10.5005/jp-journals-10006-1429

EDITORIAL

CoQ10-Mitochondrial Energizer in Ageing Oocytes and female infertility

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How to cite this article detail: Garg R, Bora NM, Agrawal V, Kumari SS, Devineni K. CoQ10-Mitochondrial Energizer in Ageing Oocytes and female infertility. J South Asian Feder Obst Gynae 2016;8(4):253-255.

Source of support: Nil

Conflict of interest: None

Date of received: 10 July 2016

Date of acceptance: 12 September 2016

Date of publication: October 2016

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.[2]

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.

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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 oolemna 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.[4]

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]

There are many studies which have shown an age related CoQ to decline.

[10] 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 PDSS@ 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.[11]

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 triosomy 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.[12]

Granulose/cumulus cells play a nurturing role in oocyte development.[13] The gap junctions facilitate the transfer of amino acids , glucose metabolites(pyruvate), nucleotides, and cholesterol from the cumulus cellsprovidind the metabolic demands of the growing oocyte.[14]

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.[15-16]

The need for the junctional mitochondria has been provided by the fact that induced mitochondrial damage resulted in arrested oocyte maturation, compromised meitic spindle configuration, and chromosomal misalignment. [17]

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.[18-19]

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 C0Q10 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.[20]

REFERENCES

1. O' Connor KA, Holman DJ, Wood JW. Declining fecundity and ovarian ageing in natural fertility populations. Maturitas 1998 Oct 12;30(12):127-136.
2. Freeman SB, Yang Q , Allran K, Taft LF, Sherman SL. Women with a reuced ovarian compliment may have an increased risk for a child with down syndrome. Am J hum Genet 2000;66:1680-1683.
3. Faddy MJ. Follicle dynamics during ovarian ageing . Mol Cell Endocrinol 2000;134:455-465.
4. May-Panloup P, Chretein MF, Malthiery Y, Reynier P. Mitochondrial DNA in the oocyte and the developing embryo. Curr Top Dev Biol 2007;77:51-83.
5. Loish, H.; Berk, A.; Zipursky, SL.; Matsudaira, P.; Baltimore, D.; Darnell, J.Molecular cell biology. 4th ed. New York: W.H. Freeman; 2000. Chapter 16, Cellular energetic: glycolysis , aerobic oxidation and photosynthesis.
6. Dada LA, Chandel NS, Ridge KM, Pedemonte C, Bertorello AM, Snajder JI. Hypoxia induced endocytosis of Na-K ATPase in alveolar epithelial cells ismediated by mitochondrial reactive oxygen species and PKC-zeta . J Clin Invest 2003 Apr;111(7):1057-1064.
7. Nemoto S, Finkel T . Redox regulation of forkhead proteins through a p66shc-dependant signalling pathway. Science 2002; 295:2450-2452.
8. Werner E, Werb Z. Integrins engage mitochondrial function for signal transduction by a mechanism dependant on Rho GtPases. J Cell Biol 2002 Jul 22;158(2):357-368.
9. Crane FL. Biochemical functions of coenzyme Q10. J Am Coll Nutr 2001 Dec;20(6):591-598.

10. Quinzii CM, Lopez LC, Gilkerson RW, Dorado B, Coku J, Naini AB, Lagier- Tourenne C, Schuelke M, Salviati L, Carrozo R, et al. Reactive oxygen species, oxidative stress and cell death correlate with level of CoQ10 deficiency. FASEB J 2010 Oct;24(10):3733-3743.
11. Peng M, Falk MJ, Haase VH, King R, Polyak E, Selak M, Yudkoff M, Hancock WW, Meade R, Saiki R, et al. Primary coenzyme Q deficiency in pdss2 mutant mice causes isolated renal diseases. PLoS Genet 2008 Apr 25;4(4):e1000061.
12. Albertini DF, Combelles CM, Benecchi E, Carabatsos MJ. Cellular basis for paracrine regulation of ovarian follicle development. Reproduction 2001 May;121(5):647-653.
13. Simon AM, Goodenough DA, Li E, Paul DL. Female infertility in mice lacking connexion 37. Nature 1997 Feb 6;385(6616): 525-529.
14. Su YQ, Sugiura K, Eppig JJ. Mouse oocyte control of granulose cell development and function: paracrine regulation of cumulus cell metabolism. Semin Reprod Med 2009 Jan; 27(1):32-42.
15. Wilding M, Dale B, Marino M, di Matteo L, Alviggi C, Pisaturo ML, Lombardi L, De Placido G. Mitochondrial aggregation patterns and activity in human oocytes and preimplantation embryos. Hum Reprod 2001 May;16(5):909-917.
16. Tsai HD, Hsieh YY, Hsieh JN, Chang CC, Yang CY, Yang JG, Cheng WL, Tsai FJ, Liu CS. Mitochondria DNA deletion and copy numbers of cumulus cells associated with *in vitro* fertilization outcomes. J Reprod Med 2010 Nov-Dec;55(11-12):491-497.
17. Takeuchi T, Neri QV, Katagiri Y, Rosenwaks Z, Palermo GD. Effect of treating induced mitochondrial damage in embryonic development and epigenesist. Biol Reprod 2005 Mar;72(3): 584-592.
18. Kalén A, Appelkvist EL, Dallner G. Age-related changes in the lipid composition of rat and human tissues. Lipids 1989 Jul;24(7):579-584.
19. Miles MV, Horn PS, Tang PH, Morrison JA, Miles L, DeGrauw T, Pesce AJ. Age-related changes in plasma coenzyme Q10 concentration and redox state in apparently healthy children and adults. Clin Chim Acta 2004 Sep;347(1-2):139-144.20. Marriage BJ , Clandinin MT, Macdonald IM, Glerum DM. Cofactor treatment improves ATP synthetic capacity in patients with oxidative phosphorylation disorders. Mol Genet Metab 2004 Apr;81(4):263-272.