

## IVM IN PCO PATIENTS

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In-Vitro Fertilization (IVF) is known worldwide as a successful technique for the treatment of infertility. In order to obtain more oocytes, more embryos and higher pregnancy rates, ovarian hyperstimulation is given.(1). However, ovarian stimulation prior to the collection of mature oocytes carries the risk of Ovarian Hyperstimulation Syndrome (OHSS). The incidence of severe OHSS is 0.6-1.9% but may be as high as 6% in high-risk groups such as young women with polycystic ovaries.(2). None of the strategies used to predict and prevent this potentially life-threatening complication have been proven to eliminate the risk. The only reliable way is to avoid ovarian stimulation altogether. Additionally, the cost of down regulation and stimulation drugs cannot be ignored. The risk of OHSS and the costs associated with IVF can be avoided by utilizing In-Vitro Maturation of oocytes (IVM). IVM was first suggested by Pincus and Enzmann in 1935 and later by Edwards in 1969. The first IVM pregnancy resulted in triplets and was reported by Cha in 1991.(3-5). Since then, around a thousand pregnancies have been reported worldwide.

IVM is done in an unstimulated menstrual cycle. The number and measurement of the antral follicles are monitored by trans-vaginal ultrasound scans during the follicular phase. In order to enhance oocyte maturity, hCG is given 38 hours prior to collection. The oocytes are collected and the GV oocytes are then cultured for 24-48 hours until the metaphase II stage. The MII oocytes are then fertilized by Intra-Cytoplasmic Sperm Injection (ICSI). To enable synchronous endometrial maturation, estradiol is started on the day of oocyte collection and progesterone on the day of fertilization. The embryos are transferred 2-3 days after fertilization. However, transfer of blastocysts has been performed as well. Clinical predictors for the success of IVM treatment are: antral follicle count, number of GV oocytes collected, maximal ovarian velocity (Vmax) and size of the leading follicle on the day of collection (in menstruating patients).(6,7)

The pregnancy rate for IVM treatment is around 35% per transfer and up to 40% in selected groups of patients. IVM was initially considered for patients with polycystic ovaries but the indications are widening to include various diagnoses of infertility, among which are: IVM for over responders and poor responders, IVM for patients who have had previous failed IVF cycles with poor quality embryos, IVM for oocyte donation and IVM for fertility preservation. The two most exciting indications for IVM are fertility preservation for cancer patients prior to gonadotoxic treatments and oocyte donation.(8,9)

**Fertility preservation:** Malignant diseases are common. However, survival rates are increasing. Unfortunately, one of the long-term side effects of cytotoxic therapies is premature ovarian failure.(8). Women suffering from autoimmune diseases such as SLE are also treated with potentially gonadotoxic treatments.(10). Several options for fertility preservation are available; ovarian tissue cryopreservation is available for both pre- and post-puberty patients, but requires two surgical procedures (+/- IVF). To date, five live births have been reported after transplantation of frozen/thawed ovarian tissue.(11-14). However, this option carries the theoretic risk of reintroducing neoplastic cells in transplanted tissue. Embryos can be banked but this technique is available only to women with a partner. For women without a partner, oocytes could be preserved. The survival rates of frozen/thawed oocytes are increasing, especially when oocyte vitrification is used. Hundreds of pregnancies have been reported after fertilization of frozen/thawed oocytes collected after ovarian stimulation. However, the time interval needed for ovarian stimulation (2-6 weeks) may not be available for cancer patients, and ovarian stimulation is associated with high hormone levels which may not be safe in cases of hormone sensitive tumors such as breast cancer. We recently reported the first four live births after vitrification of in-vitro matured oocytes.(15). Therefore, collection of immature oocytes from unstimulated ovaries followed by IVM and vitrification of mature oocytes could be offered to patients with hormone-sensitive disease and/or when there is not enough time to stimulate the ovaries. An additional strategy of fertility preservation combines ovarian tissue cryobanking with the retrieval of immature oocytes from excised ovarian tissue, followed by in-vitro maturation (IVM) and vitrification of the oocytes.(16).

At the McGill Fertility Preservation Center, 82 women underwent oocyte retrieval without ovarian stimulation followed by IVM. In 49 IVM cycles, the matured oocytes were vitrified. In 33 IVM cycles, where the patient had a partner, the matured oocytes were fertilized and the resulting embryos were vitrified

**IVM oocyte donation:** The worldwide shortage of oocyte donors is frustrating to both patients and fertility physicians. However, some women would consider donating if no ovarian stimulation were involved. We recently reported our preliminary experience with 12 oocyte donors. Of the 12 recipients, 6 conceived, 4 delivered, and 2 miscarried.(9).

**Outcome of IVM pregnancies:** IVM is a relatively new ART technique. Only a handful of studies have been published on the status of babies born after IVM. These studies have not demonstrated a significantly higher congenital malformation rate or other disorders in IVM babies. Analysis of the first live births after IVM treatment indicates that the obstetrical, neonatal and infant outcomes were no different from the results for IVF pregnancies of the same order. (17-19).

**Summary:** IVM treatment offers simple monitoring without stimulation and its attendant risk of OHSS and saves the cost of ovarian stimulation. Pregnancy rates are comparable to those achieved through the use of IVF at many fertility centers. The outcome seems to be safe. IVM may be considered for PCOS-related infertility, for PCO patients with other indications for ART, for over responders and for oocyte donors. IVM may potentially prove to be beneficial for poor responders and after repeated IVF failures. Finally, for fertility preservation, the collection of immature oocytes from unstimulated ovaries followed by IVM and vitrification should be offered to patients with hormone-sensitive disease and/or when there is not enough time to stimulate the ovaries.

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