

Summary. Sirard

“Genomic evidence for the importance of inflammation on IVF outcomes”

Sirard, MA., Fortin, C.; Mahutte, N.; Leader, A.; Gysler, M.; Villeneuve

Centre de recherche en reproduction, développement et santé intergénérationnelle (CRDSI), Université Laval, Québec, Canada

Hormonal stimulation prior to IVF influences the ovarian environment and therefore impacts oocytes and subsequent embryo quality. The response to hormonal stimulation is highly variable among patients, but there is currently no way to characterize the patient's response and to know in which way its oocytes were affected by the treatment. Few studies have analysed what went wrong in failed IVF cycles. Having such information would allow clinicians to adapt and personalize the treatment, which would potentially improve success rate.

Follicular cells principally composed of granulosa cells were obtained from a total of 200 consenting patients undergoing IVF treatment in 4 Canadian fertility clinics. Samples were analyzed according to the outcome of the IVF cycle. Positive group refers to patients for which pregnancy (heart beat) was confirmed and negative group refers to the failed IVF cycles (no pregnancy after the used of all embryos from the stimulation cycle). Using microarray, 32 samples (16 from negative group vs 16 from positive group) were compared to determine how gene expression is affected in follicles from failed cycles. Functional analysis of the differentially expressed genes was performed using ingenuity pathway analysis. In a larger cohort of patients (n=97), quantitative RT-PCR was used to validate the microarray results and to analyze potential markers of failure. A total of 165 genes were differently expressed ($P < 0.05$, fold change > 1.5) in the negative group compared to the pregnancy group, including many pro-inflammatory cytokines or other factors related to inflammation. Several factors, some of which act upstream from vascular endothelial growth factor (VEGF), were also overexpressed in the non-pregnant group. The functional analysis highlighted the importance of the immune system and inflammatory reactions and showed an imbalance between pro-inflammatory and anti-inflammatory mediators which may account for the failure to conceive following ovarian stimulation. In addition, other differentially expressed genes appear related to abnormal differentiation and increased apoptosis. After hierarchical clustering, 3 distinct subgroups were identified and characterized: 1) Follicles still in the growing mode 2) hyper inflammation response; 3) follicular heterogeneity including overgrown follicles. Together these results indicate that inflammation could be an important factor to consider to explain cycle failure.