

Newsletter 2023 – August

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Human IVM in the making

***In-vitro* maturation of oocytes versus conventional IVF in women with infertility and a high antral follicle count: a randomized non-inferiority controlled trial.**

Vuong LN et al., Hum Reprod. 2020;35(11):2537-2547

Background

In vitro maturation (IVM) of human immature cumulus oocyte complexes (COCs) is emerging as an integral facet of fertility preservation in conjunction with cryopreservation of ovarian tissue (OTC). This innovative approach of freezing and transplanting ovarian tissue with the non-growing primordial follicles has enabled access to surplus ovarian tissue that were hitherto inaccessible for research purposes. Consequently, novel investigations into human small antral follicles and their associated immature COCs, a historically challenging pursuit, are now feasible. Presently, various facets of IVM are capturing attention:

1. The *ex vivo* collection of COCs from surgically removed ovarian tissue.
2. Ongoing development of *in vivo* aspiration of COCs from small antral follicles.
3. Advances in maturation techniques to yield *in vitro* oocytes with robust developmental potential.

This newsletter is to highlight the progress of a method allowing the acquisition of oocytes from small antral follicles *in vivo*, circumventing the need for ovarian stimulation and for surgical removal of ovarian tissue.

Perspectives

This *in vivo* approach will be an important addition to collection of immature COCs *ex vivo*, in conjunction with OTC, where usually at least one ovary is retained in its original position and with both ovaries in place, will offer an additional reservoir of immature oocytes. Should this approach prove to be successful, it holds the promise of, not only enhancing fertility preservation, but also attracting broader interest within the realm of assisted reproduction.

Collection of human immature oocytes can be accomplished in two different scenarios:

1. Partial or complete removal of one ovary: encompassing the retrieval of immature oocytes from the retained ovary *in situ* alongside *ex vivo* collection from the excised ovary
2. Preservation of both ovaries in their original position

Diverse patient groups stand to benefit from immature oocyte collection:

1. In addition to individuals undergoing fertility preservation via OTC, new groups of patients with conditions like leukemia currently receiving OTC with a risk of ovarian involvement, and those with ovarian malignancies (given the non-malignant nature of oocytes) can now be considered. Importantly, COCs may be sourced from both ovaries.
2. Patients undergoing ovarian surgery (e.g., endometriosis), those with a genetic predisposition to premature ovarian insufficiency, and anovulatory women with polycystic ovary syndrome.

Summary of the Paper

This paper aims to determine whether one cycle of IVM is non-inferior to one cycle of conventional in vitro fertilization (IVF) in terms of live birth rates for women with a high antral follicle count. Spanning 546



ISFP – Newsletter

patients within a randomized controlled trial (RCT), the study fails to establish a significant disparity in reproductive outcomes between the two groups.

Notably, the Vietnamese group describes a ground-breaking technique where they aspirate COCs from small antral follicles measuring 2-10 mm following a brief FSH priming. The aspiration of immature oocytes employs a double needle system with a 17G outer needle and a 19-21G inner catheter, featuring a short 20 cm tube. COCs are retrieved through aspiration and curettage without flushing; heparin is added to the flushing medium. The procedure takes approximately 20-30 minutes.

While the IVM group records an average of five fewer aspirated oocytes compared to the IVF group, they still manage to collect an average of 14 immature COCs. With a maturation rate of 63% for oocytes in the IVM group, the quality of resulting embryos is similar to that of the IVF group. Moreover, pregnancy rates and neonatal outcomes exhibit parity between the two groups.

Critical evaluation of the paper

The paper primarily focuses on the clinical outcomes among women undergoing infertility treatment within a conventional assisted reproductive technology (ART) framework. The study does not detect statistically diminished outcomes in the IVM group concerning the initial embryo transfer. However, the cumulative outcomes suffer in the IVM group due to reduced number of oocytes collected.

Crucially, this study describes original findings on several fronts: •

- Successful collection of COCs from small antral follicles with creditable efficacy.
- Effective maturation of these COCs.
- Generation of embryos with implantation potential similar to conventional IVF treatment.
- Comparable outcomes in neonatal parameters for babies born from in vitro matured oocytes and those from conventional IVF procedures.

Substantial additional research is warranted to enhance efficacy across these dimensions, which, if successful, is likely to enhance efficacy of the fertility preservation offered to many groups of patients.

Conclusion

IVM, utilizing oocytes harvested from small antral follicles, has reached a point where it can significantly contribute to fertility preservation efforts.

Offspring originating from oocytes derived from small antral follicles appears similar to those born using standard IVF protocols.

Several patient groups previously overlooked for fertility preservation can now benefit, wherein IVM may become a primary method for safeguarding fertility.

Additionally, IVM and oocyte aspiration can be performed on short notice, yielding nearly as many oocytes following conventional ovarian stimulation protocols.

Furthermore, if one ovary is excised for OTC (as is common), the opportunity arises to collect additional oocytes from the ovary left *in situ* during the procedure.

Although still in development, the present state-of-the-art IVM technology already offers a promising avenue for many women, who might otherwise face limited prospects for future fertility.

References:

Vuong LN, Ho VNA, Ho TM, Dang VQ, Phung TH, Giang NH, Le AH, Pham TD, Wang R, Smits J, Gilchrist RB, Norman RJ, Mol BW. *In-vitro* maturation of oocytes versus conventional IVF in women with infertility and a high antral follicle count: a randomized non-inferiority controlled trial. *Hum Reprod.* 2020;**35**:2537-2547.

*Please note: The newsletter reflects the opinion of the author and not of the ISFP.