The use of mitochondrial nutrients to improve the outcome of infertility treatment in older patients

We present a hypothesis emphasizing the role of mitochondrial dysfunction in reproductive senescence and suggesting the use of mitochondrial nutrients as an adjuvant treatment in older patients with infertility. (Fertil Steril® 2010;93:272–5. ©2010 by American Society for Reproductive Medicine.)

During the past few decades, because of cultural and social changes, women in the developed world have significantly delayed childbirth (1). It is well known that pregnancy rates (PR) at age more than 35 years are significantly lower, both naturally and with assisted reproduction. The decline in live birth rate reflects a decline in response to ovarian stimulation, reduced embryo quality and PRs, and an increased incidence of miscarriages and fetal aneuploidy. At present there is no known intervention to improve the pregnancy outcome of older patients.

In this article we expand on the hypothesis that mitochondrial dysfunction has a major role in reproductive senescence and propose that reproductive function in older women may be improved by the use of mitochondrial nutrients.

OOCYTES AND AGING

Primordial oocytes are formed during fetal development and may reside within the ovary for as long as 50 years before growth and development into mature oocytes. Ovulation leads to resumption of meiosis in the oocyte. This involves alignment and separation of the chromosomes by the nuclear spindle so that the mature oocyte contains 23 chromosomes, whereas 23 chromosomes are isolated outside the oolema in the first polar body. When penetrated by a normal sperm, the oocyte extrudes 23 sister chromatids to form the second polar body and the fertilized zygote has a normal copy of the chromosomes by the nuclear spindle so that the mature oocyte is provided solely by mitochondria. The oocyte has the largest number of mitochondria and mitochondrial DNA (mtDNA) copies of any cell (~2 x 10^6 copies) (2), even more than cells that have high energy requirements, such as muscle cells and neurons, which contain several thousand copies. During the recruitment of the follicles there is a marked increase in the mitochondrial mass, from 6,000 mtDNA copies to an average of 200,000, representing about half of the total DNA content of the oocyte.

The mitochondrial genome is contained in double-stranded, circular DNA containing 16,569 base pairs that are organized in nucleotides, which unlike nuclear DNA do not contain histones or introns, making the mtDNA more vulnerable to mutations and deletions (Fig. 1). The mtDNA encodes 37 genes including those for 13 proteins, 22 transfer RNA genes, and 2 for ribosomal RNA. All of the encoded proteins are part of the respiratory chain complexes involved in adenosine triphosphate (ATP) production (3). The inheritance of mtDNA is strictly maternal, as paternal mitochondria are thought to be degraded by ubiquitination and eliminated during embryogenesis (4).

Aging and Mitochondria

Aging and age-related pathologies are frequently associated with loss of mitochondrial function mainly due to the accumulation of mtDNA mutations and deletions. In oocytes, low levels of mitochondrial oxidative phosphorylation may occur for up to 40 years before follicle maturation and ovulation, further increasing the risk for mtDNA mutations. The maintenance and repair of mtDNA relies on the same enzymes that maintain the nuclear genome. However, those enzymes are less available and not properly suited for the mtDNA, making its repair less efficient (5). One of the more frequent mtDNA deletions is the “common deletion” of 4977 base pairs, almost a third of the whole mtDNA genome. This deletion was shown to have a high prevalence in unfertilized oocytes (2,3) and there is a marked increase in the mitochondrial mass, from 6,000 mtDNA copies to an average of 200,000, representing about half of the total DNA content of the oocyte.

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and ATP production in the follicle is impaired in older women. It has been demonstrated that embryo implantation potential is correlated with the ATP content of the embryo (11–13). Wilding et al. (14) demonstrated that a reduced capacity of oocytes to produce ATP was associated with an abnormal nuclear spindle and chaotic chromosomal distribution. Cytoplasmic transfer from young oocytes into the oocytes of older women with a history of reproductive failure (12, 15, 16) demonstrated improved embryo development and delivery of live offspring with mitochondrial heteroplasmy (presence of mitochondria from two different sources) (17). The health impact of induced mitochondrial heteroplasmy in children is as yet unknown, although we have demonstrated that a mouse model of persistent heteroplasmy resulted in a phenotype consistent with the metabolic syndrome (18).

