

# In Vitro Maturation of Oocytes

Subjects: [Allergy](#)

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In vitro maturation (IVM) of transvaginally aspirated immature oocytes is an effective and safe assisted reproductive treatment for predicted or high responder patients. Currently, immature oocytes are also being collected from the contralateral ovary during laparoscopy/laparotomy and even ex vivo from the excised ovary or the spent media during ovarian tissue preparation prior to ovarian cortex cryopreservation. The first live births from in vitro-matured ovarian tissue oocytes (OTO-IVM) were reported after monophasic OTO-IVM, showing the ability to achieve mature OTO-IVM oocytes. However, fertilisation rates and further embryological developmental capacity appeared impaired. The introduction of a biphasic IVM, also called capacitation (CAPA)-IVM, has been a significant improvement of the oocytes maturation protocol. However, evidence on OTO-IVM is still scarce and validation of the first results is of utmost importance to confirm reproducibility, including the follow-up of OTO-IVM children. Differences between IVM and OTO-IVM should be well understood to provide realistic expectations to patients.

in vitro maturation

OTO-IVM

## 1. Introduction

The potential application of in vitro maturation (IVM) of oocytes as an alternative to in vitro fertilization (IVF) of in vivo-matured oocytes has gained increasing interest in the last two decades. IVM involves the in vitro maturation of immature cumulus–oocyte complexes (COCs) collected from antral follicles, with or without follicle-stimulating hormone (FSH) priming, from the germinal vesicle (GV) stage to metaphase II (MII) <sup>[1][2][3][4]</sup>. Since the first observation in 1934 by Pincus and Enzmann <sup>[5]</sup> of rabbit oocytes capable of undergoing spontaneous in vitro maturation and fertilization, IVM has successfully been carried out in different species, with Cha et al. <sup>[6]</sup> being the first to report, in 1990, an IVM birth in humans from immature oocytes retrieved from donors <sup>[6]</sup>. The first IVM birth from the mother's own immature oocytes followed four years later <sup>[7]</sup>. The intriguing history of IVM has been summarized in 2018 by Shirasawa et al. <sup>[8]</sup> and more recently (2020) by De Vos M et al. <sup>[9]</sup>.

Although promising, the rollout of IVM was initially hampered by the reduced oocyte maturation rate of this method. Subsequent improvements were made to optimize both in vitro cytoplasmic and meiotic maturation and the developmental competence of oocytes by means of preparatory treatments in patients and optimisation of laboratory protocols. One of the procedures explored to optimize maturation rate was FSH priming before oocyte retrieval <sup>[3][9]</sup>. For this purpose, patients were prepared with a short regime of FSH and triggered with human chorionic gonadotropin (hCG) and/or gonadotropin-releasing hormone (GnRH) agonist (termed hCG-primed IVM or truncated IVF in the first case, and truncated IVF without FSH in the second case) <sup>[3][9]</sup>. Likewise, laboratory

protocols were optimized from monophasic or single-step IVM to biphasic IVM or pre-IVM to support the synchrony in cytoplasmic and nuclear maturation [10]. The biphasic protocol includes a pre-maturation culture or 'capacitation' (CAPA) which increases oocyte maturation potential [11]. This protocol is now known as 'CAPA-IVM'.

IVM was initially introduced in clinical practice as a safer alternative for conventional ovarian stimulation to avoid ovarian hyperstimulation syndrome (OHSS) and ovarian torsion [12][13]. Thus, IVM constitutes a promising alternative to in vitro fertilization of in vivo-matured oocytes conventional in predicted or expected high responders, such as polycystic ovary syndrome (PCOS) patients [9][13][14][15][16]. Encouraging results have been reported in these patients, with maturation rates up to 84% [17], fertilization rates up to 80% [18], clinical pregnancy rates up to 50% per cycle [19] and live birth rates up to 33% [19] as reviewed by the Cochrane library in 2018 [13]. Subsequently, IVM indications have been broadened to include fertility preservation and rare conditions where a controlled ovarian stimulation failed to result in mature oocytes, such as resistant ovary syndrome or repeated deficient oocyte maturation [16][20].

## 2. Current Insight on Oocytes

Several studies reporting ongoing pregnancies and live births after OTO-IVM have provided evidence on the potential of this methodology for the optimization of fertility potential. The first live births from OTO-IVM embryos were reported using the monophasic protocol, which clearly showed the ability of this protocol to achieve mature OTO-IVM oocytes. However, fertilisation rates and further embryological developmental capacities of the resulting oocytes seemed to be impaired.

The introduction of the biphasic IVM (or CAPA-IVM) protocol, where nuclear and cytoplasmic maturation is enhanced, has been an important step forward in the COCs maturation protocol. In CAPA-IVM, the meiosis of immature COCs was arrested using CNP in the capacitation medium before moving COCs into a meiosis-promoting medium, which contains AREG in order to achieve both nuclear and cytoplasmic maturation. When trying to transpose the CAPA-IVM protocol to OTO, it should be noted that evidence supporting this methodology (and IVM in general) stems from highly respondent patients (PCOS patients) in whom COCs had been retrieved by in situ ovarian transvaginal aspiration. This is important, since overall maturation rates after OTO-IVM have shown to be lower than after IVM [21][22][23][24][25][26][27][28]. Besides this, other important aspects are to be taken into account to have realistic expectations when considering CAPA-IVM for OTO.

