In vitro maturation: a committee opinion

Practice Committees of the American Society for Reproductive Medicine, the Society of Reproductive Biologists and Technologists, and the Society for Assisted Reproductive Technology

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The results of in vitro maturation (IVM) investigations suggest the potential for wider clinical application. This document discusses the efficacy of IVM as reported in the published literature to date. This document replaces the document of the same name, last published in 2013. (Fertil Steril® 2021;115:298-304. ©2020 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

In vitro fertilization (IVF) typically involves ovarian stimulation with the use of exogenous gonadotropins to induce the maturation of gonadotropin-sensitive follicles and inhibit the atresia of nondominant follicles (1, 2). The classic use of the term in vitro maturation (IVM) refers to the maturation of immature cumulus-oocyte complexes (COCs) in culture from prophase I (i.e., from the germinal vesicle [GV] stage) through meiosis I to reach metaphase II (MII) after their recovery from follicles that have not been exposed to the preovulatory trigger (3). This was defined largely in nonhuman animal studies. In clinical human IVF, however, the term IVM is often used to refer to in vitro maturation of oocytes retrieved at the GV or metaphase I (MI) stage from follicles after exposure to exogenous FSH and/or hCG ("follicle priming") to increase the likelihood of obtaining some mature oocytes (4, 5). Interpretation of studies reported in the literature could be clarified if specific terminology was used to delineate between IVM with and without short gonadotropin stimulation, and with and without hCG exposure before retrieval (6, 7). Table 1 provides some definitions of IVM currently in use.

The human oocyte reaches its full size (~100–120 μm in diameter) at the small antral stage, during which time the follicular diameter is only a fraction of its final ovulatory diameter. The ability of an oocyte to resume and complete meiosis is closely linked to follicular diameter (12–15). In humans, the kinetics of oocyte maturation have been studied with the use of oocytes obtained from oophorectomy specimens from nonmalignant gynecologic disorders and then cultured to undergo IVM, reaching MII after 36–48 hours (3).

It should be noted that even if an immature oocyte progresses to the MII stage with the use of IVM (i.e., completes nuclear maturation), it may not necessarily have undergone cytoplasmic maturation and achieved full developmental competence. For a mature oocyte to undergo successful fertilization and subsequent development, synchronization of nuclear and cytoplasmic maturation must occur (16). Nuclear maturation consists of GV breakdown induced by the LH surge followed by resumption of meiosis and extrusion of the first polar body (MII) (3). Cytoplasmic maturation refers to an accumulation of factors that prepare the cytoplasm for fertilization and embryonic development (17, 18). Epigenetic processes are a component of nuclear and cytoplasmic oocyte maturation, influencing development after fertilization (19, 20). For this reason, the potential for epigenetic disruption, such as abnormal methylation of maternally expressed genes, warrants careful evaluation in oocytes matured in vitro (21).

POTENTIAL APPLICATIONS OF IVM

The clinical application of IVM may be limited by alternative evidence-based strategies to successfully mitigate the risk of ovarian hyperstimulation syndrome (OHSS) in high-risk populations. Historically, candidates for IVM have included those at risk for OHSS, including women with polycystic ovary syndrome (PCOS) or polycystic ovary (PCO)–like ovaries and women with estrogen-sensitive cancers. Because significantly less medication is used for stimulation with the use of IVM, and the stimulation is of shorter duration requiring fewer injections and less monitoring, the financial and emotional burden is reduced compared with traditional IVF cycles. In addition, patients with limited time before potentially gonadotoxic cancer treatments may be candidates to use IVM for fertility preservation (22, 23). Finally,

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TABLE 1

Definitions of IVM.

Term in literature	Oocyte maturation	Exposure to hormones	Reference
Biological definition of IVM	GV to MII	No exposure to hCG or LH	Edwards 1965 (3)
Variations on definition of IVM			
Truncated IVF without FSH	GV or MI to MII	hCG primes intermediate follicles, no FSH	Chian 1999 (8)
Follicle priming with FSH	GV or MI to MII	Minimal FSH stimulation, no HCG	Wynn 1998 (9)
Mild-stimulation IVF/ truncated IVF	GV or MI to MII	Minimal FSH stimulation and early hCG administration to prime intermediate follicles	Fadini 2009 (10)
Rescue IVM	Any immature oocytes at retrieval to MII	Controlled ovarian hyperstimulation cycle resulting in GV or MI oocytes denuded of cumulus cells	Sacha 2018 (11)

Note: GV = germinal vesicle; IVF = in vitro fertilization; IVM = in vitro maturation; MI = metaphase I; MII = metaphase II.

