The aging oocyte—can mitochondrial function be improved?

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In recent years, social and cultural trends have resulted in women delaying childbirth, thereby leading to reproductive senescence as a growing public health problem. We discuss potential etiologies for age-related female reproductive decline. We bring supportive evidence to the central role of mitochondrial dysfunction and oxygen radicals in the process of aging in general and reproductive senescence specifically. We also explore the role of coenzyme Q10 deficiency as a contributing factor and the effects of its administration. (Fertil Steril® 2013;99:18–22. ©2013 by American Society for Reproductive Medicine.)

Key Words: Reproductive senescence, reactive oxygen species, mitochondrial dysfunction, mitochondrial nutrients, coenzyme Q10

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Female fertility peaks around age 25 and after age 35 suffers a rapid decline. For most women, the beginning of the fifth decade of life marks the end of their reproductive life. This decline is primarily due to an age-related decrease in oocyte quality rather than changes in endometrial receptivity, as indicated by the continuous high rate of success of donor oocytes in in vitro fertilization (IVF) treatments for recipients of advanced age (1). Cultural and social trends have resulted in an increased number of women delaying childbirth, thereby increasing the burden of reproductive senescence on public health.

The main reasons for the poor reproductive performance of older patients are reduced ovarian reserve and an increased rate of chromosomal aberrations, which leads to an increased risk of miscarriages and aneuploidy (2, 3). The estimated incidence of trisomy 21 at age 25 is 1 in 1,500, at age 40 is 1 in 60, and at age 49 is 1 in 11 (3). However, chromosome 21 is only one out of 23 pairs of chromosomes. Sher et al. (4) performed oocyte and embryo numeric karyotyping using comparative genomic hybridization (CGH). This method enables determination of the number of copies of all the chromosomes. Their findings suggested that the incidence of oocyte aneuploidy for women at a mean age of 27.0 ± 2.5 years was 65% and would presumably be even higher in older women. In that study, euploid embryos were far more likely to survive and develop to the blastocyst stage by day 5 than were aneuploid embryos (93% vs. 21%). In addition, oocytes with a proper chromosomal number almost always retained correct ploidy after fertilization, as 87% of the euploid oocytes developed into euploid embryos. Their findings show that embryo ploidy is linearly propagated after fertilization, which underscores the immense importance of oocyte euploidy in early embryo survival. These reproductive changes associated with aging are also accompanied by decreased ovarian reserve (5), thought to be due to follicle atresia as a result of programmed cell death.

There are two leading theories regarding the age-related decline in oocyte quality. The first is that selection of the highest-quality oocytes during early reproductive years leaves the less favorable oocytes for more advanced age. The other 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 aging and its effects on somatic cells as well as oocytes is still largely unknown. However, recent data suggest a central role for mitochondria. One of the hallmarks of aging is accumulation of point mutations and deletions of mitochondrial DNA (mtDNA) (6). These mutations are unevenly distributed, can accumulate clonally, and can cause a mosaic pattern of respiratory chain deficiencies in tissues characterized by energy consumption. The cause of these mutations has been strongly debated.

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A very elegant study by Trifunovic et al. (7) examined this question by creating homozygous knock-in mice that express a proofreading-deficient version of PolgA, the catalytic subunit of mtDNA polymerase. The result was a threefold to fivefold increase in the level of point mutations and deletions of mtDNA. This increase in somatic mtDNA mutations was associated with reduced life span and premature onset of aging-related phenotypes such as weight loss, reduced subcutaneous fat, alopecia, kyphosis, osteoporosis, and anemia. Most interestingly, the mtDNA-mutator mice suffered a profound reduction in fertility. The females could not conceive after the age of 20 weeks despite being exposed to males for several months.

Wang et al. (8) studied the adverse effects of maternal diabetes on embryo development and pregnancy in a diabetic mouse model. It is well known that mothers with diabetes, which is characterized by high oxidative stress (9) resulting in mitochondrial dysfunction (10), experience poor reproductive outcomes similar to older patients, with an increased risk of miscarriages, birth defects, and fetal aneuploidies. This poor reproductive performance was found to be associated with mitochondrial dysfunction similar to that found in the embryos of older mothers, including an alteration in mitochondrial ultrastructure and increased mtDNA copy number accompanied by markedly reduced levels of adenosine 5′-triphosphate (ATP) and tricarboxylic acid (TCA) cycle metabolites. Furthermore, oocytes from diabetic mice displayed a higher frequency of spindle defects and chromosome misalignment in meiosis, resulting in increased aneuploidy rates in ovulated oocytes. The investigators concluded that the toxic conditions to which oocytes are exposed in diabetic mothers induce significant mitochondrial damage. Because mitochondria are solely inherited from the mother, the embryo inherits a dysfunctional energy-producing mechanism for the support of the crucial stages of its development.

