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.

Keywords: 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].

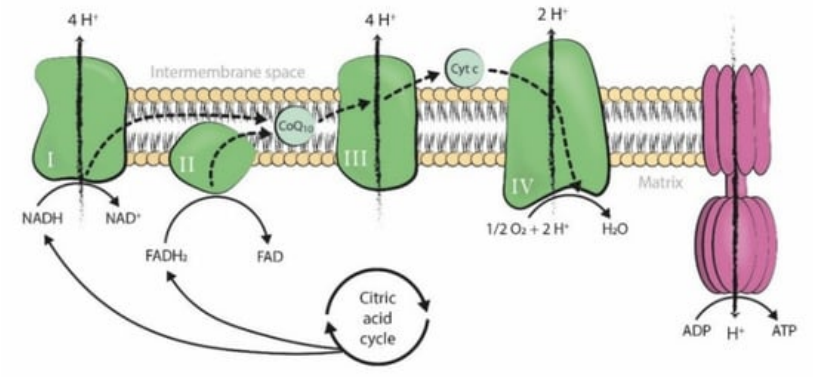

Figure 1. Mitochondrial respiratory chain (Complexes I, II, III, and IV; CoQ10, and cytochrome c) and the F1-F0 ATPase in the inner mitochondrial membrane. The movement of electrons throughout the mitochondrial respiratory chain is coupled with the transfer of protons across the membrane to the intermembrane 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.

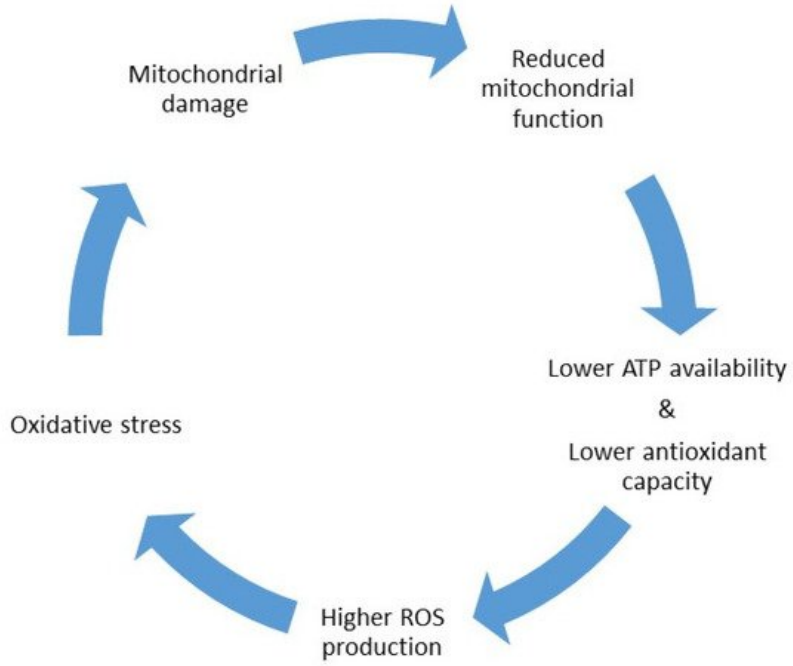

Figure 2. Vicious cycle between mitochondrial dysfunction and oxidative stress damage.

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**).

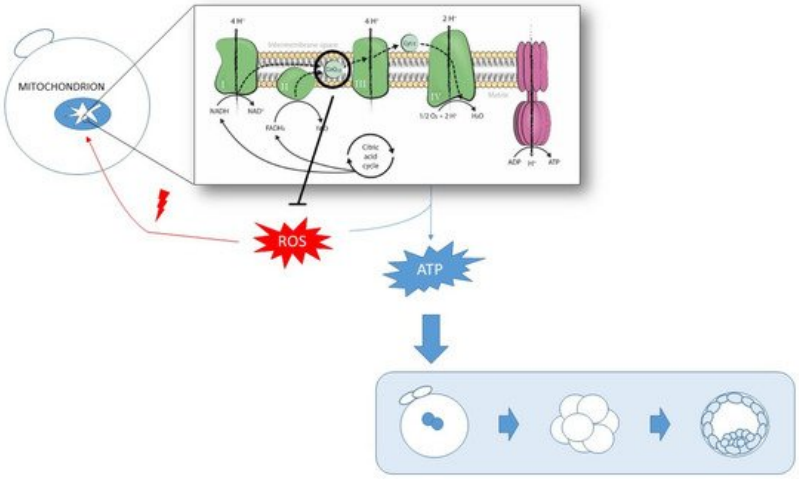

Figure 3. Schematic representation of the role of mitochondria and CoQ10 in acquiring optimal oocyte quality by means of ATP production and ROS counteraction.

