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"CAN IN-VITRO MATURATION BE AN ALTERNATIVE TREATMENT IN INFERTILITY FOR IVF/ICSI?"

Dr. Roya Rozati*	M.D (A.I.I.M.S, Delhi), F.R.C.O.G.(London), Director, Maternal Health and Research Trust (MHRT), Banjara Hills, Hyderabad-34, India.*Corresponding Author
Wajeeda Tabasum	Research Scholar Maternal Health and Research Trust (MHRT), Banjara Hills, Hyderabad-34, India
Dr. Humaira Minhaj	Research Scholar Maternal Health and Research Trust (MHRT) Banjara Hills, Hyderabad-34, India
Dr. Ayapati Mehdi Gautam	Research Scholar Maternal Health and Research Trust (MHRT) Banjara Hills Hyderabad-34 India
Dr. Vikram Aiman	Maternal Health and Research Trust (MHRT) Banjara Hills, Hyderabad-34 India
Taalia Nazeer Ahmed	Maternal Health and Research Trust (MHRT) Banjara Hills, Hyderabad-34 India

KEYWORDS :

Introduction:

In vitro maturation (IVM) of oocytes is a rapidly developing technique which could be broadly divided into two categories based on the different sources of immature oocytes [Hatirnaz S et al.,2018].

The classical IVM implies that the immature oocytes are obtained in natural cycles without any hormone treatments or with minimal stimulation and cultured to maturation in vitro, which is applicable for the patients with polycystic ovary syndrome (PCOS) during assisted reproductive technology (ART), to reduce the risk of ovarian hyperstimulation syndrome (OHSS), and also for fertility preservation of patients with cancer, especially the ones with contraindications to hormone use.

Another type of IVM implies the in vitro culture of oocytes that failed to mature in vivo during conventional ovarian stimulation cycles, aiming to increase the available embryo rate in ART and thus improve the success rate, known as rescue IVM [Lee HJ et al., 2016, Escrich L et al., 2018]

The IVM of immature oocytes involves meiotic resumption, complicated cytoplasmic changes and progression to the MII stage to allow fertilization and developmental capacity [M.C. Rodrigues-Cunha et al., 2016, X.M. Zhao ett al., 2018]. Nuclear and cytoplasmic maturation requires essential energy substrates and various nutrients. In addition to basic nutritional requirements, key growth factors and cytokines produced by granulosa cells of cultured preantral follicles, are also indispensable for IVM [Y. Hao et al., 2017, E. Zand et al., 2018]

IVM has the potential to substitute for, or be an adjuvant to, standard in vitro fertilization (IVF) protocols for several reasons. It requires no or very little gonadotropin supplementation in vivo and it has been proposed as an alternative assisted reproduction approach to reduce drawbacks of controlled ovarian induction (COI) [Lim KS et al., 2013]

In vitro maturation (IVM) allows is a treatment where immature oocytes [germinal vesicle (GV) or metaphase I (MI) oocytes] to mature using in vitro culture systems. (R.C. Chian et al., 2014). The basis of IVM is the maturing in vitro of oocytes from the germinal

vesicle (GV) stage of development to the metaphase II (MII) stage.

Oocytes are retrieved transvaginally under ultrasound guidance from antral follicles of 2–10 mm diameter and are matured in vitro. A high proportion of the in-vitro Matured oocytes are able to resume meiosis and reach the MII stage. Their ability to be fertilized after 28–36 h of IVM is also high and a similar proportion is able to undergo

Early cleavage-stage development comparable to conventional IVF and intracytoplasmic sperm injection (ICSI) embryos. The IVM protocol is a practical treatment has an increasing use in reproduction technology for infertile women. (Fadini et al., 2009a; Son et al., 2008).

Sources of immature oocytes

The differences include the different sources of immature oocytes, the different protocols used to induce ovulation, and the different time of oocyte retrieval. These factors may lead to the situation where the immature oocytes retrieved clinically are not in the GV stage. The use of human chorionic gonadotropin (hCG) to induce ovulation prior to clinical retrieval of oocytes may lead to the initiation of endogenous oocyte maturation, and hence some of the retrieved immature oocytes may have undergone germinal vesicle breakdown (GVBD) or entered the MI stage. Although immature oocytes in the MI stage have initiated the process of in vivo maturation, they still need to participate in the procedure of in vitro culture and maturation. Therefore, the definition of clinical IVM treatment should include the in vitro culture of immature oocytes in the GV and MI stages.

Oocyte retrieval from caesarean section or gynaecological surgery

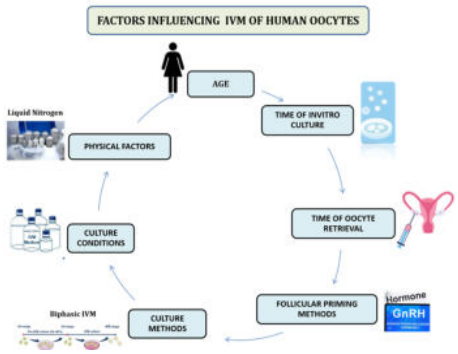
Immature oocytes retrieved from the ovarian cortex during caesarean section can be cultured in vitro to achieve maturation, fertilization, and healthy progeny. The mature oocytes cultured in this way are expected to be used as the source of oocytes to preserve female fertility Immature Oocytes can also be obtained via gynaecological surgery in the follicular phase or luteal phase. The number of retrieved oocytes is mainly related to the age, pathological status and stage of menstrual cycle of the patient.

