was the pool of respiring mitochondria found to be decreased in aged oocytes, but mitochondrial membrane potential was also abnormally elevated. Supplementation of 22 mg kg⁻¹ CoQ10 three times a week for 12 weeks was able to rescue the number of respiring mitochondria to that of young controls (7-week-old virgin dams), as well as restore membrane potential.

Supporting these findings, M. Zhang et al. (2019) examined mitochondria and their distribution patterns. In young murine controls, mitochondria were seen to have two patterns of distribution; polarised distribution accumulated peripherally around

chromosomes and homogenous distribution in the cytoplasm. Aged murine models exhibited a dramatically increased proportion of mitochondria abnormally distributed in clusters in the cytoplasm, with more than 40% of oocytes displaying this pattern. Supplementation with 50 μ M CoQ10 in vitro was able to dramatically decrease this abnormal patterning to only 25% of oocytes, suggesting that CoQ10 could improve impaired mitochondrial dynamics.

Mitochondrial membrane potential (MMP) is an important marker of mitochondrial quality because alongside the proton gradient, it forms the transmembrane potential of hydrogen ions which is used to generate ATP (Zorova et al., 2018). M. Zhang et al. (2019) demonstrated with MMP staining that the ratio of high to low membrane potential was significantly lower in aged oocytes than young oocytes but was rescued when treated with CoQ10. Al-Zubaidi et al. (2021) additionally compared MMP between 1 month old pre-pubertal mice and 18-month-old mice as an aged model. It was observed that there was a significant decrease in MMP at 18 months. In the presence of 50 nM MitoQ during IVM, MMP was significantly increased in both the young and old mouse oocytes when compared to controls

Furthermore, both M. Zhang et al. (2019) and Ben-Meir et al. (2015) explored the expression of genes involved in mitochondrial metabolism that decreased with advancing age. Expression of both *Sdha* (a gene encoding a subunit of mitochondrial complex II, which is a key respiratory enzyme linking the Krebs cycle and electron transport chain (Gill, 2012)) and *Ndof3* (a gene encoding an assembly factor of mitochondrial complex I which is associated with ubiquinone reduction (Baertling et al., 2017)) was significantly decreased in the aged group but increased in the CoQ10 treated group. Contrastingly, CoQ10 had no significant impact on the expression of genes

involved in chromatin organisation or transcription, suggesting that supplementation of CoQ10 primarily has an impact on mitochondria.

Mechanisms of CoQ10 in an aged oocyte

Co-enzyme Q10 as a defence against oxidative stress

Oxidative stress and DNA damage occur when there is an imbalance between the production of ROS, such as superoxide, and antioxidant defences. Furthermore, increases in DNA damage and oxidative stress contribute to oocyte apoptosis, which in turn leads to the deterioration and degradation of regulators of oocyte maturation and fertilisation (Mailloux et al., 2013; M. Zhang et al., 2019). M. Zhang et al. (2019) found that superoxide levels measured by Dihydroethidium (DHE) staining were upregulated in aged murine oocytes compared to young controls, however, levels could be significantly reduced with 50µM of CoQ10 added to the culture media. Furthermore, M. Zhang et al. (2019) quantified DNA damage by measuring the fluorescence intensity of γH2AX signals, which are produced as a result of an early cellular response to DNA double-strand breaks (Mah et al., 2010). Damage was found to be significantly increased in aged models compared to young controls, but the addition of CoQ10 was able to significantly reduce DNA damage.

Finally, M. Zhang et al. (2019) evaluated the rate of apoptosis via AnnexinV staining. The rate was found to be dramatically higher in aged murine oocytes compared to young controls (23.6 vs 2.7%, $p < 0.01$), but this rate was decreased by CoQ10 supplementation (11.9%, $p < 0.05$) in aged models.

Effect of Co-enzyme Q10 on ATP production and the Krebs Cycle

During completion of meiosis I, ATP demands are dramatically increased (Dalton et al. 2014), however, ATP output by mitochondria dramatically decreases with ageing (Ben-Meir et al., 2015; Niu et al., 2020), preventing completion of meiotic stages, leading to impaired mature oocytes. Ben-Meir et al. (2015) and M. Zhang et al. (2019) confirmed that supplementation with CoQ10 prevented the age-induced reduction in ATP levels. Consistent with the outcomes of ATP findings, Ben-Meir et al. (2015) additionally found that metabolites of the Krebs cycle, including citrate, malate and fumarate, were reduced with ageing, and could be elevated back to levels seen in young controls with CoQ10 supplementation.