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**).

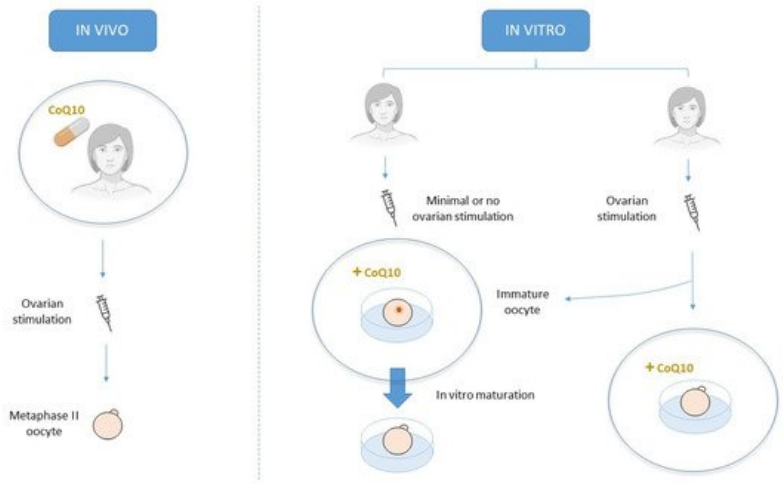

Figure 4. Schematic description of the main three approaches for CoQ10 treatment.

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.

References

1. Isabella Peixoto De Barcelos; Richard H. Haas; CoQ10 and Aging. *Biology* **2019**, *8*, 28, 10.3390/biology8020028.
2. Cristina Rodríguez-Varela; Elena Labarta; Clinical Application of Antioxidants to Improve Human Oocyte Mitochondrial Function: A Review. *Antioxidants* **2020**, *9*, 1197, 10.3390/antiox9121197.
3. UyenPhuong C. Tran; Catherine F. Clarke; Endogenous synthesis of coenzyme Q in eukaryotes. *Mitochondrion* **2007**, *7*, S62-S71, 10.1016/j.mito.2007.03.007.
4. Leo Marcoff; Paul D. Thompson; The Role of Coenzyme Q10 in Statin-Associated Myopathy: A Systematic Review. *Journal of the American College of Cardiology* **2007**, *49*, 2231-2237, 10.1016/j.jacc.2007.02.049.
5. Catarina M. Quinzii; Michio Hirano; Coenzyme Q and mitochondrial disease. *Developmental Disabilities Research Reviews* **2010**, *16*, 183-188, 10.1002/ddrr.108.
6. Serena Bianchi; Guido Macchiarelli; Giulietta Micara; Cesare Aragona; Marta Maione; Stefania Annarita Nottola; Ultrastructural and morphometric evaluation of aged cumulus-oocyte-complexes. *IJAE* **2014**, *118*, 28, 10.13128/ijae-13929.
7. Hiroyuki Sasaki; Toshio Hamatani; Shintaro Kamijo; Maki Iwai; Masato Kobanawa; Seiji Ogawa; Kenji Miyado; Mamoru Tanaka; Impact of Oxidative Stress on Age-Associated Decline in Oocyte Developmental Competence. *Frontiers in Endocrinology* **2019**, *10*, 811, 10.3389/fendo.2019.00811.
8. Li-Ya Wang; Da-Hui Wang; Xiang-Yang Zou; Chen-Ming Xu; Mitochondrial functions on oocytes and preimplantation embryos. *Journal of Zhejiang University SCIENCE B* **2009**, *10*, 483-492, 10.1631/jzus.b0820379.
9. Serena Bianchi; Stefania Annarita Nottola; Diana Torge; Maria Grazia Palmerini; Stefano Necozione; Guido Macchiarelli; Association between Female Reproductive Health and Mancozeb: Systematic Review of Experimental Models. *International Journal of Environmental Research and Public Health* **2020**, *17*, 2580, 10.3390/ijerph17072580.
10. Cai-Xia Yang; Zhi-Qiang Song; Su-Rui Pei; Xiao-Xia Yu; Jia-Kun Miao; Hao Liang; Yi-Liang Miao; Zhi-Qiang Du; Single cell RNA-seq reveals molecular pathways altered by 7, 12-dimethylbenz[a]anthracene treatment on pig oocytes. *Theriogenology* **2020**, *157*, 449-457, 10.1016/j.theriogenology.2020.08.020.
11. Alberto Revelli; Luisa Delle Piane; Simona Casano; Emanuela Molinari; Marco Massobrio; Paolo Rinaudo; Follicular fluid content and oocyte quality: from single biochemical markers to metabolomics. *Reproductive Biology and Endocrinology* **2009**, *7*, 40-40, 10.1186/1477-7827-7-40.
12. Angelo Turi; Stefano Raffaele Giannubilo; Francesca Brugè; Federica Principi; Silvia Battistoni; Fabrizia Santoni; Andrea Luigi Tranquilli; Gianpaolo Littarru; Luca Tiano; Coenzyme Q10 content in follicular fluid and its relationship with oocyte fertilization and embryo grading. *Archives of Gynecology and Obstetrics* **2011**, *285*, 1173-1176, 10.1007/s00404-011-2169-2.

