ADVANCEMENTS AND CLINICAL IMPLICATIONS OF OOCYTE IN VITRO MATURATION IN ASSISTED REPRODUCTIVE TECHNOLOGIES: A COMPREHENSIVE REVIEW OF PROTOCOLS, APPLICATIONS, AND FUTURE PERSPECTIVES

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ABSTRACT

In vitro maturation (IVM) has emerged as a promising alternative to conventional in vitro fertilization (IVF), particularly for patients with polycystic ovary syndrome (PCOS) and those requiring fertility preservation, such as cancer patients. Unlike traditional IVF, IVM does not rely on extensive ovarian stimulation, reducing the risk of ovarian hyperstimulation syndrome (OHSS) and offering a more patient-friendly approach with fewer injections and procedures. This narrative review evaluates recent advancements in IVM, focusing on various protocols, including standard, biphasic, and hCG-primed IVM, along with their respective advantages and challenges. Additionally, the review discusses clinical applications, ethical considerations, and economic aspects, highlighting IVM's potential for improving patient outcomes while minimizing treatment burdens. Despite ongoing challenges such as lower maturation rates and variable success in poor responders, IVM has shown promising results for specific patient populations, including those with oocyte maturation defects, resistant ovary syndrome (ROS), and those at risk for OHSS. While clinical uptake remains limited, future research aimed at improving protocols, enhancing oocyte recovery, and expanding indications for IVM could further integrate this technique into assisted reproductive technologies (ART), making it a vital tool for fertility preservation and ART optimization.

Keywords: In vitro maturation (IVM); Assisted reproductive technologies (ART); Oocyte maturation; Polycystic ovary syndrome (PCOS); Fertility preservation

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INTRODUCTION

Assisted reproductive technologies (ARTs) were initially developed to address infertility and support family-building for sub-fertile individuals. Since the birth of Louise Brown in 1978, ARTs have evolved into a pivotal component of modern medicine, extending beyond infertility treatment to serve a broader population than originally envisioned. Among these advancements, oocyte in vitro maturation (IVM) has emerged as a promising alternative to conventional in vitro fertilization (IVF). The first successful IVF cycle was achieved in 1978 by Steptoe and Edwards (1), while the first successful IVM cycle was reported by Cha et al. in 1991 (2). Despite this later clinical adoption, the concept of IVM was first introduced by Edwards in 1965, demonstrating the ability to mature mammalian oocytes in vitro (3).

IVM is now precisely defined as the induction of meiotic maturation from prophase I to metaphase II in vitro, utilizing oocytes retrieved from small antral follicles (2–10 mm) in unstimulated or minimally stimulated ovaries (4). Unlike conventional IVF, which relies on ovarian hyperstimulation for oocyte retrieval from large antral follicles, IVM utilizes immature oocytes collected from unstimulated small antral follicles, as illustrated in Figure 1.