Cytoplasmic transfer between oocytes was initially developed to treat infertility patients who exhibited persistent poor embryonic development and recurrent implantation failure after IVF. The technique was based on the assumption that the ooplasm of eggs, particularly from older women, was defective and could be rescued by the introduction of ooplasm from eggs of younger donors. The procedure involved microinjection of 5% to 15% of the ooplasm from a young, presumably fertile donor oocyte into a putative defective recipient oocyte (11). This treatment was based on results of earlier animal experiments involving mouse embryos from strains that experience a developmental block. Injection of cytoplasm from an oocyte of a nonblocking into a blocking strain increased cleavage rates of the recipient embryos compared with noninjected controls, suggesting the presence of an ooplasmic factor capable of rescuing the developmental block (12). Transfer of ooplasm from healthy fertile donors into oocytes of patients with repeated embryonic developmental failure has been used clinically, resulting in the birth of several children worldwide (11–14). Despite the fact that many different cytoplasmic components are injected, it is commonly believed that the beneficial effects are derived from the mitochondria. Children born as a result of this technique have demonstrated heteroplasmy (15), the presence of two different strains of mitochondrial DNA in their genome; as a result, there is now a moratorium on ooplasm transfer in the United States and Canada.

These examples, in which the process of reproductive senescence was induced at an early age by insults to mitochondrial function and corrected by the transfer of healthy mitochondria to an affected oocyte, suggest that reproductive aging is not the result of a preferential selection of oocytes but rather the effect of the aging process and, more specifically, the aging effect on the function of the mitochondria.

Oogenesis and the formation of the ovarian follicles start in fetal life. Both the oocyte and the primordial follicle may reside within the ovary for as long as 50 years before growth and development into mature oocytes. Immature oocytes in the ovarian cortex are diploid, containing 46 chromosomes arrested in prophase of the first meiotic division. After follicle growth and maturation, the onset of the luteinizing hormone surge or the human chorionic gonadotropin trigger during assisted reproduction treatment leads to resumption of meiosis in the oocyte. During this process, the chromosomes condense, align in pairs, and then separate via pulling apart of the chromosomes by the spindle fibers, resulting in a mature oocyte that contains 23 chromosomes. The other set of chromosomes is isolated outside the oolemma in the first polar body. The second meiotic division commences with the penetration of a viable sperm. The oocyte then extrudes 23 sister chromatids, resulting in a second polar body and a fertilized zygote that has a normal diploid complement of 46 chromosomes. 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 the mitochondria.

The oocyte has, by far, the largest number of mitochondria and mtDNA copies of any cell (approximately 2×10^5 copies) (16), at least one or two orders of magnitude more than somatic cells like muscle and neurons that have high energy requirements. Primordial germ cells contain only a few copies of a founder mitochondrial genome (~200 mtDNA copies) enclosed in immature mitochondria that replicate and eventually populate the new organism. It was originally thought that this process (mitochondrial bottleneck theory) resulted in selection of mitochondria with the best mtDNA while eliminating possibly mutated mtDNA, and resulting in a more homogenous mtDNA population in primordial germ cells. However, a recent study (17) showed that selection of mitochondria and mtDNA in the oocyte is a random process that does not screen for the intact wild-type mitochondrial genome. Therefore, mitochondria with abnormal mtDNA are just as likely to be inherited by the offspring as normal mitochondria. During the process of mitochondrial replication and expansion, oocytes will dramatically amplify their population of mitochondria, thereby supplying each gamete with a large copy number of both normal and abnormal mtDNA.

Mitochondrial replication is controlled by several nuclear encoded transcription factors that stabilize (TFAM) and unwind (Peo1/SSbp1) mtDNA. Mitochondrial DNA integrity is maintained by mtDNA polymerase (Polga/b) (18). These factors are mainly involved with modulation of mtDNA copy number rather than mitochondrial function. There are