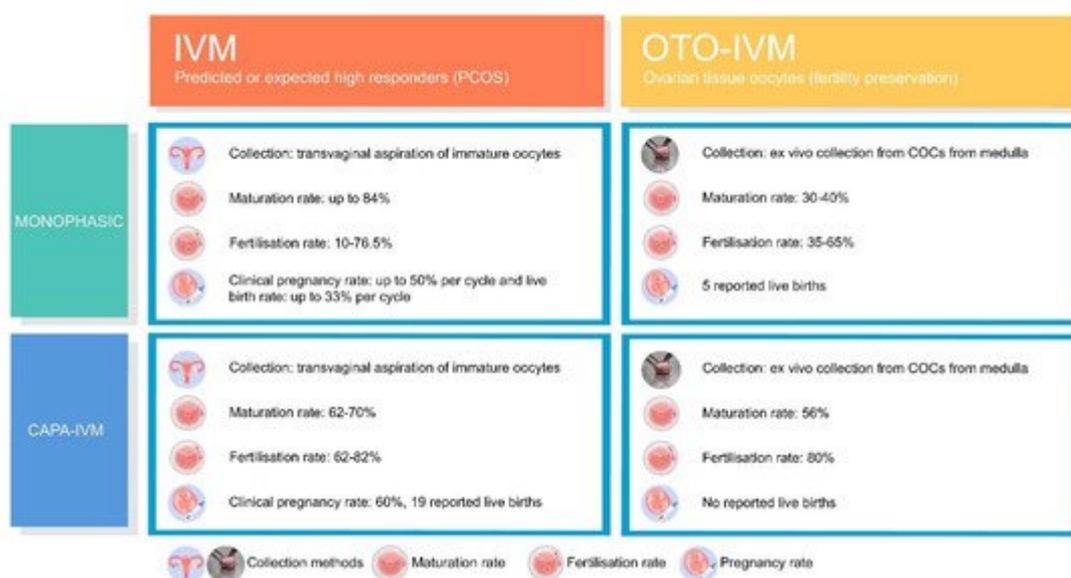
First, the differences in collection methods lead to COCs retrieved from a different follicle size. While COCs collected by transvaginal follicle aspiration are obtained from larger and, hence, more mature follicles, COCs retrieved ex vivo from an excised OT or spent media during cortex preparation come from very small, thus more immature, follicles. This results in a higher IVM rate in the first case, some adjustments to the IVM laboratory protocol will eventually be required.

Secondly, patient cohorts where OTO-IVM has been studied are particularly heterogeneous, comprising mainly oncological patients, but more recently also transgender men. OT cryopreservation has become standard of care

for fertility preservation in pre-pubertal girls. This population is highly heterogeneous in terms of hormonal profile and ovarian constitution [22]. It has been hypothesized that pre-pubertal ovaries need a maturation phase to obtain optimal follicle function [22][29][30], which would imply the difficulty of harvesting COC in vitro or obtaining COC at all, these will show low maturity (18–33%) [22][31][32]. When performing COC retrieval after gender confirmation testosterone treatment, OTO-IVM showed that transgender men have lower developmental ability compared with cancer patients [28]. This may indicate that long-term testosterone treatment has an adverse effect on the development of oocytes [28]. For this reason, prior OT cryopreservation testosterone withdrawal can be recommended.

Thirdly, conversely to IVM, patient cohorts where OTO-IVM has been studied are heterogenous, these are comprised of mainly oncological patients, but more recently also transgender men. OTO-IVM has shown low developmental capacity in transgender men when compared to oncologic patients when COC retrieval is performed after gender-affirming testosterone treatment [28]. This might indicate a deleterious effect of prolonged testosterone treatment on the development competence of oocytes [28]. For this reason, testosterone withdrawal prior to the cryopreservation of OT is recommended. OT cryopreservation has become the standard of care for fertility preservation in prepubertal girls. This population is highly heterogeneous in terms of hormonal profile and ovarian constitution [22]. It has been hypothesized that prepubertal ovaries need a maturation phase to obtain optimal follicle function [22][29][30], which would imply the impossibility of harvesting COCs ex vivo or, if COCs could be obtained, whether these would present with lower maturation capacity (18–33%) [22][31][32].

**Figure 1** aims to provide objective information about the effectiveness of current IVM methods and chances, so that shared, informed decisions can be made.



**Figure 1.** Overview of success ratios achieved with current IVM methods [11][13][22][23][25][27][33][34][35][36][37].

Biphasic IVM has been clinically performed with so-called ‘mild stimulation IVF’ (i.e., with a short treatment of gonadotropins prior to ultrasound-guided oocyte aspiration), as this approach has shown to improve oocyte

maturation rates, fertilisation rates and to result in higher amounts of embryos and blastocysts. A proof of concept for using biphasic OTO-IVM [27] provides new options for patients needing urgent fertility preservation. FSH priming is not always feasible or safe when the timeframe needed is impossible or when FSH priming appears to be unsafe given the underlying diagnosis.

The analysis and follow-up of newborn children after OTO-IVM from immature oocytes from PCOS patients has provided evidence of the safety of this protocol [9][37][38]. It remains unknown if this evidence is enough to guarantee the safety of OTO-IVM. In this context, some concerns have been expressed regarding possible epigenetic risks for IVM children [9]. Despite promising initial reports, evidence on OTO-IVM is still scarce and validation of the first results is of utmost importance. A multicentric study confirming the reproducibility is necessary to validate the technique and outcomes in larger cohorts. Special attention should be given to the efficacy in the different patient populations using this approach. A correct follow-up of OTO-IVM children is mandatory, including the (epi)genetic safety of this laboratory protocol.

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