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Review Article

In vitro Maturation: Methodology, Limitations and Scope

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Abstract

In vitro maturation is the collection and maturation of gametes (particularly eggs/oocytes), outside a human body. The process involves retrieval of oocytes from antral follicles. The retrieval protocol is followed by maturation in laboratory (*in vitro*) and fertilisation (IVF). In this literature, the process, history, methodology, scope and limitations of IVM are explained in detail.

Keywords: Fertilization; Maturation; Methodology

History

The first *in vitro* maturation experiment was done on immature rabbit oocyte in 1935by Pincus and Enzmann. Later in 1965, spontaneous maturation of immature human oocytes, was observed by Dr. Robert Edwards. However the first IVM baby birth, using mother's own immature oocytes, was report in 1994. There have been a numberof controversies regarding a proper definition of IVM. Eventually, according to Turkish Journal of Obstetrics and Gynaecology, a clinical definition of IVM was introduced- 'The aspiration of small or intermediate-sized follicles for oocyte retrieval in the ovaries carrying follicles less than 13mm in diameter'.

IVF and IVM

IVF (*in vitro* fertilisation) and IVM (*in vitro* maturation) both are Assisted Reproduction Techniques which share a baseline of egg retrieval and fertilization outside the body. However, a major difference can be drawn between IVF and IVM. Patients undergoing IVF are required to take multiple hormonal injections in order to help the egg retrieval process to encourage egg maturation. However, there is no use of hormonal injections in IVM as the eggs are retrieved prior to maturation from unstimulated or minimally stimulated ovaries. On an economic aspect, the cost of IVM (*in vitro* maturation) is much lower than IVF (*in vitro* fertilisation). According toAmerican Pregnancy Association, at times, IVM patients are required to take hormonal injections. Even in those extreme cases, the dosage is cut short to 90% to that of the dosage which is given to patients undergoing IVF.

Indications for IVM

Coming to the patient selection, IVM is highly effective for the females with PCOS- Poly Cystic Ovarian Syndrome. This is a common medical condition which interfereswith the regular hormonal levels in a woman. As it is a syndrome, it involves a number of conditions such as cysts in ovaries, production of androgens (higher than normal levels), and irregular or no menses. PCOS is also associated with 'hirsutism'-excessive hair growth. In PCOS patients, often the egg is not released hence ovulation does not happen. Thus, IVM is said to be the best methodology to help PCOS (Poly cystic ovarian syndrome) patients get pregnant by a minor surgical procedure of immature egg retrieval. IVM is generally performed in candidates with high antral follicle count. An antral follicles is basically a secondary ovarian follicle. AFC (Antral Follicle Count) is generally a total number of antral follicles present in both the ovaries. In a normal healthy female, a typical AFC is 10-15. But, in patients with Poly cystic ovarian syndrome, the count shoot up to 20-30 or even more. AFC (Antral Follicle Count) is an essential factor in IVM

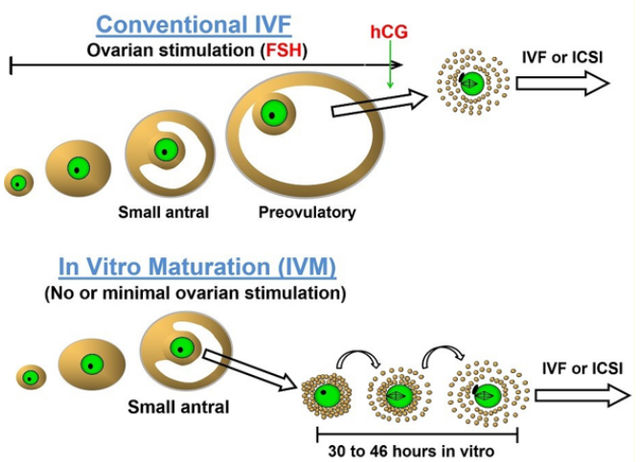

Figure 1

as, if the count is too low for therecovery, the success rates drop to almost negligible. A minimum Antral Follicle Count required to proceed for IVM is 7. IVM is performed at a very decreased risk of OHSS - Ovarian Hyper-stimulation Syndrome.

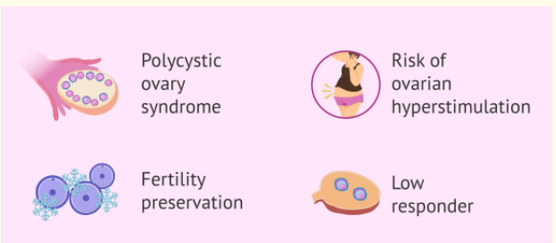

Figure 2

According to CERM - Clinical and Experimental Reproductive Medicine Journal, the parameters for selecting a woman to undergo IVM are- 'Age ≤36 years, Body mass index <30 kg/m^2, FSH (Follicle Stimulating Hormone) <10 mIU/mL, Estradiol <250 pmol/mL, AFC (Antral Follicle Count) >7, and Anti-Müllerian Hormone (AMH) >1.3 mg/mL'.