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a study has shown the effectiveness of IVM in patients with repeated assisted reproduction failure due to resistant ovary syndrome (24).

IVM IN CLINICAL PRACTICE

Follicular Priming

There have been several clinical studies comparing IVM with conventional IVF using in vitro matured human oocytes in PCO-like and PCOS patients (25–29) and in ovulatory women (26, 30, 31). Several trials have also evaluated the utility of follicular priming versus the retrieval of oocytes from unstimulated antral follicles (10, 25). Three methods of follicular priming have been reported. One method is to minimally stimulate ovaries with low doses of FSH for 3–6 days, followed by retrieval on cycle day 7–10 in the absence of hCG administration. Other approaches use only hCG (single 10,000 IU injection) to "prime" intermediate-sized follicles 36 hours before oocyte retrieval, as well as the addition of minimal FSH stimulation before this hCG priming. This form of priming with hCG is physiologically different than late follicular administration of hCG in a traditional IVF cycle.

Priming with FSH and a single priming injection of hCG on cycle day 6, followed by IVM, in 921 PCOS women resulted in a cumulative live birth rate per cycle of 33.7% (32). A retrospective cohort study comparing IVM with the use of FSH and an hCG priming injection versus conventional IVF in 919 women with high antral follicle count (AFC) reported that although the number of mature oocytes and good-quality embryos was lower in the IVM group, the cumulative live birth rate after one cycle of IVM was 239/608 (39.3%) versus 155/311 (49.8%) for IVF (29).

The combination of gonadotropin and hCG priming compared with single-agent follicular priming has been studied with disparate results. A large randomized trial in 400 women with normal ovaries showed that when both FSH and hCG were used for priming, the percentage of oocytes that matured in vitro and the total number of available mature oocytes was improved, although 20% of recovered oocytes were matured in vivo in this treatment group. Clinical pregnancy rates after fresh embryo transfer were highest when both FSH and hCG were used, 26.5%, compared with 11.8%, 5.4%, and 13.7% in the nonprimed, hCG-primed, and FSH-primed groups, respectively (10). However, embryos in this group likely arose from a combination of both in vivo and in vitro matured oocytes, complicating interpretation of these results.

In several studies from Belgium in which IVM was conducted after a short (3-day) FSH stimulation with no hCG, clinical pregnancy rates have been reported. In a small study of 39 PCO/PCOS patients and 73 IVM cycles, after vitrified-warmed embryo transfer, the ongoing clinical pregnancy rate per transfer was 7/22 (31.8%) (33). A larger study of 121 patients and 239 IVM cycles in which 3 days of FSH and no hCG was administered and oocytes were retrieved from follicles no larger than 6 mm, an ongoing clinical pregnancy rate of 9/24 (37.5%) after vitrified-warmed embryo transfer was reported (34). Pregnancy rate after fresh embryo transfer was significantly lower in both of these studies.

Subsequently, a "freeze-all" IVM strategy was used in a study of 79 PCOS patients, resulting in a cumulative live birth rate per patient of 17/78 (21.8%) (35). Further supporting the notion that freeze-all strategies are better for FSH priming of IVM cycles, a recent study showed a very high miscarriage rate after IVM when fresh transfers were compared with frozen-thawed embryo transfers (36.8% vs. 4.5%) (28). One thing to bear in mind with all of these studies is that there is a high level of attrition from retrieved immature COCs to good-quality blastocysts, owing in part to low maturation success after IVM. The chance of a single immature oocyte resulting in a live birth was only 1.1% (35). In addition, interpretation of these studies is complicated not only by significant variation in the stimulation protocols used, but also by inconsistent reporting of the stage of meiotic maturation of the oocytes at retrieval (GV vs. MI, as well as any mature MII oocytes recovered).