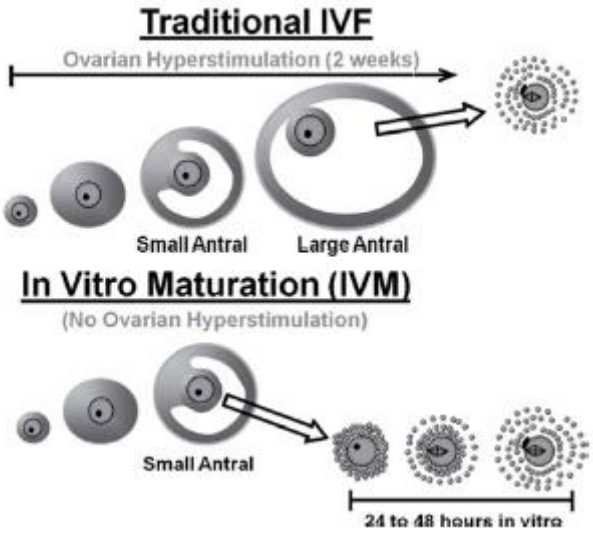

Figure 1. *Oocyte Retrieval in IVM vs. Conventional IVF. (Adapted from 5)*

IVM stands out from IVF due to its notable advantages, including reduced or absent gonadotropin stimulation, a lower risk of ovarian hyperstimulation syndrome (OHSS), and a more comfortable oocyte retrieval process (6, 7). The typical IVM cycle differs significantly from IVF, as it involves minimal administration of follicle-stimulating hormone (FSH) or human menopausal gonadotropin (hMG) before oocyte retrieval and no ovulation trigger with human chorionic gonadotropin (hCG) (4). There are three major clinical IVM protocols: standard IVM, biphasic IVM, and hCG-primed IVM (8).

Standard IVM involves a one-step maturation process where germinal vesicle (GV)-stage cumulus–oocyte complexes

(COCs) develop to metaphase II (MII) in vitro, with or without prior FSH priming. Biphasic IVM introduces an additional pre-IVM culture phase, deliberately pausing meiosis for approximately 24 hours before exposure to meiosis-promoting conditions. Examples include the SPOM- and CAPA-IVM protocols, which require FSH priming but exclude hCG priming to maintain intact compact COCs. In hCG-primed IVM, patients receive an hCG bolus before oocyte retrieval, with or without prior FSH priming. This results in a subset (10–20%) of oocytes being MII at retrieval, while others remain in various stages of meiosis, necessitating differential laboratory handling. Additionally, although it is not regarded as a clinical IVM procedure, post-IVF rescue IVM involves the maturation of GV-stage oocytes collected from stimulated IVF cycles after ovulation triggering, typically with hCG. These oocytes, often considered non-viable and discarded in conventional practice, are cultured in a denuded state from GV to MII. Different IVM protocols are illustrated in Figure 2.