Discussion

The use of CoQ10 in improving the success of IVF and IVM treatment

The literature indicates that both exogenous treatment and oral supplementation of CoQ10 may benefit older women undergoing IVF. Whilst all studies reviewed here evaluated varying parameters to determine the benefit of CoQ10, in all cases CoQ10 was shown to improve fertilisation or maturation defects caused by ageing, which could potentially improve pregnancy rates and IVF treatment success. Bentov et al. (2014) was the only study to evaluate pregnancy rates when CoQ10 was administered orally and established that they improved; however, no statistical significance could be determined due to the limited sample size. Whilst initial studies are promising in favour of improved pregnancy rates and IVF success until findings detailing statistically significant improved pregnancy rates and live birth rates are completed, it cannot be determined that CoQ10 improves IVF outcome.

A key difference identified between each study used in the literature analysis was the lack of consistency with the dosage of CoQ10 administered. While Bentov et al. (2014) saw an increase in the number of top-quality embryos with a 600mg supplementation, Giannubilo et al. (2018) saw a similar improvement in embryo quality with a supplementation of only 200mg. Additionally, a study by Maside et al. (2019) which used a young pig model found that all dosages of treatment (0, 10, 25, 500 and 100 μ M of CoQ10) resulted in no difference in fertilisation rate, and furthermore, 100 μ M significantly reduced blastocyst production. Thus, the study concluded that too high a concentration of CoQ10 may be detrimental. The efficacy of different dosages needs to be confirmed in human models, in order to establish the optimum dose to see benefits from CoQ10 administration and establish it as a supplementary aid during IVF treatment.

The impact of CoQ10 on oocyte quality

In terms of oocyte quality, CoQ10 was able to ameliorate the effects of ageing to improve chromosomal appearance, reduce chromosomal aneuploidy rates and reduce oocyte fragmentation rates. Additionally, CoQ10 was noted to improve mitochondrial quality, which can be implicated in oocyte quality and competency. Thus, results are promising in support of CoQ10 as a nutraceutical to improve oocyte quality in aged individuals.

However, all studies identified and discussed in this review assessing the impact of CoQ10 on oocyte quality used animal models, predominantly mouse models. While the murine system is widely used as a model for embryogenesis and IVF, several differences exist between species that may implicate the mouse as a poor model (Neuber & Powers, 2000). Physiological processes, such as embryogenesis, are

accelerated, taking only a few weeks in mice, but several months in humans.

Additionally, it has also been noted through phylogenetic analysis of proteins involved in fertilisation that human oocytes are more closely related to bovine oocytes than they are to mouse oocytes (Ménézo & Hérubel, 2002; Santos et al., 2014). These key differences cause difficulties in applying murine model findings to humans.

Furthermore, the life span of mice is considerably shorter than that of humans, therefore in studies such as Ben-Meir et al. (2015) when CoQ10 was administered over a period of 12 weeks, this would account for around 1/16th of a mouse's life (Perlman, 2016), whereas in humans this would account for far less. Hence, it is difficult to extrapolate findings as the relative time over which CoQ10 is administered is so different.

Mechanisms of CoQ10 in the oocyte

The main findings regarding mechanisms by which CoQ10 may operate are highlighted in Figure 2 below. One of the main factors contributing to loss of oocyte quality with ageing, is believed to be ROS production and oxidative imbalance, however this theory has been subject to scrutiny. While the theory implies that increased antioxidant levels would be able to reduce oxidative stress and age-related defects, an increasing number of studies have found that altering antioxidant levels may have detrimental effects. Mockett et al. (2010) found that in some cases antioxidant proteins were capable of extending lifespan, while in others their overexpression provided no benefit. Additionally, Van Raamsdonk & Hekimi (2009) found that increased antioxidant production may even shorten lifespan, while decreased antioxidant function may extend it.

Furthermore, while it is believed to be beneficial that MitoQ availability is 100-500-fold that of CoQ10, some studies have reported detrimental effects. A study by

Pokrzywinski et al. (2016) reported that MitoQ can increase ROS production in some cancer cells, which is associated with a decrease in MMP. Furthermore, Sun et al. (2017) noted that MitoQ was able to induce autophagy in liver cells. As MitoQ accumulates in mitochondria at high levels, it is possible that it has other effects on mitochondrial function, not just ROS production.

