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Content

Nutrition and Female Fertility in General

There is an increasing awareness in patients and health care providers alike, that lifestyle, diet and targeted orthomolecular support can make a valuable contribution to succesfull fertility treatment.

Nutrition and Female Fertility: An Interdependent Correlation

Erica Silvestris, Domenica Lovero, and Raffaele Palmirotta*

Besides aging, a number of non-modifiable lifestyle-related factors, such as smoking, elevated consumption of caffeine and alcohol, stress, agonist sports, chronic exposure to environmental pollutants, and other nutritional habits exert a negative impact on a women's fertility. In particular, metabolic disorders including diabetes, obesity, and hyperlipidemia commonly associated to hypercaloric diets are suspected to affect a woman's fertility either by direct damage to oocyte health and differentiation, or by indirect interference with the pituitary-hypothalamic axis, resulting in dysfunctional oogenesis. Obese women show decreased insulin sensitivity determining persistent hyperinsulinemia, which may be involved in the pathogenesis of Polycystic Ovary Syndrome. Thus, the reduced insulin secretion induced by dietary adjustments is an attractive non-pharmacological treatment to prevent infertility, and a Mediterranean diet aimed at maintaining normal body mass may be

effective in the preservation of ovarian health and physiology. Furthermore, in relation to the oxidative stress as a co-factor of defective oocyte maturation, an appropriate intake of proteins, antioxidants and methyl-donor supplements (1-Carbon Cycle) may decrease the bioavailability of toxic oxidants resulting in the protection of oocyte maturation.Besides aging, a number of non-modifiable lifestyle-related factors, such as smoking, elevated consumption of caffeine and alcohol, stress, agonist sports, chronic exposure to environmental pollutants, and other nutritional habits exert a negative impact on a women's fertility. In particular, metabolic disorders including diabetes, obesity, and hyperlipidemia commonly associated to hypercaloric diets are suspected to affect a woman's fertility either by direct damage to oocyte health and differentiation, or by indirect interference with the pituitary-hypothalamic axis, resulting in dysfunctional oogenesis. Obese women show decreased insulin sensitivity determining persistent hyperinsulinemia, which may be involved in the pathogenesis of Polycystic Ovary Syndrome. Thus, the reduced insulin secretion induced by dietary adjustments is an attractive non-pharmacological treatment to prevent infertility, and a Mediterranean diet aimed at maintaining normal body mass may be effective in the preservation of ovarian health and physiology. Furthermore, in relation to the oxidative stress as a co-factor of defective oocyte maturation, an appropriate intake of proteins, antioxidants and methyl-donor supplements (1-Carbon Cycle) may decrease the bioavailability of toxic oxidants resulting in the protection of oocyte maturation.

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Reproductive Aging

As a woman becomes older, her reproductive capacity decreases. Healthy pregnancy requires interaction of neuroendocrine factors, uterine factors, as well as good oocyte quality. Consistent live-birth rate of pregnancies from oocyte donation in aging women suggests that decline in oocyte quality is the major contributing factor responsible for age-related fertility loss.

The oocyte is the largest cell in multicellular organisms, and more mitochondria are found per oocyte than any other cellular organelle. Mitochondria provide energy for transcription and translation during oocyte maturation, fertilization, and embryonic development.

Studies have shown that content of mitochondrial DNA (mtDNA) of human oocytes is inversely associated with maternal age and ovarian reserve indicators and that mitochondrial dysfunction is associated with oocyte aging as well. It is thought that lack of mitochondria as well as mitochondrial deficiency result in inadequate ATP supply. ATP deficiency in oocytes has been found to be associated with increased incidence of aneuploidy due to defects in chromatid separation and chromosome decondensation, as well as spindle detachment causing chromosomal misalignment.

After fertilization, the mitochondria of the sperm are degraded, and embryonic mitochondria are derived exclusively from the oocyte. The quality of oocyte mitochondria thus determines the quality of the embryo.

Aging and the Environment Affect Gamete and Embryo Potential: Can We Intervene?