Process

A generic methodology of IVM involves obtaining a basic ultrasound scan which is done between 2 and 5 days of menstrual cycle. In case of patients with amenorrhea, hormones are injected to induce menstrual cycle. Primer is attached to obtain better results. Priming is done with hCG (Human Chorionic Gonadotropin) which is knownto improve the maturation rates in oocytes (cultured *in vitro*). Endogenous productionof hCG is avoided by cryopreservation of embryos. After the ultrasound results and few blood tests, an extraction time or stage is determined and thus eggs are retrieved. With the use of a hollow needle, guided by an ultrasound imaging, the eggs are collected. The immature cells can be matured by hormones or by c-AMP. (Cyclic Adenosine Mono Phosphate). cAMP is a cell-signalling molecule that promotes maturation in oocytes. After a certain period of time, say, 24-48 hours, ICSI (Intra Cytoplasmic Sperm Injection) can be performed to fertilised the *in vitro* matured eggs. Finally, the embryos are transferred further for implantation and the rest of the follow up procedures are done.

Molecular biology of IVM

Coming on to the molecular details, the follicle selected should be a dominant follicle. A dominant follicle is selected when the large follicle reaches about 10mm. IVM protocols involve providing a single injection of hCG (Human Chorionic Gonadotropin) at least 36 hours prior to the egg retrieval. Also, FSH (Follicle- Stimulating Hormone) priming can be added along with hCG priming, to increase thenumber of oocytes retrieved and enhance the maturation. But hCG priming over shines the FSH with hCG priming as successful implantation rates were higher in hCG priming group than FSH with hCG priming group. The retrieval process employs a smaller-diameter needle with lower-aspiration pressure. Aspiration pressure is generally lower than 100mm Hg. Retrieval is generally done under GA.IVM is generally performed avoiding the denuding of oocytes.

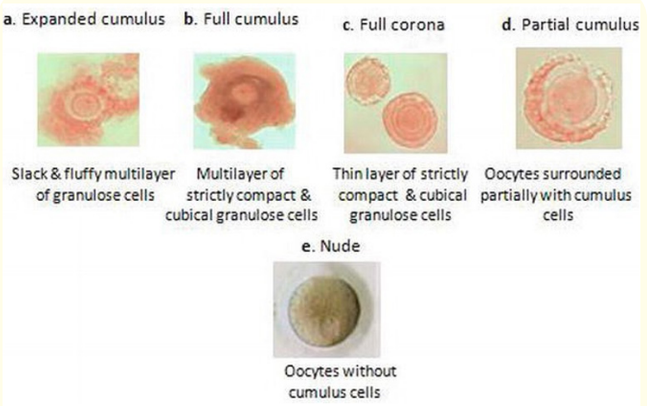

Figure 3

Hence, the eggs with cumulus cells are cultured in laboratory, with IVM medium. Matured oocytes are inseminated with the help of ICSI (Intra Cytoplasmic Sperm Injection) which is known to give higher fertilisation rates than standard inseminationprocedures. At a certain stage after insemination, the cleavage stage is attained by theembryo, where it is then implanted into the female body.

PROS and CONS

According to Dr Kirsty Horsey (Fertility Specialist HFEA) in an article, 'IVM has alower success rate that conventional IVF, but fertility doctors believe that the technique will become better and IVM will become a standard treatment'.

The major reason of performing IVM is to avoid OHSS (Ovarian Hyper-Stimulation Syndrome) as IVM involves no or minimal ovarian stimulation. The immature femalegametes, oocytes, are collected from unstimulated ovaries. There are cases of gynaecological cancers where the fertility is lost before the reproductive age or is lostafter the radiational therapies. In such cases there are a few techniques to help the patient preserve her fertility i.e., embryo cryopreservation, mature oocyte cryopreservation after IVM, immature oocyte cryopreservation, and ovarian tissue cryopreservation (OTC). However, IVM with Onco-fertility yet has lesser data and literature. The culture conditions can be improved to obtain higher success rates.

According to a research paper, 'Comparison of the obstetric and perinatal outcomes of children conceived from *in vitro* or *in vivo* matured oocytes in *in vitro* maturation treatments with births from conventional ICSI cycles', the obstetrical and perinatal outcomes of IVM (*in vitro* maturation) are similar to that of ICSI (Intra Cytoplasmic Sperm Injection). Apart from treating the infertile patients,

IVM also has made it easyto study and do research on the human oocytes. These oocytes with the help of IVM can be analysed and studied on different stages. Also, IVM has made it possible to study the expression proteins in oocytes for example, the ageing protein-cohesin.

Future aspects

IVM is clearly an emerging technology among the various techniques in ART and is asafe option to opt for, for the patients who are sensitive to gonatropins. IVM can be used safely without concern for the high estradiol levels in fertility preservation of hormone sensitive cancer patients. Very few centres across the world have achieved the expertise in *in vitro* maturation of eggs. Yet, the success rates are to be discoveredfor IVM. The long-term outcomes are also yet to be analysed for IVM such as the health of children, conceived from IVM. In the future, further improvements can be expected such as improvisation of media and additives.

According to a research entitled- 'IVM of human immature oocytes for fertility preservation and research material', in onco-fertility, reproductive endocrinologists and oncologists need to pursue a rapid, low-cost, non-invasive method of fertilitypreservation for patients facing cancer treatment, which is very well justified.

Additionally, according to a research in Oxford, England, In mouse oocytes, L- Carnitine (LC) supplementation during vitrification of germinal vesicle (GV) and their subsequent IVM improved nuclear maturation as well as meiotic spindle assembly and mitochondrial distribution in M-II oocytes. However, no data till date has proven this benefit in fetal development and birth of healthy offspring after embryo transfer. Though, this protocol could potentially improve the quality of vitrified human oocytes and embryos during IVM. Hence these are a few futuristic opportunities for the researchers in this field which can be worked upon, according tothe latest scientific literature [1-12].

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