In Vitro Maturation and Cancer

IVM could be beneficial for patients desiring fertility preservation because of impending gonadotoxic cancer treatment (36). In one study, 248 breast cancer patients, aged 18–40 years, awaiting neoadjuvant chemotherapy were candidates for oocyte vitrification following IVM, at either the follicular or the luteal phase of the cycle (36). No major differences were seen in the number of oocytes retrieved or their IVM rates, whatever the phase of the cycle at which oocyte retrieval was performed, indicating that this novel use of IVM is clinically useful.

However, another study showed that vitrified-thawed IVM oocytes had a low survival rate (59.8%), lower fertilization and cleavage rates, and significantly lower pregnancy (10.7% vs. 36.1%) and take-home baby (8.9% vs. 25.9%) rates compared with fresh IVM oocytes (37). The authors concluded that the reproductive potential of vitrified IVM oocytes is impaired owing to the vitrification-warming procedure. Similarly, another study showed very poor pregnancy and delivery outcomes from vitrified-thawed embryos derived from IVM oocytes for cancer patients (38).

Moreover, IVM of oocytes after recovery from thawed ovarian tissue frozen from postmenarchal versus premenarchal girls yielded a low rate of maturity in both groups (28.2% vs. 15.5%, respectively), which was further reduced in girls under 5 years of age (4.9%) (39). Collectively, these studies highlight the need for more research targeting improvement of IVM media, as well as IVM protocols for premenarchal girls. Recent studies have shown that using antimüllerian hormone level and AFC information can help physicians to more accurately counsel patients on the potential likelihood of successful fertility preservation with the use of this approach (40, 41).

Oocyte Retrieval and Culture

There are no established criteria to identify the ideal timing or method for oocyte retrieval, with most studies using a lead follicular diameter of up to 10 mm (31, 42). Lead follicle diameters greater than 13 mm have been associated with reduced numbers of oocytes collected and matured (43), possibly related to subsequent atresia of the nondominant follicles from withdrawal of endogenous FSH support. Some protocols require an endometrial thickness of >5 mm while others do not include endometrial thickness as a criterion.

The aspiration technique differs for immature oocytes compared with mature oocytes retrieved in traditional IVF owing to the lack of cumulus cell expansion and tighter adherence of the immature oocyte to the follicle wall. Double-lumen needles to flush follicles have been described but do not appear to be necessary to retrieve immature oocytes (44). The optimal aspiration pressure and needle design have yet to be determined, with negative pressures ranging from 80 to 120 mm Hg and needle sizes ranging from 16 to 20 gauge (9, 31). Extremely high aspiration pressure has been shown to strip the oocyte of cumulus cells and negatively affect maturation and oocyte competence (45).

There is no consensus on the medium formulation that is best suited for IVM. Media typically simulate tissue culture medium, composed of high levels of glucose and normal levels of pyruvic and lactic acids, along with essential and nonessential amino acids and frequently supplemented with FSH and hCG/LH. Several versions are available commercially. A few studies on the improvement of IVM medium for human oocytes have been reported, but significantly more research is needed in this area.

A recent development in IVM is the inclusion of a prematuration (pre-IVM) step. Some commercial IVM media have historically included a short (2 hour) preincubation step before moving the eggs into the IVM medium. However, pre-IVM medium contains reagents, such as forskolin, and/or C-type natriuretic peptide, to block meiotic resumption and maintain oocytes at the GV stage for up to 24 hours until they are moved into IVM medium. This strategy is designed to better support oocyte cytoplasmic maturation and improve oocyte competence after IVM. The first report of human IVM including this pre-IVM step and improved IVM medium containing amphiregulin and FSH reported an increase in oocyte maturation after IVM, as well as an increase in good-quality blastocysts (46).

Chromosome constitution, and DNA methylation and expression of imprinted genes, in embryos generated after pre-IVM/IVM appear to be normal (47, 48). A randomized controlled trial examined the effectiveness of pre-IVM versus standard IVM, defined as a short FSH stimulation without hCG administration. Results from that study suggested that in women with high AFC, those in the pre-IVM group had significantly higher maturation and clinical pregnancy rates, but both groups had similar live birth rates and neonatal outcomes (48).