Oocyte retrieval carried out at different stages of the menstrual cycle doesn't affect the rate of invitro maturation and the rate of fertilization of oocytes, suggesting that IVM technique can be used to preserve fertility At present, the rate of immature human oocytes can reach to 70%, but the developmental potential of mature oocytes obtained invitro is still lower than that of matured oocytes obtained in-Vivo

Factors influencing the oocytes in IVM –

Factors which are influencing the oocyte IVM is essential for improving their outcomes are

(1) Follicular priming methods and collected eggs
(2) Culture conditions
(3) Culture methods
(4) Time of oocyte retrieval
(5) Time of in vitro culture
(6) Woman's age and
(7) Cryopreservation and other physical factors



Follicular Priming Methods and Collected Eggs

IVM is usually performed in an unstimulated cycle, or a cycle with minimal gonadotropin stimulation to collect immature cumulus-oocyte complexes. According to ASRM, the follicular priming methods include low doses of FSH stimulation, single hCG injection, and minimal FSH stimulation before single hCG injection (ASRM 2021, Fadini, R et al., 2009 b Chian, R et al., 2000, Lin, Y et al., 2003, Michelson, A.L et al., 2001)

Clinical application and safety of IVM

At present, the in vitro maturation rate of immature human oocytes can reach 70%, but the developmental potential of mature oocytes obtained in vitro is still lower than that of mature oocytes obtained in vivo.

The improvement in clinical IVM technology mainly focuses on the IVM medium and the optimization of the culture environment and operation process. At present, with the improvement in the in vitro fertilization (IVF) efficiency and culture systems, a natural cycle or mild stimulation may be more suitable for women receiving IVF treatments.

Currently, the clinical application of IVM may be extended to treat patients with polycystic ovary syndrome (PCOS), ovarian hyperresponsiveness, and hypo responsiveness, as well as to preserve the fertility of cancer patients.

With the development of IVM technology, a modified protocol able to increase the success rates of natural cycle or mild stimulation IVF has been established. In this protocol, in addition to the retrieval of mature oocytes in naturally or mildly stimulated cycles, immature oocytes from small follicles are also retrieved for IVM, thereby increasing the total number of retrieved oocytes in a single treatment cycle and the clinical pregnancy rate.

Discussion:

Oocyte maturation is a lengthy process, during which the oocyte acquires the competence to be fertilized and to undergo embryogenesis. Significant progress has been made to improve pregnancy and implantation rates with in-vitro matured oocytes [Chian RC et al., 2009], but the mechanisms regulating early folliculogenesis and oocyte maturation in the human are still poorly understood [Gougeon A et al.2010]

The optimization of IVM procedure is necessary and development of a culture media that could directly improve the developmental ability of the cumulus-enclosed oocyte *in Vitro* would be a step towards this. Apart from this the counseling of patients undergoing the IVM procedure at the study centre is necessary, the recommendation of using a natural cycle or FSH plus HCG priming tries to personalize the protocols to a certain extent.

IVM in non-stimulated healthy ovaries can be usefully offered to many young couples with male and tubal factors or unexplained infertility and is also a valuable model for young women with hormonal-sensitive cancer who would like to preserve oocytes or those who want to take part in an egg donation programme.

Use of gonadotrophin priming in IVM could be efficient in women with normal ovaries and it can be concluded that the use of FSH priming alone, although it can improve some biological outcomes, does not give any defined clinical benefits.

The effectiveness of IVM for the management of women with PCOS. Other patients, such as poor responders, could also benefit from IVM (Liu et al., 2003)

Conclusion:

In conclusion, immature oocytes should be vitrified at the MII stage following IVM because oocyte maturation rates were significantly reduced when oocytes were vitrified at immature stage followed by IVM. The isolated immature oocytes itself do not contain any malignancy and MII oocytes represents fertility. Immature Oocytes are surprisingly available in large numbers. Oocytes from small follicles may provide valuable resource for boosting the number of mature oocytes for treatment. If these are further developed it may compete with normal IVF for standard practice and low-cost treatment in less developed countries.

Conflict of Interest: Nil

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Dr. Roya Rozati facilitated the initial conception of the idea to research the topic, participated in the drafting of manuscript, and read and approved the final manuscript. Dr.Roya Rozati researched the initial idea and converted the research to focus on prevalence, researched the existing literature, drafted the manuscript, and read and approved the final draft. Wajeeda Tabasum, Dr. Humaira Minhaj Khan researched the existing literature, participated in the drafting of the manuscript, and read and approved the final draft. Dr. Ayapati Mehdi Gautam, Dr. Vikram Aiman Taalia Nazeer Ahmed have contributed in completion of manuscript.

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