Exploring the epigenetic profile of women with poor ovarian reserve

Assisted reproductive technology prognoses depend essentially on the number of oocytes obtained after ovarian stimulation. On occasions, ovaries do not respond adequately and only a small number of oocytes are obtained. This affects the chances of pregnancy although, in most cases, the cause is poor ovarian reserve.

Ovarian reserve is, to a large extent, determined by the female patient's age. Follicle counts gradually decrease with age until there are very few follicles left at menopause. However, not all women of the same age have identical ovarian reserves. Accordingly, there have been a significant number of studies aimed at understanding and establishing the contributing factors, including the following: genetic mutations that cause accelerated ovarian aging, metabolomics and proteomics of the granulosa cells.

The research work carried out by Olsen et al. (1) studies the epigenetic profile of women with poor ovarian reserve and falls under this framework. Epigenetics is the study of the mechanisms that regulate gene expression without alterations in the DNA sequence. The mechanisms involved in epigenetic regulation are: DNA methylation; post-translational histone modifications; and chromatin remodelling. Granulosa cell epigenetics studies round off molecular vision and the issue of ovarian reserve by analyzing the DNA and histone modifications that determine the gene expression patterns in these cells, which are a vital part of folliculogenesis.

This research is an extension of another recently published study (2) demonstrating that granulosa cells have their own aging epigenetic profile, which differs from the one in other tissues such as leukocytes. Furthermore, it ascertains that these changes do not correlate with chronological age.

In this particular study, the authors analyze DNA methylation in 119 women categorized according to antimüllerian hormone (AMH) levels into diminished ovarian reserve (DOR), normal ovarian reserve, and high ovarian reserve. Two cell types were analyzed with the aim of understanding if the phenomena under study are tissue specific: granulosa cells (experimental group) and leukocytes as the control group.

The three groups have similar characteristics except for the parameters associated with ovarian reserve (AMH, follicular stimulating hormone (FSH), and oocytes retrieved following ovarian stimulation).

The main findings of the research are very significant, indeed. In the first instance, it ascertains that there is a difference in the epigenetic profile of the granulosa cells of women in the DOR group and women who have a normal ovarian reserve: increased methylation and variability. The increased variability denotes expression deregulation in the genes required for folliculogenesis. Second, the number of epimutations (defined for each cytosine-phosphate-guanine (CpG) island as an atypical methylation value or outlier) is greater in patients with poor ovarian reserve. Epimutations are an indication of defects that have accumulated with age. Furthermore, women in the DOR group have increased DNA methylation telomere length (DNAmTL), a biomarker of biological age. Telomere length deregulation in patients with DOR may be caused by genetic variants in DNA repair pathways that participate in telomere maintenance.

As is the case in other tissues, the methylation regions (gene repression) are enriched with other epigenetic marks that are linked to gene silencing such as trimethylation of histone H3 lysine 27 (H3K27m3). Coordination in the cells is perfect for a global expression inactivation effect caused by the different marks. In this study, the greatest methylation variability in patients with DOR was observed in H3K27m3-marked regions. Research on animals identifies a different expression mediated by human chorionic gonadotropin/luteinizing hormone receptor (hCG/LH)-induced H3K27m3 marks, suggesting a possible abnormal response to ovulation induction in patients with DOR. With regard to suppressed target genes, this includes genes involved in cell adhesion and genes involved in folliculogenesis such as insulin growth factor 2 (IGF2) and AMH.

These findings are not present in leukocytes. Regulation is tissue specific. There is no value to studying such epigenetic phenomena in other more accessible tissues such as leukocytes because there is no correlation between the events that take place in the follicle and those in the blood cells. The phenomena are local and must be analyzed and studied in the cells under examination.

In their initial analysis, the authors do not identify a link between epigenetic aging (estimated through different procedures: DNAm age and (DNAmethylationTL) and ovarian reserve (AMH). This result is somewhat confusing because, if the analysis is performed within each category, a linear link between DNAmTL and AMH is observed. Furthermore, the differences are clear or otherwise depending on if they are adjusted according to age or not. Additional research into this factor is needed if a definitive conclusion is to be reached. The results generate even greater confusion given that there is no evidence of accelerated aging because there is no increased epigenetic age acceleration across the different groups.

Furthermore, establishing the epigenomes linked to the different ovarian pathologies (3) and a reference ovarian epigenome in patients who do not undergo assisted reproductive technology would be of interest. This ought not to be done as a fixed image at the very end but rather indicating how epigenetic modifications alter as the pathologies evolve. Research ought not to be limited to DNA methylation but extended to all other epigenetic marks. This knowledge is all incredibly valuable and ought to be applied to daily clinical practice and made use of as predictive biomarkers for all these pathological processes. Prediction and anticipation play an essential role in the medicine of today.

Last, modifying the epigenome in patients with poor ovarian reserve is key. Genetic mutations cannot be reversed. However, epigenetic modification is a dynamic and reversible process. The aim would be to reprogram the ovary; using pharmaceutical drugs to reverse the modification patterns that lead to inadequate folliculogenesis. Progress of this kind is being made in other areas of medicine, such as oncology (4), meaning that it is not unreasonable to suggest such a possibility in this case.

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REFERENCES

1. Olsen KW, Castillo-Fernandez J, Chan AC, la Cour Freiesleben N, Zedeler A, Bungum M, et al. Identification of a unique epigenetic profile in women with diminished ovarian reserve. Fertil Steril 2020;115:XXX–XX.
2. Olsen KW, Castillo-Fernandez J, Zedeler A, Freiesleben NC, Bungum M, Chan AC, et al. A distinctive epigenetic ageing profile in human granulosa cells. Hum Reprod 2020;35:1332–45.
3. Makrinou E, Drong AW, Christopoulos G, Lerner A, Chapa-Chorda I, Karaderi T, et al. Genome-wide methylation profiling in granulosa lutein cells of women with polycystic ovary syndrome (PCOS). Mol Cell Endocrinol 2020; 500:110611.
4. Zhao L, Duan YT, Lu P, Zhang ZJ, Zheng XK, Wang JL, et al. Epigenetic targets and their inhibitors in cancer therapy. Curr Top Med Chem 2018;18: 2395–419.