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Editorial

In Vitro Maturation of Oocytes: Current Status and Controversies

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In vitro oocyte maturation (IVM) has carved a niche for itself in assisted reproductive technology (ART). In 1991, Cha et al. [1] reported the first collection of immature oocytes, which were matured in vitro and resulted in a live birth. Since then, IVM protocols have developed ranging from IVM without hormonal priming, to several modalities of gonadotropin primed IVM, including human chorionic gonadotropin (hCG) triggering. In polycystic ovary syndrome (PCOS) patients, there might be a benefit in administering hCG prior to oocyte retrieval [2]. Our prospective study showed improved implantation (9.6% vs 1.5%) and clinical pregnancy rates (29.9% vs 4%) after hCG priming when compared with regular cycling patients [3]. Then, we sought whether higher doses of hCG would improve metaphase-II (MII) oocyte yield by an RCT whereby patients were randomized to receive the usual 10000 IU or a higher dose of 20000 IU. The maturation, fertilization, pregnancy or implantation rates (IRs) were found to be comparable which supports the notion that there is no benefit to use the higher dose in IVM [4]. Additionally, Fadini et al. [5] reported that the combination of hCG and FSH priming, in women with regular cycles, might be superior to IVM cycles without priming. The number of mature oocytes at retrieval (20.3% vs 0%), MII oocytes after 30h culture (77.4% vs 48.4%), IRs (16.4% vs 9.2%), and clinical pregnancy rates (29.9% vs 15.3%) were found to be statistically higher with FSH priming plus hCG when compared to no priming [5]. These findings suggest that FSH and hCG might work in concert to affect oocyte maturation and fertilization potential.

IVM has the potential to substitute, or at least be an adjuvant for standard in vitro fertilization (IVF) protocols due to a number of reasons. IVM is a therapeutic alternative for women with PCOS in whom controlled ovarian stimulation (COS) places them at increased risk for OHSS [6]. While special protocols such as antagonist protocols or "coasting" reduce the risk, they do not completely prevent OHSS. Since, IVM represents an attractive strategy to eliminate the development of OHSS, the most appropriate candidates for IVM are PCO/PCOS patients [3]. In addition, IVM has a significantly lower treatment burden with less consumption of gonadotropin medication and thus lower costs. IVM might also have advantages in specific circumstances, such as estrogen-sensitive tumors and/or urgency to start therapy, which discourages the implementation of standard ovarian stimulation regimen. First, COS can require at least 10 days (even with random start protocols), which is not compatible when the initiation of urgent cancer treatment is required. Second, the supra-physiologic serum estradiol levels obtained at the end of gonadotropin administration are theoretically contraindicated in estrogen-sensitive diseases. Therefore, the development of fertility preservation has recently opened new perspectives to IVM.

However, studies show that the number of oocytes retrieved from IVM is higher in PCOS than in non-PCOS women because of their higher antral follicle counts and thus IVM in women with PCOS results in better pregnancy rates [3,7]. In general, the clinical pregnancy and IRs have reached 30% to 35% and 10% to 15%, respectively, in infertile women with PCOS [8]. Despite relatively high success rates in PCOS, pregnancy rates were found to be still lower in these women than in those with regular IVF. In a case-control trial, we compared the results of 107 PCOS women undergoing IVM with those of 107 other PCOS women treated by conventional COS-based ART. The mature oocyte and embryo yields were of 7.8 and 12.0 oocytes and 6.1 and 9.3 embryos in the IVM and regular ART groups, respectively. Likewise, pregnancy and live birth rates were lower at 26.2% and 15.9%, respectively, in IVM, as compared with 38.3% and 26.2%, respectively, in regular ART [9]. Additionally, Le Du et al. [10] found 22.5% clinical pregnancy and 13.5% live births per embryo transfer in PCOS patients triggered with 10,000 IU of hCG. However, in a more recent prospective trial comparing a total of 67 cycles of PCOS patients to IVM, agonist or antagonist protocol, IVM showed comparable success rates to conventional ART. Despite retrieval of significantly less oocytes in IVM; implantation, miscarriage and live birth rates were found to be comparable to those of IVF cycles. Although these results are encouraging, this is a small study with only 14 cycles in each group, and there are no RCTs to confirm this issue [6]. In large series, IVM clinical pregnancy rates reached 23% to 34%; however, this was likely because more embryos were transferred in the IVM group [11]. As a consequence, implantation rates are a more reliable indicator of IVM efficiency and range lower than expected for women of comparable age undergoing conventional IVF. Thus, it seems like increasing the number of embryos transferred might be an available strategy in order to reach the comparable success rates.

It is estimated that more than 5000 IVM infants have been born worldwide. Preliminary analysis indicates that birth weight and incidence of congenital anomalies appear to be comparable in IVM and IVF cycles [12]. Thus, existing data from the studies in newborns assure us that IVM might be a safe procedure provided in ART.

The technology has improved; however, implantation and live birth rates have not met those of conventional IVF. The possible explanation might be specific media requirements for immature oocytes seem to be not "ideal" for now. Therefore, we desperately need more studies in order to expedite the development of effective IVM cultures. Alternatively, insufficient development of the endometrial lining during IVM cycles before embryo transfer might be an explanation as well. There are two sets of data supporting this issue. First, the higher implantation and pregnancy rates were observed in an oocyte donation program in which donors underwent IVM treatment while the recipients were using estradiol to prepare the endometrium [13]. Second, we have found that there is a positive relationship between endometrial thickness and clinical pregnancy in IVM cycles [14]. Adequate endometrial development is essential in any ART procedure, but even more so in IVM because a dominant follicle or a corpus luteum is not routinely formed. It possibly compromises both the follicular and luteal

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sex steroid contribution to the development of the endometrium. This might cause a delayed endometrial development at the time of embryo transfer because of truncated follicular growth phase which negatively contributes to implantation. Therefore, endometrial receptivity is the key element for the success of IVM treatment and studies trying to improve implantation rates should also have the endometrium as target. In 2001, we reported a case whose embryos produced from IVM oocytes was safely cryopreserved and a healthy infant was delivered [15]. Through a small prospective cohort study, de Vos et al. [16] compared fresh versus vitrified-thawed embryo transfers in non–hCG-stimulated IVM cycles from PCOS patients and found a detrimental effect when transferring fresh embryos (IR, 6.9% vs 21.9%; clinical pregnancy rate, 9.4% vs 31.8%). They attributed these findings to endometrial dys-synchrony in fresh transferred cycles and mentioned the possible role of hCG in improving the endometrial receptivity. Their data also suggest that implantation rates might be improved by replacing cryopreserved embryos in a subsequent cycle to achieve endometrium-embryo synchrony. Since, very limited data are available comparing fresh and frozen IVM cycles; well-designed large studies are still required. Furthermore, there are concerns whether embryos from IVM cycles have a higher incidence of chromosomal abnormality limiting their implantation potential as compared with embryos from conventional IVF cycles. However, in a retrospective study, the incidence of chromosomal abnormality was found to be comparable in IVF and IVM embryos (58.7% versus 57.4%, respectively) [17].

In conclusion, today's IVM seems to be in the creeping phase like the IVF in 1980s. Increasing the number of embryos transferred or implementing frozen cycles to IVM treatment might, in the short term, enhance success rates. However, in order to clarify important controversies in IVM, further prospective studies must incorporate both the improvement in culture mediums and the development of novel strategies for endometrial preparation.

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