13. Süleyman Akarsu; Funda Gode; Ahmet Zeki Isik; Zeliha Günnur Dikmen; Mustafa Agah Tekindal; The association between coenzyme Q10 concentrations in follicular fluid with embryo morphokinetics and pregnancy rate in assisted reproductive techniques. *Journal of In Vitro Fertilization and Embryo Transfer* **2017**, *34*, 599-605, 10.1007/s10815-017-0882-x.

14. Juan D. Hernández-Camacho; Michel Bernier; Guillermo López-Lluch; Plácido Navas; Coenzyme Q10 Supplementation in Aging and Disease. *Frontiers in Physiology* **2018**, *9*, 44, 10.3389/fphys.2018.00044.

15. Assaf Ben-Meir; Elizabeth Burstein; Aluet Borrego-Alvarez; Jasmine Chong; Ellen Wong; Tetyana Yavorska; Taline Naranian; Maggie Chi; Ying Wang; Yaakov Bentov; et al. Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. *Aging Cell* **2015**, *14*, 887-895, 10.1111/acel.12368.

16. Assaf Ben-Meir; Kyunga Kim; Rosanne McQuaid; Navid Esfandiari; Yaakov Bentov; Robert F. Casper; Andrea Jurisicova; Co-Enzyme Q10 Supplementation Rescues Cumulus Cells Dysfunction in a Maternal Aging Model. *Antioxidants* **2019**, *8*, 58, 10.3390/antiox8030058.

17. Mianqun Zhang; Xiayan ShiYang; Yuwei Zhang; Yilong Miao; Ying Chen; Zhaokang Cui; Bo Xiong; Coenzyme Q10 ameliorates the quality of postovulatory aged oocytes by suppressing DNA damage and apoptosis. *Free Radical Biology and Medicine* **2019**, *143*, 84-94, 10.1016/j.freeradbiomed.2019.08.002.

18. Ying-Jie Niu; Wenjun Zhou; Zheng-Wen Nie; Dongjie Zhou; Yong-Nan Xu; Sun A. Ock; Chang-Guo Yan; Xiang-Shun Cui; Ubiquinol-10 delays postovulatory oocyte aging by improving mitochondrial renewal in pigs. *Aging* **2020**, *12*, 1256-1271, 10.18632/aging.102681.

19. C.E. Boots; A. Boudoures; W. Zhang; A. Drury; K.H. Moley; Obesity-induced oocyte mitochondrial defects are partially prevented and rescued by supplementation with co-enzyme Q10 in a mouse model. *Human Reproduction* **2016**, *31*, 2090-2097, 10.1093/humrep/dew181.

20. Pınar Özcan; Cem Fıçıcıoğlu; Ozge Kizilkale; Mert Yesiladali; Olgu Enis Tok; Ferda Ozkan; Mukaddes Esrefoglu; Can Coenzyme Q10 supplementation protect the ovarian reserve against oxidative damage?. *Journal of Assisted Reproduction and Genetics* **2016**, *33*, 1223-1230, 10.1007/s10815-016-0751-z.

