Better together than alone: the cumulus benefits

The sperm, the lesser regarded gamete in embryology since intracytoplasmic sperm injection (ICSI) was introduced in the 1990s, has not attracted sufficient attention in the last 20 years (1). With the increasing proportion of cycles undergoing ICSI, why is ICSI used so widely? Can we justify the increased trust in ICSI over conventional in vitro fertilization (IVF)? The natural selection of sperm in conventional IVF is attractive. Can the ICSI process be improved by accounting for this natural selection?

The role of granulosa/cumulus cells in oocyte maturation and growth is well documented. There is some suggestion that the cumulus has sperm chemotaxis attraction properties (2). However, with the routine removal of the cumulus prior to ICSI, these benefits are lost in the ICSI process. Can the cumulus sperm selection properties be used to improve sperm selection in ICSI?

In this issue of *Fertility and Sterility,* Wang et al. (3) present a prospective study investigating the effectiveness of cumulus oophorus complexes (COCs) in the physiological selection of spermatozoa for ICSI. By obtaining the COCs mechanically using glass pipette prior to denudation with hyaluronidase, the authors avoided the potential impact of the enzyme on the structure and efficacy of the cumulus cells. The authors performed a sibling oocyte study in couples undergoing ICSI. Sixty patients were included in the study whereby ICSI was performed with spermatozoa that traversed the collected COCs in vitro. Wang et al. (3) reported that oocytes injected with COC-selected spermatozoa had up to a 10% higher fertilization rate, with no significant effect on cleavage and top embryo rate compared with the conventional ICSI group. Interestingly, with embryos undergoing extended culture, COC-ICSI lead to 10% more blastocysts, 14% more top blastocyst rate and close to 20% more usable blastocysts. Consequently, oocyte utilization rate was significantly improved.

The small number of patients, sixty, meant that the study was not powered to assess clinical impact with regards to implantation and clinical pregnancy rates. For clinical outcome, the fresh and frozen transfers were not randomized as embryos were selected for transfer based on morphology, leading to unbalanced transfers between the two groups. Nevertheless, inclusion of frozen embryo transfer allowed the addition of a reasonable number of transferred embryos and the cumulative pregnancy rates between the two groups, although not statistically different, was slightly higher in the COC-ICSI compared to the conventional ICSI group.

This study represents a proof of concept supporting the author's hypothesis, through the best model available, sibling oocytes. They have therefore been able to ascertain a potential benefit of COC on fertilization rate and embryo quality. Although the embryo quality description could be improved with time-lapse assessment, sample size is adequate to address the author's study question. This study will set the precedent for future studies, which are obviously required.

There are particular aspects of this paper that may limit the potential implementation in other clinics. For instance, they avoided the use of discontinuous gradient to prepare sperm which may have a potential impact on spermatozoa maturation. However, it could be argued that density gradient separation may not be adequate for effective sperm recovery in semen samples of low semen quality, as determined by the strict inclusion criteria for ICSI in this study (progressive motility below 5%, total number of progressive sperm under 2 million).

The authors further retrospectively analyzed the embryo culture outcomes of conventional IVF enrolled in the same inclusion and exclusion criteria during the same period and made a comparison between the conventional IVF and COC-ICSI groups. Surprisingly, they found that in a comparable group of patients, the embryo culture results of conventional IVF were closer to those in the COC-ICSI group.

Embryo development and subsequent pregnancy outcome may be potentially affected by sperm quality (4), but the conventional procedures to be applied for sperm selection based on morphology may have limitations related to high levels of DNA fragmentation (5). There is a need to look for new and reliable methods for selecting the best sperm cells available in the ejaculate, avoiding altered or arrested embryo development, higher risk of pregnancy loss, or even chromosome alterations or offspring defects.

We have improved sperm selection techniques which are based on the intense assessment of sperm morphology and the molecular characteristics of sperm cells. Still conflicting results are present in the literature, because the improved outcomes are difficult to be properly proven or the procedures may be expensive or time-consuming. As embryologists, we have been using intracytoplasmic morphologically selected sperm injection with motile sperm organelle morphology examination, sperm-HA binding, sperm polarization microscopy, zona bound spermatozoa, electrophoresis and magnetic activated cell sorting between others as new objective tools to improve sperm selection, but still these are not widely used due to complexity, high cost, and conflicting evidence of effectiveness, amongst other reasons.

This study (3) suggests that COCs may play a physiological role in selection of functionally competent sperm, the mechanisms of which are only partially understood, but likely involve the presence of hyaluronic acid present in the extracellular matrix. Use of COCs might provide a physiologically less-intrusive alternative for sperm selection than the commercially available hyaluronic acid binding test. We may also take into account the effect of the secretory products of cumulus cells, such as Progesterone, lysophosphatidylcholine or phytosphingosine, which may add a chemotaxis role in sperm fertilization capabilities.

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