CoQ10-Mitochondrial Energizer in Ageing Oocytes and female infertility


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INTRODUCTION

Female infertility is one of the first physiological functions adversely affected by aging.

Fecundity of the female starts declining at age of 32 and decreases more rapidly after age of 32 and decreases more rapidly after age of 37 years.1 The fertility peaks around age of 25 and after age of 35 suffers a rapid decline.

This decline is mainly due to an age-related decrease in oocyte quality rather than changes in endometrial receptivity.

The reasons behind the poor reproductive performance of older patients are decreased ovarian reserve and increased rate of chromosomal aberration which leads to increase risk of miscarriage and aneuploidy.

In humans, the progressive loss of ovarian follicles is nonlinear and becomes accelerated with age.3

There are many theories regarding the age-related decline in the oocyte quality. The first one is that the selection of the highest quality oocyte during the early reproductive years leaves the less favorable oocytes for more advanced age.

The other theory behind it is that the process of aging itself may exert an unfavorable influence on the oocytes that remain dormant in the ovary before being selected in the ovulatory cohort.

The process of oogenesis and the formation of ovarian follicles start in the fetal life. The immature oocytes in the ovarian cortex are diploid, having 46 chromosomes arrested in the prophase of the first meiotic division. After this phase, the luteinizing hormone surge or the hCG trigger during assisted reproduction technology leads to resumption of meiosis in the oocyte. During this process, the chromosomes condense, align in pairs, and then separate via pulling apart of chromosomes by the spindle fibers, resulting in a mature oocyte that contains 23 chromosomes. The other set of chromosome is isolated outside the oolemma in the first polar body.

The second meiotic division commences with the penetration of viable sperm. The oocyte then extrudes 23 sister chromatids, resulting in a second polar body and a fertilized zygote.

The process of pulling chromosomes outside the egg to form the first and second polar bodies requires a significant amount of energy which is provided by ATP from oxidative phosphorylation in mitochondria. The oocyte has by far the largest number of mitochondria and mitochondrial DNA copies of any cells.

The oocyte drives the energy produced by mitochondria via oxidative phosphorylation (OxPHOS).5

Complex I and II oxidize products of the tricarboxylic acid and transfer the electrons to ubiquinone, also known as coenzyme Q. The electrons are transferred to complex III and IV creating a proton gradient which culminates in the generation of ATP by complex V. One of the by products of mitochondrial respiration is the production of reactive oxygen species (ROS). About 90% of it is produced by the mitochondria. In the past, it was thought that generation of ROS was “leakage” or an unproductive side reaction. More recently, it has been suggested that mitochondrial ROS may actually be very important signalling process and in aging clock.6-8

CoQ is pleomorphic having critical antioxidant properties, controlling cellular redox, altering various signalling pathways, and influencing transcripted activity of cells and is required for activity of succinate dehydrogenas.9

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There are many studies which have shown an age related CoQ to decline. Studies by Quinzii et all has examined the effects of different level of CoQ10 deficiency on ROS production, mitochondrial functions and cell viability.

The deficiency of CoQ 10 to an intermediate level will cause an increased production of the ROS, lipid oxidation and cell death. This has been proven by the fact that supplementation of CoQ10 will normalize the bioenergetic status and the oxidative balance.

The hypothesis that the decrease in the energy production in oocytes with the age is related to the decline in the CoQ10 has been proven by the fact that it occurs due to the decrease in the level of enzymes that produces CoQ10.

This has also been proven by the fact that the qualitative real time polymerase chain reaction of growing stage oocyte revealed a significant decrease in CoQ6 and CoQ 9 expressions but no change in Pdssl/2 transcript levels in the mouse.

In the humans, it has also been studied which shows a significant decline in CoQ6 expression in the oocytes of older patients. The western blot analysis of ovaries isolated from young and old dans revealed reduction in both PDS5@ and CoQ 6 patients.

CoQ10 is essential for the mitochondrial activity as point mutations in enzymes responsible for CoQ10 synthesis are characterized by phenotype involving high energy consuming tissue, such as the CNS skeletal muscles and the kidney and these symptoms can be partially alleviated by CoQ10.

Thus, it has shown that the supplementation of mitochondrial nutrients, such as CoQ10 and r- alpha linoleic acid may be able to reduce the risk of trisomy and other types of chromosomal aneuploidies related to oocyte aging via increasing energy for chromosomal disjunction.

Thus, it is believed that supplementation of mitochondrial nutrients will in time help to improve the quality.

It has also been studied that the oocyte development in the cumulus oocyte complex requires bidirectional communication which is maintained by gap junction through connexin 37. Granulose/cumulus cells play a nurturing role in oocyte development. The gap junctions facilitate the transfer of amino acids, glucose metabolites(pyruvate), nucleotides, and cholesterol from the cumulus cellsprovinding the metabolic demands of the growing oocyte.

Studies show that as the age advances is linked to dysfunctional mitochondria in the oocyte and cumulus/ granulose cells resulting in reduced energy production by OXPHOS and leading to abnormal chromosomal segregation.

The need for the junctional mitochondria has been provided by the fact that induced mitochondrial damage resulted in arrested oocyte maturation, compromised meiotic spindle configuration, and chromosomal misalignment.

It has been shown that the decrease in the level of coenzyme Q10 shows that it leads to dysfunctional mitochondrial respiratory chain (MRC) electron transport. Coenzyme, a lipid soluble electron transporter, transports electron from complex I and II to complex II in the MRC and is essential for the stability of complex III. It also participates in the transport of the protons and drives ATP formation through ATP Synthetase.

Age-related decline in CoQ10 levels with certain drugs, such as statins and mutations of genes involving in CoQ10 synthesis leads to CoQ10 deficiency and is characterized by clinical disorders involving mitochondrial dysfunction in the nervous system, skeletal muscles, and endocrine gland.

It is proven in the studies by the fact that CoQ10 in vitro culture of bovine embryo found a superior rate of early embryo cleavage, blastocyst formation, percentage of expanding blastocyst, and larger cell mass. These changes are associated with an increased ATP content in the group of embryos cultured with CoQ10.

REFERENCES