21. Maria Fernanda Hornos Carneiro; Nara Shin; Rajendiran Karthikraj; Fernando Barbosa; Kurunthachalam Kannan; Monica P. Colaiácovo; Antioxidant CoQ10 Restores Fertility by Rescuing Bisphenol A-Induced Oxidative DNA Damage in the Caenorhabditis elegans Germline. *Genetics* **2020**, *214*, 381-395, 10.1534/genetics.119.302939.

22. Carolina Maside; Cristina A Martinez; Josep M. Cambra; Xiomara Lucas; Emilio A. Martinez; María Antonia Gil; Heriberto Rodriguez-Martinez; Inmaculada Parrilla; Cristina Cuello; Supplementation with exogenous coenzyme Q10 to media for in vitro maturation and embryo culture fails to promote the developmental competence of porcine embryos. *Reproduction in Domestic Animals* **2019**, *54*, 72-77, 10.1111/rda.13486.

23. M. K. Abdulhasan; Q. Li; J. Dai; H. M. Abu-Soud; E. E. Puscheck; D. A. Rappolee; CoQ10 increases mitochondrial mass and polarization, ATP and Oct4 potency levels, and bovine oocyte MII during IVM while decreasing AMPK activity and oocyte death. *Journal of In Vitro Fertilization and Embryo Transfer* **2017**, *34*, 1595-1607, 10.1007/s10815-017-1027-y.

24. Sergio Romero; Ricardo Pella; Ingrid Zorrilla; Paola Berrío; Francisco Escudero; Ygor Pérez; Mario García; Carla Gonzalez; Patricia Orihuela; Coenzyme Q10 improves the in vitro maturation of oocytes exposed to the intrafollicular environment of patients on fertility treatment. *JBRA Assisted Reproduction* **2020**, *24*, 283-288, 10.5935/1518-0557.20200003.

25. Catherine K. Yeung; Frederic T. Billings IV; Adam J. Claessens; Baback Roshanravan; Lori Linke; Mary B. Sundell; Suhail Ahmad; Baohai Shao; Danny D. Shen; T. Alp Ikizler; et al. Coenzyme Q10 dose-escalation study in hemodialysis patients: safety, tolerability, and effect on oxidative stress. *BMC Nephrology* **2015**, *16*, 1-8, 10.1186/s12882-015-0178-2.

26. Serena L Orr; Sunita Venkateswaran; Nutraceuticals in the prophylaxis of pediatric migraine: Evidence-based review and recommendations. *Cephalalgia* **2014**, *34*, 568-583, 10.1177/0333102413519512.

27. Gaku Yamanaka; Kanako Kanou; Tomoko Takamatsu; Mika Takeshita; Shinichiro Morichi; Shinji Suzuki; Yu Ishida; Yusuke Watanabe; Soken Go; Shingo Oana; et al. Complementary and Integrative Medicines as Prophylactic Agents for Pediatric Migraine: A Narrative Literature Review. *Journal of Clinical Medicine* **2021**, *10*, 138, 10.3390/jcm10010138.

28. Daniel A. Dumesic; Joanne S. Richards; Ontogeny of the ovary in polycystic ovary syndrome. *Fertility and Sterility* **2013**, *100*, 23-38, 10.1016/j.fertnstert.2013.02.011.

29. Sandro C. Esteves; Matheus Roque; Giuliano Bedoschi; Alessandro Conforti; Peter Humaidan; Carlo Alviggi; Defining Low Prognosis Patients Undergoing Assisted Reproductive Technology: POSEIDON Criteria—The Why. *Frontiers in Endocrinology* **2018**, *9*, 461, 10.3389/fendo.2018.00461.

30. Itai Gat; Sonia Blanco Mejia; Hanna Balakier; Clifford Librach; Anne Claessens; Edward A.J. Ryan; The use of coenzyme Q10 and DHEA during IUI and IVF cycles in patients with decreased ovarian reserve. *Gynecological Endocrinology* **2016**, *32*, 534-537, 10.3109/09513590.2015.1137095.