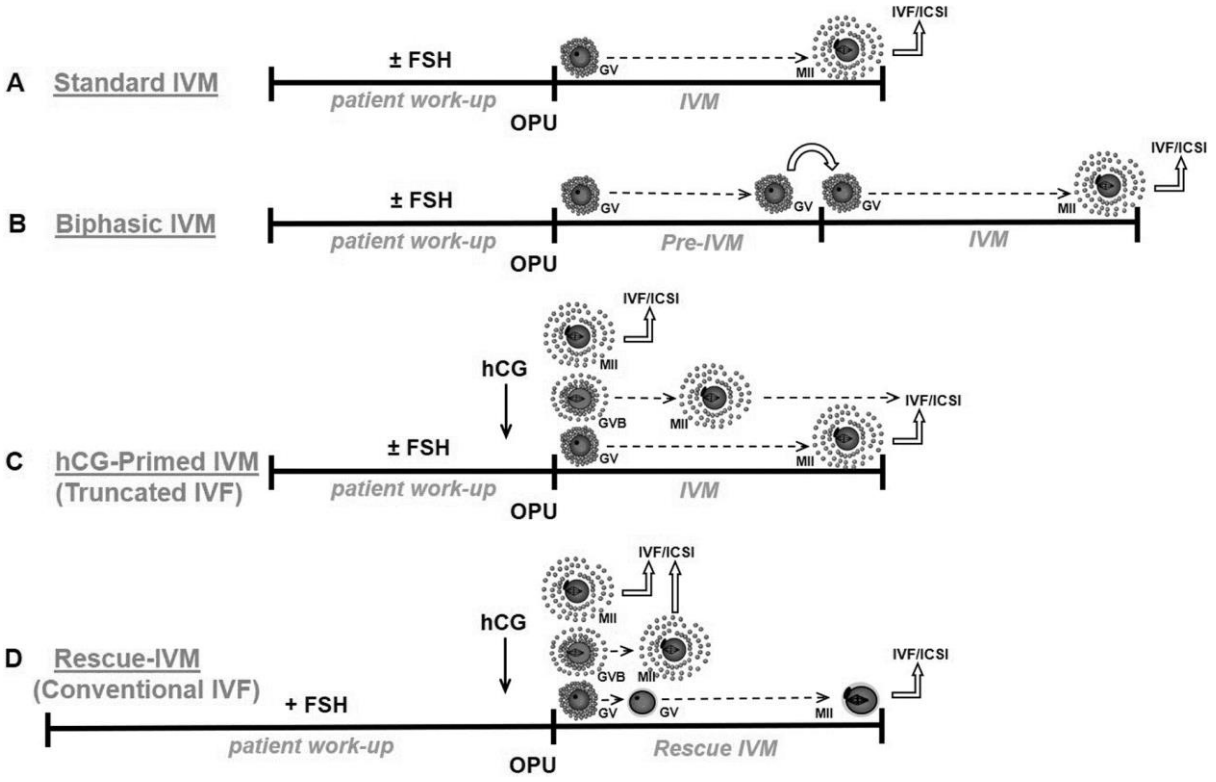

Figure 2. *Major IVM protocols. Adopted from (9)*

This review provides a comprehensive summary of the latest advancements, existing challenges, and future perspectives in oocyte in vitro maturation (IVM). Particular focus is given to technical aspects, clinical applications, ethical and economic considerations, and barriers to its widespread implementation in assisted reproductive technologies (ART). By evaluating the current literature, this review aims to assess whether recent advancements in IVM demonstrate potential for optimizing outcomes. This article follows the Narrative Review reporting checklist.

METHODS

This manuscript is a qualitative narrative review conducted using PubMed as the primary database for literature searches. The search terms included: "oocyte in vitro maturation (IVM)," "oocyte maturation," and "IVM and PCOS." The review focused on studies published between 2014 and 2024, emphasizing advancements, clinical applications, ethical considerations, and economic aspects of IVM. Only studies published in English were included. Priority was given to peer-reviewed articles, but relevant abstracts and case reports meeting the search criteria were also considered. Additionally, references cited within the reviewed studies were examined to broaden the scope of the analysis. Table 1 provides a detailed summary of the research strategy employed for this review.

Table 1. *Summary of Research Strategy*

Category	Details
Date of search	Searches performed between December 15, 2024 and January 1, 2025
Database	PubMed
Search Terms	"oocyte in vitro maturation (IVM)," "oocyte maturation," "IVM and PCOS"
Timeframe	Studies published between 2014 and 2024
Language	English-only studies were included
Inclusion Criteria	Peer-reviewed articles, abstracts, and case reports related to IVM
Exclusion Criteria	Non-English studies and publications unrelated to advancements, clinical applications, ethical or economic aspects of IVM
Focus Areas	Advancements in IVM, clinical applications, ethical considerations, economic aspects
Additional Sources	References cited in the reviewed studies were further explored

RESULTS

As with any emerging assisted reproductive technology, an anticipated barrier to clinical uptake of IVM will be access to clinical and laboratory knowhow of how to perform IVM. Consequently, many clinical practitioners are unclear about the current clinical status of IVM (9). A major gap for the field has been the need for a consensus statement on the clinical practice of IVM, something that in many respects has been addressed by the recent ASRM Committee Opinion on IVM declaring IVM non-experimental (10). In the last decade, IVM protocols have improved, particularly with the development of biphasic IVM culture accounting for better pregnancy and live birth rates (11). Alternatives to IVF, such as IVM, often receive limited attention in clinical practice and research due to insufficient evidence regarding their efficacy in specific patient populations. Notably, when IVF is performed during a follow-up visit after an unstimulated IVM cycle, it can result in pregnancy outcomes comparable to those of an initial IVF cycle without negatively impacting subsequent pregnancy outcomes (12). Mostinckx et all. in their paper evaluate the size of the efficiency gap between IVM and OS followed by IVF in predicted hyper responders, across a range of serum AMH cut-off levels. They concluded that in sub fertile women eligible for ART, IVM and ovarian stimulation (OS) demonstrated similar reproductive outcomes in those with serum AMH levels ≥10 ng/ml (13). With currently available IVM systems, clinical outcomes are lower than those after conventional ovarian stimulation in most women, but for some infertile women

and after appropriate counselling, the improved safety and a simplified clinical approach will outweigh lower efficacy (9).