David R Meldrum, Robert F Casper, Antonio Diez-Juan, Carlos Simon, Alice D Domar, Rene Frydman

Optimal maturation of the oocyte depends on its environment and determines embryo competence, because the embryonic genome is not active until the cleavage stage and

new mitochondria are not produced until blastulation. Adverse environmental factors include aging, andropause, oxidative stress, obesity, smoking, alcohol, and psychologic stress, whereas androgen supplementation, a prudent diet, exercise, nutritional supplements, and psychologic interventions have beneficial effects. Mitochondrial function and energy production deteriorate with age, adversely affecting ovarian reserve, chromosome segregation, and embryo competence. In aging mice, the mitochondrial cofactor coenzyme Q10 reverses most of these changes. Early human experience has been encouraging, although only a small study using a shorter duration of intervention compared with the murine model has been carried out. Mitochondrial metabolic stress can result in an abnormal compensatory increase in mitochondrial DNA, which can be assessed in biopsied blastomeres of trophectoderm as a predictive biomarker of implantation failure. Psychologic stress may reduce oocyte competence by shifting blood flow away from the ovary as part of the classic "fight or flight" physiologic response, and methods to reduce stress or the body's reaction to stress improve pregnancy success. Enhancing oocyte competence is a key intervention that promises to reduce the number of euploid embryos failing to produce viable deliveries.

Fertil Steril. 2016 Mar;105(3):548-559. doi: 10.1016/j.fertnstert.2016.01.013. Epub 2016 Jan 23.

Mitochondria in Oocyte Aging: Current Understanding

D Zhang , D Keilty , Z F Zhang , R C Chian

The oocyte is the largest cell found in multicellular organisms. Mitochondria, as the energy factories for cells, are found in high numbers in oocytes, as they provide the energy for oocyte maturation, fertilization, and embryo formation via oxidative phosphorylation. Failure of assisted reproduction is mainly attributed to oocyte aging and increased aneuploidy. As the most numerous organelle in the oocyte, the mitochondrion has been confirmed as a crucial player in the process of oocyte aging, which is highly influenced by mitochondrion dysfunction. Every mitochondrion contains one or more mitochondrial DNA (mtDNA) molecule, which, at about 16.5 KD in length, encodes 13 proteins. In this review, we discuss the function of mitochondria and the relationship between mtDNA and oocyte aging. We also discuss technologies that aim to enhance oocyte developmental potential and delay ovarian aging.

Facts Views Vis Obgyn. 2017 Mar;9(1):29-38.

Aging and the environment affect gamete and embryo potential: can we intervene?

David R. Meldrum, M.D.,a Robert F. Casper, M.D.,b,c,d Antonio Diez-Juan, Ph.D.,e Carlos Simon, M.D., Ph.D.,f,g, Alice D. Domar, Ph.D.,h and Rene Frydman, M.D., Ph.D.i

Optimal maturation of the oocyte depends on its environment and determines embryo competence, because the embryonic genome is not active until the cleavage stage and new mitochondria are not produced until blastulation. Adverse environmental factors include aging, andropause, oxidative stress, obesity, smoking, alcohol, and psychologic stress, whereas androgen supplementation, a prudent diet, exercise, nutritional supplements, and psychologic interventions have beneficial effects. Mitochondrial function and energy production deteriorate with age, adversely affecting ovarian reserve, chromosome

segregation, and embryo competence. In aging mice, the mitochondrial cofactor coenzyme Q10 reverses most of these changes. Early human experience has been encouraging, although only a small study using a shorter duration of intervention compared with the murine model has been carried out. Mitochondrial metabolic stress can result in an abnormal compensatory increase in mitochondrial DNA, which can be assessed in biopsied blastomeres of trophectoderm as a predictive biomarker of implantation failure. Psychologic stress may reduce oocyte competence by shifting blood flow away from the ovary as part of the classic ''fight or flight'' physiologic response, and methods to reduce stress or the body's reaction to stress improve pregnancy success. Enhancing oocyte competence is a key intervention that promises to reduce the number of euploid embryos failing to produce viable deliveries.

Fertil Steril_ 2016;105:548–59. _2016 by American Society for Reproductive Medicine.

Coenzyme Q10 and ovarian aging

During oocyte aging, there is a decline in mitochondrial function and thus energy supply. This leads to impaired oocyte maturation, chromosomal misalignment and embryo development. In mitochondrial ATP production, complexes I and II of the respiratory chain oxidize the tricarboxylic acid (TCA) cycle products and transfer the electrons to ubiquinone, also known as coenzyme Q10 (CoQ10). In children and young adults, CoQ10 is produced endogenously. However, rate of synthesis declines with age and leads to decreased respiratory chain function, Supplementation of CoQ10 can then improve mitochondrial activity.

Co-Enzyme Q10 Supplementation Rescues Cumulus Cells Dysfunction in a Maternal Aging Model.

Ben-Meir A, Kim K, McQuaid R, Esfandiari N, Bentov Y, Casper RF, Jurisicova A.