Postcompaction embryos display a marked increase in oxygen consumption (19) and a switch toward glucose utilization (20). Because there is no mitochondrial replication until the blastocyst stage (21), the initial population of mitochondria must be partitioned into the increasing number of blastomeres during embryo cleavage. The metabolic activity of the smaller population of mitochondria per cell must increase to meet the increasing demands of cellular activity. Therefore, it is reasonable to suggest that the documented relationship between maternal age and chromosomal abnormalities with diminished mitochondrial activity in the oocyte might lead both to chromosomal nondisjunction and to arrested embryo development.

FIGURE 1
Mitochondrial DNA. The double-stranded circular mitochondrial genome. The allocation of genes is highlighted by their color. The site of the common deletion is demonstrated by the arch on the lower right side of the drawing.

Hypothesis
We hypothesize that dietary supplementation of mitochondrial nutrients may improve the availability of mitochondrial energy production for the maturing oocyte and developing embryo, thereby reducing the rate of chromosomal nondisjunction and improving implantation in elderly infertile patients.

Preliminary Animal Data
We pretreated 52-week-old ICR mice with the mitochondrial nutrients coenzyme Q10 (CoQ10), r-alpha lipoic acid, and resveratrol before ovarian stimulation and flushing of oocytes from the fallopian tubes. Our preliminary data demonstrated that CoQ10 treatment, but not the other two nutrients, was associated with increased oocyte numbers and oocyte mitochondrial activity parameters, similar to oocytes from young ICR controls.

Coenzyme Q10
Coenzyme Q10 is a lipid-soluble component of virtually all cell membranes. It is an isoprenylated benzoquinone that transports electrons from complexes I and II to complex III in the mitochondrial respiratory chain (Fig. 2). It also transports protons in the mitochondria to build up membrane potential and drive ATP formation through ATP synthetase (22). Coenzyme Q10 is essential for the stability of complex III (23). It is also a major cellular antioxidant, with its tissue concentration being 5–10-fold higher than the other main lipid soluble antioxidant, vitamin E (24). Coenzyme Q10 had not been considered as a vitamin requiring supplementation because all normal tissues synthesize their own supply (25). However, tissue levels of CoQ10 are decreased with age (26) and with certain drugs such as the statins (27). Deficiency states due to mutations of genes involved in CoQ10 synthesis are characterized by clinical disorders involving high energy consuming tissues such as the nervous system, skeletal muscles, and endocrine glands (28). Coenzyme Q10 is generally administered in dosages of 100–3,000 mg/day (29) and resulted in a significant increase of CoQ10 concentrations in the plasma, muscle, and sperm (30–32). Interestingly, a comparative analysis of dietary CoQ10 in various tissues showed a remarkable uptake to the adrenal gland and the ovary, which more than doubled their initial concentrations of the co-enzyme (33).

Studies had found CoQ10 administration effective in the treatment of congestive heart failure (34), resistant massive hypertriglyceridemia (35), hypertension (36), improvement of endothelial function in diabetic patients (37), Friedreich’s ataxia (38), Parkinson’s disease (39), migraine prophylaxis (40), macular degeneration (41), and asthenozoospermia (40). All of these conditions are at least in part the result of mitochondrial dysfunction.

One study has looked into the effect of CoQ10 as a supplement for the in vitro culture of bovine embryos and found a significantly higher rate of early embryo cleavage, blastocyst formation rate, hatching rate, percentage of expanding blastocysts, and a larger size of the inner cell mass (ICM). In addition, there was an increased ATP content in the group of embryos cultured with CoQ10. All of those parameters suggest better quality embryos.

A meta-analysis that reviewed RCTs involving CoQ10 administration noted no side effects or adverse events in any of the studies (42). In addition, CoQ10 is naturally present in the fetal circulation (43).
In conclusion, we have presented evidence for mitochondrial involvement in age-related changes in the oocyte. In light of the prior literature and our preliminary animal data, we believe that supplementing the diets of older women with mitochondrial nutrients may result in an improvement of oocyte and embryo quality, and subsequently, better pregnancy outcome. By increasing energy for chromosomal disjunction, this intervention may be able to reduce the risk of trisomy and other types of chromosomal aneuploidies related to oocyte aging. In addition, increased mitochondrial energy production may improve embryo cleavage and reduce cytoplasmic fragmentation.

Mitochondrial nutrients are naturally occurring vitamins that have been used successfully to treat conditions associated with diminished energy production from mitochondria, and appear to be very safe in the doses studied. We believe that a clinical trial looking at the role of CoQ10 supplementation as a way to improve oocyte and embryo quality is worthwhile and hence we have initiated a randomized placebo-controlled study to test the validity of this hypothesis in older women undergoing fertility treatments.

REFERENCES