Major IVM Protocols: Advantages and Disadvantages

In vitro maturation (IVM) of oocytes has evolved into a viable assisted reproductive technology (ART), offering an alternative to conventional ovarian stimulation methods. Various IVM protocols have been developed, each with distinct advantages and limitations. Based on the literature review, the following section provides a detailed overview of major IVM protocols, focusing on their respective benefits and drawbacks.

Standard IVM

The standard IVM protocol is one of the most straightforward techniques for oocyte maturation. A major advantage of this approach is its use of a simple, one-step culture system, which simplifies the laboratory procedure (8, 18). Furthermore, all oocytes begin the maturation process at the same immature meiotic stage, ensuring a uniform starting point for culture (14, 15). However, this approach is not without its disadvantages. The most notable limitation is the relatively low maturation rate, with around 50% of oocytes reaching the metaphase II (MII) stage (15, 16, 17). Additionally, this method yields modest embryo numbers and live birth rates, which can be a concern for patients seeking high success rates in ART procedures (15, 16, 17).

Biphasic IVM

Biphasic IVM represents a more advanced technique, offering several improvements over the standard IVM method. One of the key advantages is the relatively higher MII rates, approximately 70%, compared to the standard approach (18). This increase in maturation rates is accompanied by better embryo yield and live birth outcomes, making biphasic IVM a promising option for ART (17, 18, 19). However, this method does come with its drawbacks. The additional day of culture required for biphasic IVM leads to an increased laboratory burden, potentially complicating the clinical workflow (18). Furthermore, this protocol has only recently been introduced and is limited to a small number of IVM laboratories, which restricts its accessibility and widespread implementation (19, 20).

hCG-Primed IVM

hCG-primed IVM involves the use of human chorionic gonadotropin (hCG) to stimulate oocyte maturation prior to collection. This method is advantageous due to its relatively high MII rates, also around 70% (21). However, the hCG-primed protocol presents a series of challenges. One significant disadvantage is that oocytes are retrieved at various meiotic stages, complicating the consistency of the maturation process (22). Furthermore, this method imposes an additional laboratory burden, as at least two rounds of intracytoplasmic sperm injection (ICSI) are required per oocyte retrieval (OPU) (4). The IVM of germinal vesicle breakdown (GVB) oocytes also tends to be suboptimal, as the extent of their meiotic progression at the start of

culture cannot be precisely determined (22). While this protocol offers relatively high maturation rates, live birth rates remain modest (15, 22). Additionally, hCG-primed IVM is prohibitive for pre-IVM culture approaches, limiting its flexibility in certain ART protocols (23).

Rescue IVM

Approximately 15–30% of oocytes retrieved after ovarian stimulation (OS) are at the metaphase I (MI) or germinal vesicle (GV) stage (30). Rescue IVM is often employed in cases where germinal vesicle (GV) oocytes are present in conventional IVF patients, offering a potential means to improve embryo yield and increase the chances of transfer (24). A key advantage of this approach is its ability to generate additional embryos for transfer, potentially benefiting patients with limited oocyte availability. However, the rescue IVM protocol has several significant disadvantages. Oocytes in this cohort are often associated with meiotic defects, leading to lower-quality outcomes (25). Moreover, IVM without the support of cumulus cells, which is typical in rescue IVM, results in poor oocyte quality and diminished maturation potential (26, 27, 28). Concerns regarding the safety of rescue IVM have also been raised, further questioning its widespread use in clinical practice (28, 29).

Why IVM and Who Is It For?

In vitro maturation (IVM) offers an alternative to traditional ovarian stimulation (OS), which involves significant hormone use. One of the primary advantages of IVM is its reduced reliance on hormones, which has several benefits for patients. These include avoiding ovarian hyperstimulation syndrome (OHSS) and other complications related to OS, reducing the cost of medications and care, and increasing convenience due to fewer injections and examinations (31, 32). Additionally, IVM places less emotional burden on patients by minimizing the number of invasive procedures.