Over the past four decades, due to cultural and social changes, women in the developed world have significantly delayed childbirth. This trend is even worse for patients who attend infertility clinics. It is well-known that live birth rates in women older than 35 are significantly lower than in those younger, both naturally and with assisted reproduction. Fertility decline is, in part, due to an increase in oocyte aneuploidy that leads to a reduced embryo quality, as well as an increased incidence of miscarriages and birth defects. Here we show that aging-associated malfunction is not restricted to the oocyte, as cumulus granulosa cells also display a series of defects linked to mitochondrial activity. In, both, human and mouse model, a decline in cumulus cell function due to increased maternal age is accompanied by a decreased expression of enzymes responsible for Coenzyme Q (CoQ) production, particularly Pdss2 and CoQ6. In an aged mouse model supplementation with Coenzyme Q10-a potent stimulator of mitochondrial function-restored cumulus cell number, stimulated glucose uptake, and increased progesterone production. CoQ10 supplementation might, thus, improve oocyte and cumulus cells quantity and quality, by improving the mitochondrial metabolism in females of advanced maternal age.

Antioxidants (Basel). 2019 Mar 8;8(3). pii: E58. doi: 10.3390/antiox8030058.

Coenzyme Q10 ameliorates the quality of postovulatory aged oocytes by suppressing DNA damage and apoptosis.

Zhang M, ShiYang X, Zhang Y, Miao Y, Chen Y, Cui Z, Xiong B.

Postovulatory aging is known to compromise the oocyte quality as well as subsequent embryo development in many different animal models, and becomes one of the most intractable issues that limit the outcome of human assisted reproductive technology (ART). However, the strategies to prevent the deterioration of aged oocytes and relevant mechanisms are still underexplored. Here, we find that supplementation of CoQ10, a natural antioxidant present in human follicular fluids, is able to restore the postovulatory aging-induced fragmentation of oocytes and decline of fertilization. Importantly, we show that CoQ10 supplementation recovers postovulatory aging-caused meiotic defects such as disruption of spindle assembly, misalignment of chromosome, disappearance of actin cap, and abnormal distribution patterns of mitochondria and cortical granules. In addition, CoQ10 protects aged oocytes from premature exocytosis of ovastacin, cleavage of sperm binding site ZP2, and loss of localization of Juno, to maintain the fertilization potential. Notably, CoQ10 suppresses the aging-induced oxidative stress by reducing the levels of superoxide and DNA damage, ultimately inhibiting the apoptosis. Taken together, our findings demonstrate that CoQ10 supplementation is a feasible and effective way to prevent postovulatory aging and preserve the oocyte quality, potentially contributing to improve the successful rate of IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection) during human ART.

Free Radic Biol Med. 2019 Nov 1;143:84-94. doi: 10.1016/j.freeradbiomed.2019.08.002. Epub 2019 Aug 6.

Coenzyme Q 10 Supplementation in Aging and Disease

Juan D Hernández-Camacho , Michel Bernier , Guillermo López-Lluch , Plácido Navas

Coenzyme Q (CoQ) is an essential component of the mitochondrial electron transport chain and an antioxidant in plasma membranes and lipoproteins. It is endogenously produced in all cells by a highly regulated pathway that involves a mitochondrial multiprotein complex. Defects in either the structural and/or regulatory components of CoQ complex or in non-CoQ biosynthetic mitochondrial proteins can result in a decrease in CoQ concentration and/or an increase in oxidative stress. Besides CoQ10 deficiency syndrome and aging, there are chronic diseases in which lower levels of CoQ10 are detected in tissues and organs providing the hypothesis that CoQ10 supplementation could alleviate aging symptoms and/or retard the onset of these diseases. Here, we review the current knowledge of CoQ10 biosynthesis and primary CoQ10 deficiency syndrome, and have collected published results from clinical trials based on CoQ10 supplementation. There is evidence that supplementation positively affects mitochondrial deficiency syndrome and the symptoms of aging based mainly on improvements in bioenergetics. Cardiovascular disease and inflammation are alleviated by the antioxidant effect of CoQ10. There is a need for further studies and clinical trials involving a greater number of participants undergoing longer treatments in order to assess the benefits of CoQ10 treatment in metabolic syndrome and diabetes, neurodegenerative disorders, kidney diseases, and human fertility.

Front Physiol. 2018 Feb 5;9:44. doi: 10.3389/fphys.2018.00044. eCollection 2018.

Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial

Yangying Xu, Victoria Nisenblat2, Cuiling Lu, Rong Li, Jie Qiao, Xiumei Zhen and Shuyu Wang

Abstract

Background: Management of women with reduced ovarian reserve or poor ovarian response (POR) to stimulation is one of the major challenges in reproductive medicine. The primary

causes of POR remain elusive and oxidative stress was proposed as one of the important contributors. It has been suggested that focus on the specific subpopulations within heterogeneous group of poor responders could assist in evaluating optimal management strategies for these patients. This study investigated the effect of anti-oxidant treatment with coenzyme Q10 (CoQ10) on ovarian response and embryo quality in young low-prognosis patients with POR.
Methods: This prospective, randomized controlled study included 186 consecutive patients with POR stratified according to the POSEIDON classification group 3 (age < 35, poor ovarian reserve parameters). The participants were randomized to the CoQ10 pre-treatment for 60 days preceding IVF-ICSI cycle or no pre-treatment. The number of high quality embryos was a primary outcome measure.
Results: A total of 169 participants were evaluated (76 treated with CoQ10 and 93 controls); 17 women were excluded due to low compliance with CoQ10 administration. The baseline demographic and clinical characteristics were comparable between the groups. CoQ10 pretreatment resulted in significantly lower gonadotrophin requirements and higher peak E2 levels. Women in CoQ10 group had increased number of retrieved oocytes (4, IQR 2–5), higher fertilization rate (67.49%) and more high-quality embryos (1, IQR 0–2); $p < 0.05$. Significantly less women treated with CoQ10 had cancelled embryo transfer because of poor embryo development than controls (8.33% vs. 22.89%, $p = 0.04$) and more women from treatment group had available cryopreserved embryos (18.42% vs. 4.3%, $p = 0.012$). The clinical pregnancy and live birth rates per embryo transfer and per one complete stimulation cycle tended to be higher in CoQ10 group but did not achieve statistical significance.
Conclusion: Pretreatment with CoQ10 improves ovarian response to stimulation and embryological parameters in young women with poor ovarian reserve in IVF-ICSI cycles. Further work is required to determine whether there is an effect on clinical treatment endpoints.
Xu et al. Reproductive Biology and Endocrinology (2018) 16:29 https://doi.org/10.1186/s12958-018-0343-0

Can Coenzyme Q10 supplementation protect the ovarian reserve against oxidative damage?

Pınar Özcan & Cem Fıçıcıoğlu & Ozge Kizilkale & Mert Yesiladali & Olgu Enis Tok & Ferda Ozkan & Mukaddes Esrefoglu

Purpose We investigated antioxidant effects of CoQ10 supplementation on the prevention of OS-induced ovarian damage to evaluate the protective effect of such supplementation against OS-related DNA damage.
Methods Twenty-four adult female Sprague–Dawley rats were randomly divided into three groups (8 rats per group): group 1 (control): saline, ip, and orally; group 2 (cisplatin group): cisplatin, 4.5 mg/kg ip, two times with an interval of 7 days; and group 3 (cisplatin + CoQ10 group): cisplatin, 4.5 mg/kg ip, two times with an interval of 7 days, and 24 h before cisplatin, 150 mg/kg/day orally in 1 mL of saline daily for 14 days. Serum concentrations of anti-Mullerian hormone (AMH), number of AMH-positive follicles, the assessment of the intensity of 8'OHdG immunoreactivity, the primordial, antral and atretic follicle counts in the ovary were assessed.
J Assist Reprod Genet (2016) 33:1223–1230 DOI 10.1007/s10815-016-0751-z

Coenzyme Q-dependent Mitochondrial Respiratory Chain Activity in Granulosa Cells Is Reduced With Aging

Assaf Ben-Meir , Shlomi Yahalomi , Brit Moshe , Yoel Shufaro , Benjamin Reubinoff , Ann Saada

Objective: To examine coenzyme Q10 (CoQ10)-dependent mitochondrial respiratory chain (MRC) activity in granulosa cells (GC) with aging and examine the effect of in vitro CoQ supplementation.

Design: Experimental study.

Setting: Hospital laboratory.

Patient(s): Ten younger (<32 years) and 10 older (>39 years) patients undergoing in vitro fertilization (IVF) treatment.

Intervention(s): Measurement of succinate-cytochrome c reductase (MRC complex II + III) activity in the presence and absence of CoQ1 (a soluble CoQ analog).

Main outcome measure(s): MRC enzymatic activity in human GC via complex II + III measured in GC homogenate by spectrophotometry and compared with CoQ in dependent MRC complex II and citrate synthase (CS).

Result(s): Complex II + III activity was 1.9 times higher in young patients compared with older patients (18.3 ± 5.8 and 9.6 ± 3 nmol/min/mg, respectively) whereas II and CS were not statistically significantly different. Increased II + III activity in the presence CoQ1 was observed in both groups but was statistically significantly higher in the older patients, reaching similar levels. Compared with baseline (II + III + Q/II + III), the increase was 2.47 times higher in older patients compared with young patients (6.5 ± 2.0 and 2.62 ± 0.83, respectively).