Fertilization

In a randomized control trial of standard insemination versus intracytoplasmic sperm injection (ICSI) for sibling IVM oocytes from patients with PCOS, there was no difference reported for all outcomes measured, including fertilization rates and blastocyst development (49). Although IVF can readily be used to fertilize IVM oocytes, ICSI has been advocated as the preferred method. However, although fertilization rates appear to be increased with the use of ICSI for IVM oocytes, developmental competence may be impaired, as demonstrated in one comparative trial (27).

The fertilization success rate of matured oocytes in patients who did not receive gonadotropins was only 37.7% (229/608 matured oocytes) with the use of conventional IVF compared with 69.3% (318/459 mature oocytes) when ICSI was used. Despite lower fertilization results, the implantation rate was significantly higher in embryos derived from oocytes fertilized with the use of conventional IVF versus ICSI (24.2% vs. 14.8%; $P<.05$) as was the clinical pregnancy rates per embryo transfer (34.5% vs. 20.0%; $P<.05$) (27). However, with the more recent adoption of preimplantation genetic testing for aneuploidies (PGT-A) in many laboratories, ICSI is often the fertilization method of choice. In addition, PGT-A provides some confidence before embryo transfer that IVM-produced embryos are, at minimum, chromosomally normal (50).

In Vitro Maturation: Safety Concerns

Scientific studies on the safety of IVM did not demonstrate an increase in imprinting errors after IVM (51), and cellular morphology in IVM oocytes does not differ from in vivo matured oocytes according to transmission electron microscopy (52). The neonatal health and developmental outcome of children conceived with the use of IVM has been studied in small numbers and are thus far reported to be no different than children born through traditional IVF with or without ICSI (53–57). However, the relatively small number of children conceived through IVM compared with IVF limits the accuracy of malformation and anomaly rates, and developmental outcomes cannot yet be adequately assessed.

SUMMARY

- Stimulation protocols with no FSH or short FSH stimulation, followed by hCG priming of intermediate follicles or no hCG, can be successfully used to retrieve oocytes for clinical human IVM. Most recent work in this area has focused on a 3-day stimulation with FSH, with or without hCG administration, and retrieval of oocytes from small follicles. In studies that manipulate the timing of meiotic maturation in vitro to improve oocyte competence, only FSH is used.
- A high level of attrition from oocyte to blastocyst is observed in IVM, owing in large part to suboptimal nuclear and cytoplasmic maturation. There is a clear need for more research in this area to increase the efficiency of IVM for clinical application.
- The use of ICSI is typically, but not always, combined with the use of IVM. At this time, vitrification of immature oocytes is not recommended owing to reports of poor outcomes.
- Because a relatively small number of children have been conceived with the use of IVM, information on the safety of IVM regarding malformation and developmental outcomes cannot yet be fully assessed. However, initial studies are reassuring.

CONCLUSIONS

- Candidates for IVM may include women at risk for OHSS, including women with PCOS or PCO-like ovaries. Efficacy of IVM in the context of estrogen-sensitive cancers, or in women with limited time for initiating fertility preservation before undergoing potentially gonadotoxic cancer treatments, is still not clear.
- IVM provides an alternate treatment protocol for these groups of women, with reduced patient burden due to shorter stimulation cycles, fewer injections, and associated reduced drug and monitoring costs.
- IVM should be offered by those with expertise gained by specific training, and should always be accompanied by appropriate counseling about expected results and informed consent. This technology is no longer considered experimental.
- IVM is not applicable to every patient; only those with a high AFC are good candidates. However, at this time, patients should be made aware that blastocyst conversion is lower and that implantation and pregnancy rates may be reduced compared with conventional IVF.
- Large trials comparing clinical outcomes of promising newer methods of IVM versus standard IVF, as well as long-term follow-up studies of neonatal health and developmental outcomes of offspring, are necessary.

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Maduración in vitro: opinión de un comité.

Los resultados de las investigaciones en maduración in vitro (MIV) sugieren la posibilidad de una aplicación clínica más amplia. Este documento analiza la eficacia de MIV según lo informado en la literatura publicada hasta la fecha. Este documento reemplaza al documento del mismo nombre, publicado por última vez en 2013.