While IVM has largely been replaced by IVF/ICSI antagonist cycles that use GnRH agonists and a "freeze-all" strategy, it continues to be a focus of research due to its potential benefits and new indications, such as fertility preservation (31). IVM may also serve as a viable option for women at risk for OHSS, including those with polycystic ovary syndrome (PCOS) or polycystic ovarian (PCO)-like ovaries.

Candidates for IVM

Women with PCOS, a common endocrine condition affecting approximately 10% of women, are among the most suitable candidates for IVM. PCOS patients often have high numbers of immature oocytes, which compensates for IVM's lower efficiency compared to conventional OS for IVF (33,34). Many women with PCOS experience excessive responses to OS, while others, particularly those with hyperandrogenism or obesity, may have a narrower window for optimal ovarian response. For these women, IVM provides a more controlled approach with reduced monitoring and flexibility in scheduling oocyte retrieval. After counselling, many women with PCOS may choose IVM as a less burdensome ART option.

Moreover, Anti-Müllerian hormone (AMH) levels, which correlate with the

severity of PCOS, can help predict the success of IVM. For instance, women with the classical PCOS phenotype A, characterized by PCO-like morphology, ovulatory dysfunction, and hyperandrogenism, exhibit the highest AMH levels and are more likely to achieve higher cumulative live birth rates (CLBR) after IVM (35). However, future studies are needed to compare the success rates of IVM and conventional OS in PCOS patients, particularly those with PCOS type A.

IVM for Fertility Preservation

Fertility preservation (FP) is an essential consideration for women who may face fertility threats, such as those undergoing cancer treatments. While conventional OS is the most common approach for FP, it is not feasible for prepubertal girls or women with oestrogen receptor-positive cancers due to the risks posed by hormone treatments. In these cases, IVM, either by collecting oocytes via transvaginal follicular aspiration or extracting them from ovarian tissue, presents a potential option. However, the lower meiotic and developmental potential of IVM oocytes, compared to those retrieved after conventional OS, may impact live birth rates in future use.

The feasibility of IVM for FP has been demonstrated in various cancer patients. Study with 248 breast cancer patients undergoing IVM before neoadjuvant chemotherapy found that IVM resulted in the cryopreservation of a mean of 6.4 mature oocytes per patient. IVM has also been shown to be effective in emergency settings for women diagnosed with hematologic diseases, where immediate fertility preservation is necessary (36, 37).

IVM for Resistant Ovary Syndrome

Resistant ovary syndrome (ROS), characterized by hypergonadotropic anovulation, is a rare condition that often leads to infertility. For women with ROS, IVM is currently the only viable alternative to egg donation, with several live births reported following this procedure (38, 39).

IVM for Poor Responders

Women who exhibit a poor response to OS, particularly those of advanced reproductive age or with low ovarian reserve, face challenges in achieving pregnancy. Although high doses of gonadotropins have not been shown to improve outcomes for poor responders, IVM has been explored as an option. However, IVM has limited success in poor prognosis patients due to the unpredictable retrieval of immature oocytes and the lower maturation rates (around 50%) associated with IVM (40). Consequently, poor responders may not be ideal candidates for IVM.

IVM for Women with Oocyte Maturation Defects

Some infertile women experience oocyte meiotic maturation defects, in which immature oocytes are retrieved even after conventional OS cycles. For these women, IVM is currently one of the few available treatment options. While some patients show promising results, others have genetic defects that may not respond to IVM, leading to disappointing outcomes. Future improvements in IVM protocols, such as the use of biphasic systems, may offer hope for these patients, particularly in

inducing meiosis in vitro during the maturation phase (23).