Conclusion(s): Coenzyme Q10-dependent MRC activity in GC reduces with aging. This reduction is diminished upon in vitro CoQ1 supplementation, indicating that CoQ10 deficit is the underlying cause for the mitochondrial dysfunction. The results show that functional CoQ10 status can be assessed by measuring complex II + III activity in GC and might provide a useful monitoring tool for future clinical studies of oral CoQ10 supplementation to older patients undergoing IVF treatment.

Fertil Steril. 2015 Sep;104(3):724-7.doi: 10.1016/j.fertnstert.2015.05.023. Epub 2015 Jun 11.

Coenzyme Q10 Restores Oocyte Mitochondrial Function and Fertility During Reproductive Aging

Assaf Ben-Meir, Eliezer Burstein, Aluet Borrego-Alvarez, Jasmine Chong, Ellen Wong, Tetyana Yavorska, Taline Naranian, Maggie Chi, Ying Wang , Yaakov Bentov, Jennifer Alexis, James Meriano, Hoon-Ki Sung, David L Gasser, Kelle H Moley, Siegfried Hekimi, Robert F Casper, Andrea Jurisicova

Female reproductive capacity declines dramatically in the fourth decade of life as a result of an age-related decrease in oocyte quality and quantity. The primary causes of reproductive aging and the molecular factors responsible for decreased oocyte quality remain elusive. Here, we show that aging of the female germ line is accompanied by mitochondrial dysfunction associated with decreased oxidative phosphorylation and reduced Adenosine tri-phosphate (ATP) level. Diminished expression of the enzymes responsible for CoQ production, Pdss2 and Coq6, was observed in oocytes of older females in both mouse and human. The age-related decline in oocyte quality and quantity could be reversed by the administration of CoQ10. Oocyte-specific disruption of Pdss2 recapitulated many of the mitochondrial and reproductive phenotypes observed in the old females including reduced ATP production and increased meiotic spindle abnormalities, resulting in infertility. Ovarian reserve in the oocyte-specific Pdss2-deficient animals was diminished, leading to premature

ovarian failure which could be prevented by maternal dietary administration of CoQ10. We conclude that impaired mitochondrial performance created by suboptimal CoQ10 availability can drive age-associated oocyte deficits causing infertility

Aging Cell. 2015 Oct;14(5):887-95. doi: 10.1111/acel.12368. Epub 2015 Jun 26.

Coenzyme Q10 Supplementation and Oocyte Aneuploidy in Women Undergoing IVF-ICSI Treatment

Yaakov Bentov, Thomas Hannam, Andrea Jurisicova, Navid Esfandiari, Robert F Casper

Background: The age-related reduction in live-birth rate is attributed to a high rate of aneuploidy and follicle depletion. We showed in an animal model that treatment with Coenzyme Q10 (CoQ10) markedly improved reproductive outcome. The aim of this study was to compare the post-meiotic oocyte aneuploidy rate in in vitro fertilization (IVF) and intra cytoplasmic sperm injection (ICSI) patients treated with CoQ10 or placebo.

Methods: We conducted a double blind placebo controlled randomized trial that included IVF-ICSI patients 35-43 years of age. The patients were treated with either 600 mg of CoQ10 or an equivalent number of placebo caps. We compared the post-meiotic aneuploidy rate using polar body biopsy (PBBX) and comparative genomic hybridization (CGH). According to the power calculation, 27 patients were needed for each arm.

Results: Owing to safety concerns regarding the effects of polar body biopsy on embryo quality and implantation, the study was terminated before reaching the target number of participants. A total of 39 patients were evaluated and randomized (17 CoQ10, 22 placebo), 27 were given the study medication (12 CoQ10, 15 placebo), and 24 completed an IVF-ICSI cycle including PBBX and embryo transfer (10 CoQ10, 14 placebo). Average age, base line follicle stimulating hormone (FSH), peak estradiol and progesterone serum level, as well as the total number of human menopausal gonadotropin (hMG) units-did not differ between the groups. The rate of aneuploidy was 46.5% in the CoQ10 group compared to 62.8% in the control. Clinical pregnancy rate was 33% for the CoQ10 group and 26.7% for the control group.

Conclusion: No significant differences in outcome were detected between the CoQ10 and placebo groups. However, the final study was underpowered to detect a difference in the rate of aneuploidy.

Clin Med Insights Reprod Health. 2014 Jun 8;8:31-6. doi: 10.4137/CMRH.S14681. eCollection 2014.