Relationship between diminished ovarian reserve and mitochondrial biogenesis in cumulus cells

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STUDY QUESTION: What part do mitochondria play in cases of diminished ovarian reserve (DOR)?
SUMMARY ANSWER: Mitochondrial biogenesis in cumulus cells may be linked with impaired oocyte competence in patients with DOR.
WHAT IS KNOWN ALREADY: DOR, one of the causes of infertility even in young women, is characterized by the depletion of the ovarian pool associated with a decline in oocyte competence. Mitochondria, which play a role in oocyte quality, could be involved in the pathogenesis of DOR. The study of cumulus cells offers an interesting non-invasive approach for evaluating oocyte quality and the metabolic processes on which it depends. If mitochondrial dysfunction is involved in DOR, it is likely to have an impact on the functioning of cumulus cells.
STUDY DESIGN, SIZE, DURATION: This is an observational study of 74 immature oocyte-cumulus complexes retrieved from 47 women undergoing in vitro fertilization with intracytoplasmic sperm injection at the University Hospital of Angers, France, from March 2013 to March 2014. The women were divided into two groups: one group included 26 women with DOR, and the other, which included 21 women with a normal ovarian reserve (NOR), served as a control group.
PARTICIPANTS/MATERIALS, SETTINGS, METHODS: The oocyte mitochondrial content and the average mitochondrial content of the cumulus cells were assessed by mitochondrial (mt)DNA quantification using a quantitative real-time PCR technique. Microfluidic-based quantitative RT-PCR assays were used to quantify the expression of 13 genes involved in mitochondrial functions such as apoptosis and antioxidant activity or in mitochondrial biogenesis. We used orthogonal partial least-squares discriminant analysis (OPLS-DA) to distinguish between the DOR group and the NOR group of patients, and an OPLS model to predict the value of the oocyte mtDNA content that could be used as a critical marker of oocyte quality.
MAIN RESULTS AND THE ROLE OF CHANCE: The OPLS-DA model showed a good predictive capability (Q2 = 0.543). Using the variable importance in projection (VIP) metric we found three mitochondrial variables distinguishing the DOR group from the NOR group of patients, i.e. the oocyte mtDNA content (VIP = 0.92), the cumulus cell mtDNA content (VIP = 0.95) and the expression in cumulus cells of peroxisome proliferator-activated receptor ɣ coactivator 1 alpha (PPARGC-1A) (VIP = 1.10), all of which were lower in the DOR group than in the NOR group of patients. The OPLS model was able to satisfactorily predict the oocyte mtDNA content in only the NOR group of patients (Q2 = 0.506). We found four new variables positively linked to the oocyte mitochondrial mass, i.e. the cumulus cell mtDNA content (VIP = 1.19), and the expression in cumulus cells of three factors of mitochondrial biogenesis: polymerase gamma (POLG) (VIP = 2.13), optic atrophy 1 (OPA1) (VIP = 1.89) and the transcription factor associated with mitochondria (TFAM) (VIP = 1.32).
LIMITATIONS, REASONS OF CAUTION: This is a descriptive study. Because of ethical concerns in human clinical practice, this study has been performed only on immature oocytes and corresponding cumulus cells, which are usually discarded during in vitro fertilization procedures.
WIDER IMPLICATIONS OF THE FINDINGS: Cumulus cells may govern mitochondrial biogenesis, creating an adequate oocyte mitochondrial pool to promote embryonic development. The alteration of this process in patients with DOR may account for the impairment of oocyte quality. This suggests that some mitochondrial characteristics of cumulus cells may serve as indicators of oocyte competence and that oocyte quality may be improved by products enhancing mitochondrial biogenesis.
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