Let's rescue oocytes: in vitro maturation 2.0 is coming

Are clinicians and embryologists aware of the recent achievements in vitro maturation (IVM)? Or is this now considered an old-fashioned procedure? Unfortunately, not unlike the fashion field, reproductive medicine is subject to the influence of trends and opinion leaders—but we must pay greater attention to the recent advances in IVM research. After conventional ovarian stimulation, IVM is a feasible rescue method for patients who have yielded a higher-than-expected proportion of oocytes at the immature germinal vesicle (GV) stage. Not only can IVM obtain more embryos to improve the efficiency of a cycle, but it may provide the sole option for obtaining any viable embryos.

Numerous studies in natural cycles or with soft stimulation in women with polycystic ovary syndrome (PCOS) have shown that GV oocytes can resume meiosis after prolonged culture, fertilization, and cleavage—in some cases at a rate comparable to oocytes matured in vivo—and give rise to newborns (1). However, studies on IVM in cycles stimulated as a rescue method are limited. Although these immature oocytes reach the metaphase-2 (MII) state and fertilize at different rates, depending on the maturation culture medium, the system used, and the culture duration, there is consensus that embryos derived from oocytes matured in vitro have a lower development potential than sibling embryos derived from oocytes matured in vivo (1, 2). This has generated some reluctance in the in vitro fertilization community to include cycles with IVM in the daily routine.

Because laboratory parameters play such an important role in the success of IVM, our group has focused on optimizing nuclear maturation rates and cytoplasmic competence. As shown by Escrich et al. (2), time-lapse incubators allow up to 70% of GV oocytes to mature to MII in the first 24 hours of culture, a rate of IVM similar to that found with some conventional incubators (3, 4). This percentage of maturation is higher than that obtained by the majority of IVM technicians, who show lower maturation rates or need a longer culture time for oocytes (up to 48 hours) to achieve similar rates (1, 2).

The main advantage provided by time-lapse culture is that it allows us to study the dynamics of the nuclear maturation of oocytes. Oocytes at the GV stage present a wide heterogeneity in the time required to complete nuclear meiosis in vitro. Studies of the dynamics of nuclear maturation of GV oocytes have indicated that metaphase I arrest is a transient stage of meiosis, generally of a constant 14.0 $\pm$ 0.3 hours' duration; the GV stage arrests the variable phase (2). In fact, Escrich et al. (2) defined two GV subpopulations, according to the time required for the extrusion of the first polar body: the early maturation group, comprising those that reach the MII stage in $<$23.3 hours of culture, and the late maturation group, comprising those needing $\geq$23.3 hours of culture. This allowed the selection within the early maturation group of the oocytes whose post-MII age was 4.3 hours maximum at the time of activation. This group showed a normal activation response similar to oocytes matured in vivo, unlike the early maturing oocytes in which the postmetaphasic age was higher or the oocytes that achieved nuclear maturation later.

In regards to the potential for in vitro embryo development, few studies (1, 3, 4) have shown that the rates of fertilization, division, and progression to the stage of eight cells in IVM-derived oocytes can be comparable to their sibling oocyte matured in vivo. Only one study (1) has indicated that they are also able to progress to the blastocyst stage at a level comparable to the rate of sibling in vivo oocytes. However, more diversity exists in the rates of euploidy. Escrich et al. (1) showed that 50% of the biopsied blastocysts were euploid, results that contrast with those of Nogueira et al. (4) who observed a dramatically low incidence of euploidy (2.5%) in embryos derived from mature in vitro oocytes of women aged 29 to 36 years. These data suggest that oocyte culture conditions have a greater impact than maternal age on the euploidy of the embryo, particularly for post-MII oocyte aging, another factor that can cause aneuploidy (1). The selection of early maturing oocytes among the GV population is possible thanks to close monitoring of their nuclear maturation progress through time-lapse technology. This is a decisive parameter that can determine the results obtained in IVM (1, 2).

In this issue of *Fertility and Sterility* Madkour et al. (5) offer additional evidence to support the evolution of IVM—an IVM 2.0 version. Their study demonstrates the effectiveness of a new IVM approach to rescue the immature denuded oocytes (IDO) of women with PCOS by using heterologous follicular fluid (HFF) and the supernatant of cumulus granulosa cells (CGC) to mimic the intact follicular microenvironment. The authors performed a prospective pilot study over a reasonable number of cycles with IDO obtained from PCOS patients. They compared a simple IVM system with various protocols based on supplementation with HFF and CGC. When they compared the outcomes among four treatment groups, they observed that supplementation with HFF and CGC gave the best yield of developed blastocysts per IDO. The maturation rate also improved, with significant improvement in the cleavage rate. They concluded that this adapted IVM system offers an acceptable new approach for obtaining meiotic competence and competent MII oocytes capable of developing into intact embryos.

Although their study involved a relatively small sample size, we must acknowledge that a considerable amount of clinical research work was involved in recruiting those numbers and performing that many oocyte maturation protocols. In their results, the authors provided consistent clinical data on embryo quality at day 3 and at the blastocyst stage. Unfortunately, no chromosome content was available for the embryos that resulted from IVM, which would be very helpful in evaluating this new IVM protocol.

Although more data are required to quantify the real contribution of GV rescue approaches on clinical outcomes, these recent innovations can provide immediate, long-term

benefits by reducing cancelation rates and providing additional blastocysts or transfers per attempt—potentially leading to more live pregnancies and births (1, 5).

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REFERENCES

1. Escrich L, Galiana Y, Grau N, Insua MF, Soler N, Pellicer A, et al. Do immature and mature sibling oocytes recovered from stimulated cycles have the same reproductive potential? Reprod Biomed Online. In press.
2. Escrich L, Grau N, de los Santos MJ, Romero JL, Pellicer A, Escribá MJ. The dynamics of in vitro maturation of germinal vesicle oocytes. Fertil Steril 2012;98:1147–51.
3. Lee HJ, Barad DH, Kushnir VA, Shohat-Tal A, Lazzaroni-Tealdi E, Wu YG, et al. Rescue in vitro maturation (IVM) of immature oocytes in stimulated cycles in women with low functional ovarian reserve (LFOR). Endocrine 2016;52:165–71.
4. Nogueira D, Staessen C, Van de Velde H, Van Steirteghem A. Nuclear status and cytogenetics of embryos derived from in vitro-matured oocytes. Fertil Steril 2000;74:295–8.
5. Madkour A, Bouamoud N, Kaarouch I, Louanjli N, Saadani B, Assou S, et al. Follicular fluid and supernatant from cultured cumulus-granulosa cells improve in vitro maturation in patients with polycystic ovary syndrome. Fertil Steril 2018;110:710–9.