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Could We Hack Women's Biological Clock? A Mitochondrial Hypothesis

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Abstract

Our knowledge about aging infertility suggests that oocyte quality is the major contributing factor. Assisted reproductive technologies (ART) teach us two critical facts about this topic: the reduction of reproductive capacity observed in aged women is related with the oocyte´s age, and how we can reverse the aging process getting high rates of live-birth pregnancies achieved by aged women with oocytes donated by younger women. The biologic reason why older women have a lower pregnancy rate is because aneuploid embryos are more frequently obtained from aged women. In this context, the quality of oocyte mitochondria is determinant in embryo quality, relating to euploid embryos, since mitotic non-disjunction occurs more frequently in advanced aged women [1].

Keywords: Oocytes age; Aneuploid embryos; Mitochondrial DNA; Mammalian embryos; Growth hormone; Mitochondria donation; Mitochondria transplant

Abbreviations: ART: Assisted Reproductive Technologies; mtDNA: mitochondrial DNA; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; GH: Growth Hormone

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A mitochondrial hypothesis

The oocyte is the largest cell in humans and it can contain 100.000 mitochondria. Each mitochondrion contains 1 to 15 mitochondrial DNA (mtDNA) molecules, then one single oocyte can contain between 50.000-1.500.000 copies of the mitochondrial genome [2]. mtDNA copy number per oocyte has been related with the probability of developing healthy oocytes [3,4].

mtDNA is constantly replicating during oocyte maturation, but the number is stable after maturation (metaphase II oocytes). mtDNA level in human oocytes is inversely associated with maternal age and ovarian reserve clinical indicators [5]. Mountains of evidences show that older women's embryos have higher levels of mtDNA, which is correlated with implantation failure, and there is a threshold level of mtDNA above which implantation never occurred [6]. On the other hand, mtDNA level has found raised in aneuploid embryos compared to euploid embryos, independently of the maternal age [7]. That increased mtDNA has been correlated with elevated metabolism and reduced viability, consistent also with the "quiet embryo" hypothesis. This hypothesis proposes that the viability of early mammalian embryos is associated with a metabolism that is quiet rather than active [7-9]. The process of disjunction requires a significant amount of energy, provided by ATP from the mitochondria, and therefore, mitochondrial dysfunction is associated with oocyte aging and increased incidence of aneuploidy of maternal origin [10,11]. Duran *et al*. [5] have proposed that mtDNA quantification was more closely associated with Follicle-Stimulating Hormone (FSH) predicted reproductive age than with chronological age.

The mitochondria dysfunction is also associated with mtDNA mutations. The exposition of oocytes to harmful endogenous factors, as Reactive Oxygen Species and free radicals, while they are dormant, may cause mutations in the mtDNA. For example, a 4977-pb deletion was the most common deletion found in aged women, which represents the loss of several mitochondrial genes [7]. In the same way, a low expression of the *PPARGC1A* gene, involved in mitochondrial biogenesis and antioxidant activity, has been also described in women with diminished ovarian reserve [12].

Strategies for improve ovarian quality

Do we have a strategy to hack women's biological clock? One strategy is the addition of different supplements to culture media during ART with the idea of improving the embryo in vitro development, but that strategy is not universally accepted because some adverse negative effects were described [13-15]. Silva *et al*. added antioxidants to culture media and the

expression of oxidative stress genes was reduced, and more blastocysts were developed. Sato *et al*. added resveratrol to maturation medium and *SIRT*1 expression was observed, but no effect on mtDNA copy number in oocytes was detected.

Other approach is the administration of exogenous growth hormone (GH) during standard ovarian stimulation regimens. An increase of mitochondrial function by GH has been observed in skeletal muscle cells, and also it was proposed that GH may acts increasing the FSH and luteinizing hormone (LH) receptors [16,17]. When GH was added before o during controlled ovarian stimulation, a higher embryo implantation and clinical pregnancy rates have been described, which is related with the capacity of GH to increases mitochondrial function, but it does not alter the yield of oocytes [17,18].

Finally, the most exciting approaches is "mitochondria transplant" or "mitochondria donation", a set of *in vitro* techniques based on mitochondria replacement therapy by pronuclear transfer, spindle chromosome complex transfer, or polar body transfer [19-22]. All these methods exchange old mitochondria for younger ones from oocytes donors, increasing the developmental potential of the embryo and the pregnancy rates. This strategy has been used in some clinical human cases with promising but still controversial results.

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