31. Abdelaziz El Refaeey; Amal Selem; Ahmed Badawy; Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. *Reproductive BioMedicine Online* **2014**, *29*, 119-124, 10.1016/j.rbmo.2014.03.011.
32. Sen Sharma, D; Category C: Oral Presentations: Fertility and Reproductive Medicine. *BJOG: An International Journal of Obstetrics & Gynaecology* **2017**, *124*, 9-11, 10.1111/1471-0528.2_14571.
33. Yangying Xu; Victoria Nisenblat; Cuiling Lu; Rong Li; Jie Qiao; Xiumei Zhen; Shuyu Wang; Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reproductive Biology and Endocrinology* **2018**, *16*, 1-11, 10.1186/s12958-018-0343-0.
34. Hongyan Yang; Yan Xie; Dongyu Yang; Decheng Ren; Oxidative stress-induced apoptosis in granulosa cells involves JNK, p53 and Puma. *Oncotarget* **2017**, *8*, 25310-25322, 10.18632/oncotarget.15813.
35. Yaakov Bentov; Thomas Hannam; Andrea Jurisicova; Navid Esfandiari; Robert F. Casper; Coenzyme Q10 Supplementation and Oocyte Aneuploidy in Women Undergoing IVF-ICSI Treatment. *Clinical Medicine Insights: Reproductive Health* **2014**, *8*, 31-6, 10.4137/cmrh.s14681.
36. T. Caballero; F. Fiameni; A. Valcarcel; J. Buzzi; Dietary supplementation with coenzyme Q10 in poor responder patients undergoing IVF-ICSI Treatment. *Fertility and Sterility* **2016**, *106*, e58, 10.1016/j.fertnstert.2016.07.177.
37. Panagiota Florou; Panagiotis Anagnostis; Patroklos Theocharis; Michail Chourdakis; Dimitrios G. Goulis; Does coenzyme Q10 supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. *Journal of Assisted Reproduction and Genetics* **2020**, *37*, 2377-2387, 10.1007/s10815-020-01906-3.
38. Rebecca Kile; Deirdre M. Logsdon; Catherine Nathanson; Sue McCormick; William B. Schoolcraft; Rebecca L. Krisher; MITOCHONDRIAL SUPPORT OF EMBRYOS FROM WOMEN OF ADVANCED MATERNAL AGE DURING ART. *Fertility and Sterility* **2020**, *114*, e122, 10.1016/j.fertnstert.2020.08.363.
39. Long Ma; Lingbo Cai; Mengting Hu; Jing Wang; Jiazi Xie; Yan Xing; Jiandong Shen; Yugui Cui; X. Johné Liu; Jiayin Liu; et al. Coenzyme Q10 supplementation of human oocyte in vitro maturation reduces postmeiotic aneuploidies. *Fertility and Sterility* **2020**, *114*, 331-337, 10.1016/j.fertnstert.2020.04.002.
40. Xupeng Xing; Jinjing Zhang; Jingcheng Zhang; Yongsheng Wang; Jingyi Wang; Jian Kang; Fusheng Quan; Jianmin Su; Yong Zhang; Coenzyme Q10 supplement rescues postovulatory oocyte aging by regulating SIRT4 expression. *Current Molecular Pharmacology* **2021**, *14*, 1-1, 10.2174/1874467214666210420112819.
41. L. Ma; M. Hu; X. Ma; Y. Cui; J. Liu; CoQ10 decreases aneuploidy rate and increases mitochondrial mass during in vitro maturation of human immature oocytes. *Fertility and Sterility* **2018**, *110*, e312, 10.1016/j.fertnstert.2018.07.878.
42. Jie Qiao; Zhen-Bo Wang; Huai-Liang Feng; Yi-Liang Miao; Qiang Wang; Yang Yu; Yan-Chang Wei; Jie Yan; Wei-Hua Wang; Wei Shen; et al. The root of reduced fertility in aged women and possible therapentic options: Current status and future perspects. *Molecular Aspects of Medicine* **2013**, *38*, 54-85, 10.1016/j.mam.2013.06.001.
43. Usama Al-Zubaidi; Deepak Adhikari; Ozgur Cinar; Qing-Hua Zhang; Wai Shan Yuen; Michael P Murphy; Luk Rombauts; Rebecca L Robker; John Carroll; Mitochondria-targeted therapeutics, MitoQ and BGP-15, reverse aging-associated meiotic spindle defects in mouse and human oocytes. *Human Reproduction* **2020**, *36*, 771-784, 10.1093/humrep/deaa300.