DISCUSSION

In vitro maturation of oocytes (IVM) has gained recognition as a valuable technique for minimizing the risk of ovarian hyperstimulation syndrome (OHSS), especially in women with polycystic ovary syndrome (PCOS) and those preserving fertility prior to oncological treatments. While challenges related to oocyte quality remain, recent advancements have enhanced pregnancy success rates as well as neonatal and infant health outcomes (41). IVM has become a promising method for maturing immature oocytes, with applications in IVF, PCOS treatment, and fertility preservation for cancer patients. Advances have improved pregnancy rates and outcomes, yet its clinical adoption remains limited, prompting further research to optimize protocols and broaden its use (42). This technique has been applied beyond PCOS patients to include fertility preservation in cases where ovarian stimulation is contraindicated or time-limited, as well as for poor responders. Collectively, IVM seems a viable option for some ART patients, with specific indications, by reducing the burden and risks of ovarian stimulation (11).

This narrative review was based on a qualitative synthesis of available literature retrieved primarily through PubMed, focusing on studies published in English between 2014 and 2024. While this approach enabled a focused evaluation of current advancements in IVM, it is limited by the exclusion of non-English studies and potential publication bias inherent in narrative reviews. Moreover, the heterogeneity of included study designs restricts the ability to generalize findings or conduct meta-analytical comparisons.

Future research should aim to validate emerging IVM protocols through large-scale, multicentre clinical trials and standardized outcome reporting. In particular, investigations into embryo yield optimization, improved oocyte recovery methods, and integration of patient-friendly clinical workflows will be essential for establishing IVM as a standard ART modality.

Additionally, the development of zero-stimulation ART methods could revolutionize assisted reproduction by minimizing or eliminating the need for ovarian stimulation. As research progresses, IVM has the potential to become an essential component of assisted reproductive technologies, providing accessible and less burdensome solutions for patients seeking fertility treatments.

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NAPREDAK I KLINIČKE IMPLIKACIJE IN VITRO ZRENJA OOCITA U ASISTIRANIM REPRODUKTIVNIM TEHNOLOGIJAMA: SVEOBUHVATAN PREGLED PROTOKOLA, PRIMJENA I BUDUĆIH PERSPEKTIVA

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SAŽETAK

In vitro maturacija (IVM) pojavila se kao obećavajuća alternativa konvencionalnoj in vitro oplodnji (IVF), naročito za pacijentice sa sindromom policističnih jajnika (PCOS) i one koje zahtevaju očuvanje plodnosti, poput pacijenata sa rakom. Za razliku od tradicionalnog IVF-a, IVM ne zavisi od intenzivne stimulacije jajnika, čime se smanjuje rizik od sindroma hiperstimulisanja jajnika (OHSS) i nudi pacijentima pristupačniji metod sa manjim brojem injekcija i procedura. Ovaj narativni pregled procenjuje nedavne napretke u IVM-u, fokusirajući se na različite protokole, uključujući standardni, bifazni i hCG-primed IVM, zajedno sa njihovim prednostima i izazovima. Dodatno, pregled razmatra kliničku primjenu, etičke aspekte i ekonomske faktore, naglašavajući potencijal IVM-a za poboljšanje ishoda za pacijenate uz minimiziranje opterećenja liječenjem. Uprkos izazovima kao što su niže stope zrelosti jajnih ćelija i varijabilan uspijeh kod pacijentica sa smanjenim odgovorom na stimulaciju, IVM je pokazao obećavajuće rezultate za specifične populacije pacijenata, uključujući one sa defektima zrelosti jajnih ćelija, rezistentnim sindromom jajnika (ROS) i one sa rizikom od OHSS-a. Iako je klinička primjena još uvek ograničena, buduća istraživanja usmjerena na poboljšanje protokola, poboljšanje oporavka jajnih ćelija i proširenje indikacija za IVM mogli bi dodatno integrisati ovu tehniku u asistirane reproduktivne tehnologije (ART), čineći je ključnim alatom za očuvanje plodnosti i optimizaciju ART-a.

Ključne riječi: in vitro zrijenje (IVM); asistirane reproduktivne tehnologije (ART); zrijenje oocita; policistični jajnici (PCOS); očuvanje plodnosti.

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