Additionally, while the present review discusses how CoQ10 could be correcting the primary dysfunction caused by ageing, it is documented that low success rates for older ART patients may be due to oocytes and subsequently formed embryos being more sensitive and less capable of tolerating standard IVF procedures, exposure to light and handling, fluctuation in pH and osmolarity (Marei & Leroy, 2022). The addition of CoQ10 may therefore instead be preventing these secondary effects during IVM and IVF, which may be a potential area for future exploration.

In conclusion, whilst all findings from this review hold promise for the future use of CoQ10 as a supplement to improve oocyte quality and IVF and IVM success, the data at present is lacking due to limited human studies and lack of significant outcomes regarding improvements in pregnancy rate or live birth rate.

Declaration of interest statement

The authors report there are no competing interests to declare.

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Figures

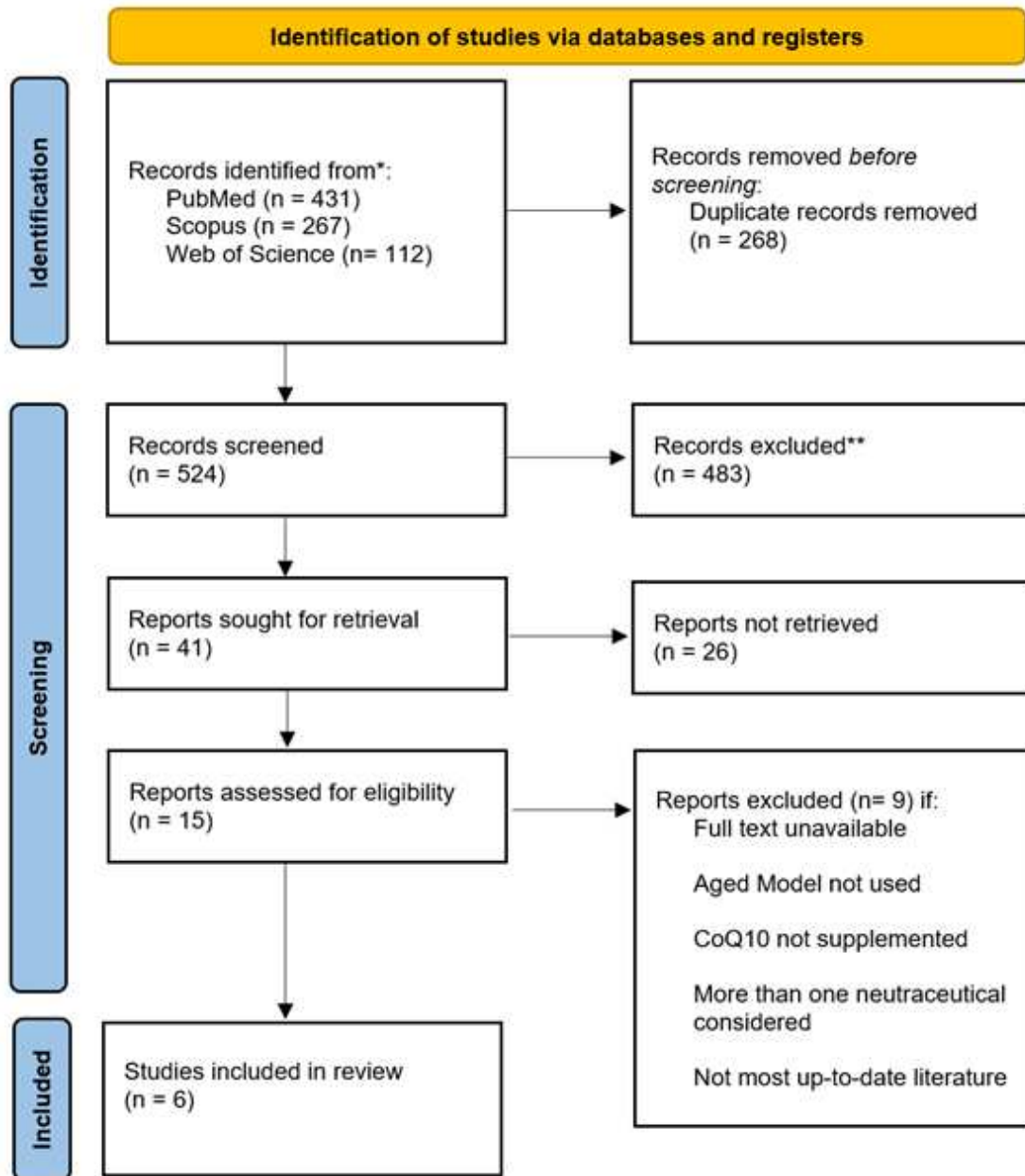


Figure 1

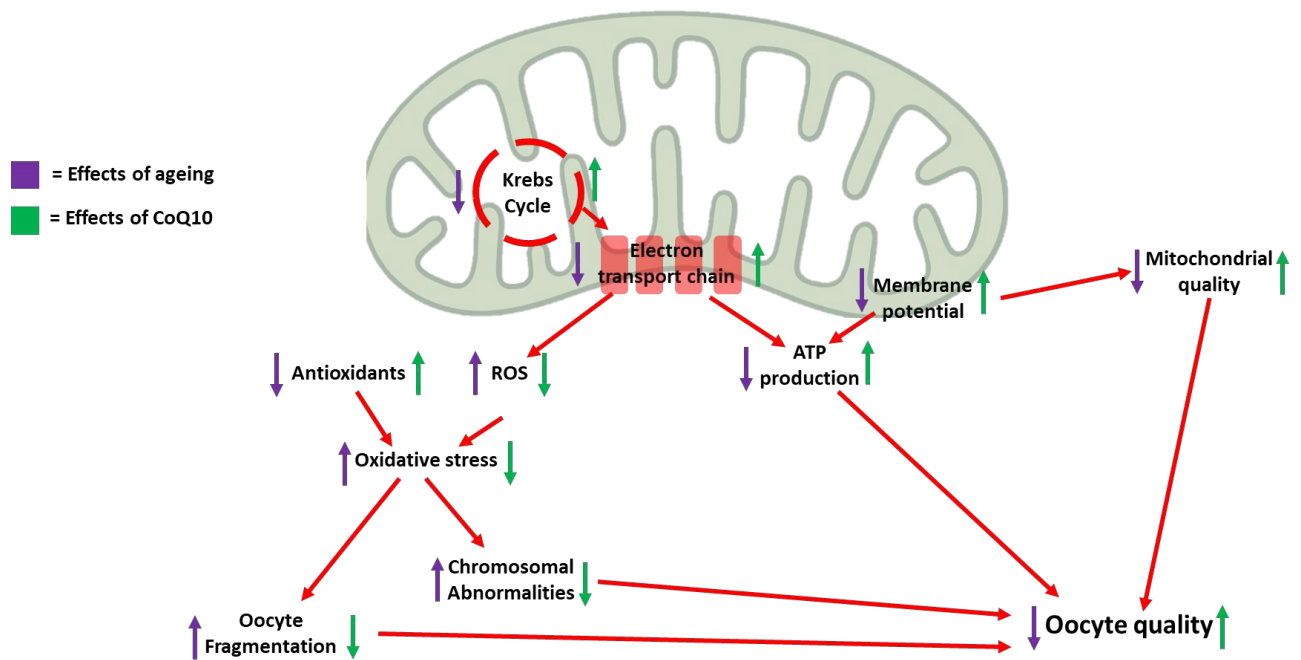


Figure 2

Figure captions

- Figure 1: PRISMA outlining the process of data collection and the number of records at each stage
- Figure 2: The suggested mechanisms by which CoQ10 ameliorates the effects of oocyte ageing. Purple arrows indicate effects of ageing, while green arrows indicate effects of CoQ10. The direction of the arrow indicates whether the element is downregulated or upregulated. CoQ10 is able to restore Krebs cycle metabolites to their original levels, which in turn boosts ATP production. Additionally, CoQ10 administration restores mitochondrial membrane potential, which both aids in ATP production and improves mitochondrial quality, leading to improved oocyte quality. The oxidative imbalance caused by overproduction of ROS species and under-production of antioxidants is restored, leading to decreased oxidative stress and subsequent improvement of oocyte fragmentation and chromosomal abnormalities leading to an improvement in oocyte quality

