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Embryo quality and selection for in Vitro Maturation: Updated technique for IVF

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ABSTRACT

In vitro maturation (IVM) of human oocytes presents a promising avenue for aiding infertile couples in achieving pregnancy. This budding technology involves the maturation of immature oocytes in culture, with or without prior exposure to gonadotropins. Although relatively new, IVM has shown comparable success to traditional IVF cycles in recent studies, leading to its rapid clinical adoption worldwide. IVM offers several advantages over standard IVF protocols, including the avoidance of large doses of gonadotropins, thereby eliminating the risk of ovarian hyperstimulation syndrome (OHSS) and reducing potential adverse effects on sensitive tissues. Additionally, IVM may be particularly beneficial for women with polycystic ovaries or related infertility, as it can effectively utilize the abundant antral follicles present in such cases.

Despite its successes, IVM is not yet widely utilized compared to IVF. However, evidence suggests that mild stimulation or modified natural cycle protocols may offer equivalent or even superior success rates, especially in women with a history of poor ovarian response. While IVM is unlikely to replace traditional IVF, it represents a valuable option for certain patient populations.

Ultimately, the goal of ART procedures like IVM is to fulfill the fundamental desires of patients for reproduction and family building. While these techniques are not without risks and challenges, they have enabled the realization of countless dreams of parenthood and the creation of many happy families. Continued innovation and refinement in IVM hold promise for further improving outcomes and expanding access to infertility treatments.

Keywords: *In vitro maturation (IVM), infertility treatment, assisted reproductive technology (ART), polycystic ovaries, ovarian hyperstimulation syndrome (OHSS), Artificial Intelligence (AI), controlled ovarian stimulation, gonadotropins, embryo quality.*

INTRODUCTION

In vitro maturation (IVM) of human oocytes, used to aid infertile couples in conceiving a pregnancy, is a budding technology that has promising prospective. [1]. In vitro maturation (IVM) refers to maturation in culture of immature oocytes at various stages that may or may not have been exposed to diminutive courses of gonadotropins. The resource of immature oocytes is an imperative feature for succeeding embryonic development, pregnancy, and healthy live births. [2,3]. In vitro maturation has the ability to replace with or at least be an adjuvant to standard IVF protocols for a number of reasons. It does not necessitate the use of large doses of gonadotropins for in vivo follicular growth and oocyte maturation, as presently is practiced with standard

controlled ovarian hyperstimulation (COH) for IVF. For patients who undergo IVM, the cost and inconvenience of injectable gonadotropin therapy are evaded, and the risk of ovarian hyperstimulation syndrome (OHSS) virtually is purged. In addition, any other potential short or long term adverse effects of supraphysiologic concentrations of gonadotropins on sex steroid hormone–sensitive tissue like ovaries, endometrium, and breasts are diminished. Finally, the requirement for injections of GnRH analogues is obviated, therefore opposing their pituitary and extrapituitary side effects [4]. It specially is useful for women with polycystic ovaries (PCO), women with previously proven fertility like after tubal ligation, and couples with a non–female infertility issue because they probably are less likely to tolerate or need the super ovulation stimulation that is connected with traditional IVF [5].

In vitro maturation is a promising novel technology that may function as a substitute for or at least as an adjuvant to traditional IVF. The driving forces that propel IVM into the dominion of ART are simplicity, patient expediency, patient safety, and lessening of costs. For IVM to replace IVF, the number of proof falls on IVM to show that it is as safe and competent as current IVF practice. The available data on safety and efficacy of IVM technology are restricted but portray it as being comparable to IVF in recent studies. The global acceptance of IVM technology as an option to IVF on the basis of the current data has been variable. The implementation of IVM technology as a viable ART option will depend on the consequences of studies directly comparing IVM with IVF, not only from an efficiency and security standpoint but also from a cost-effectiveness one [2, 6].

The relevance of in vitro maturation (IVM) of human oocytes to in vitro fertilization and embryo transfer (IVF) has been victorious in producing offspring for more than 30 years. Even for the detachment of patients for which IVM has been most successful, women with high antral follicle counts, IVM is only

used in rare patients. Primarily, there was much enthusiasm about a procedure that did not use high doses of gonadotropins, abolished the risk of uncontrolled ovarian hyperstimulation, and was otherwise gentler for patients than traditional IVF [4–6].

An appendage preceding IVM retrieval, called “priming”, is focussed at trying to optimize the aptitude of the oocytes so that they may become embryos which develop, implant, and become babies. Most frequently, these adjunctive treatments included an injection of human chorionic gonadotropin (hCG) foregoing retrieval, treatment with prescribed IU of follicle stimulating hormone (FSH) split over three days, or this same FSH treatment together with an injection of hCG [9].The use of letrozole at the commencement of an IVM cycle is reasonable since normal follicle development from the preantral stage to small antral stage has been revealed to be dependent on androgen availability [11].

The conventional approach to IVM retrieval involves aspirating numerous follicles and because of the minute volume of those follicles, removing the needle periodically to blush out oocytes contained inside the needle collection set. The IVM literature reports a broad range of miscarriage rates after pregnancy using IVM with about half of early programs, which published a miscarriage rate, accounting a clinical pregnancy loss rate of greater than 25 percent [8, 13]. This may have been due to the extensively differing uterine environments into which brand new embryos were transferred [14]. The literature forming the basis for endometrial preparation preceding to donor embryo transfer in IVF, and afterward, frozen embryo transfer (FET), is at odds with the uterine endocrine environments generally created during fresh transfer IVM cycles which may have squat estrogen levels and evidence of poor endometrial response [15, 16]. IVM transfer could be made more consistent by cryo preserving embryos and transferring them back to the patient during a routine FET cycle. Such an approach has newly been used in a program with low pregnancy loss results, but is not evenly used across all IVM programs [14, 17]. Nowadays, given the efficiency of IVF and improvements in the culture system, natural-cycle IVF or gentle stimulation may be more appropriate for women undergoing IVF treatment. Various studies have shown that natural-cycle IVF treatment has pros over standard-stimulation IVF treatment, predominantly in the management of women with low ovarian reserve. In contradiction of standard-stimulation IVF treatment, the plan of mild stimulation is to develop safer and patient friendlier etiquettes where the risks of the treatment are minimized Recuperation of immature oocytes followed by IVM is a potentially useful management for infertile women. This approach seems particularly effective for women with polycystic ovaries or polycystic ovarian syndrome related infertility, because there are plentiful antral follicles within the ovaries of this group of patients. Until date, IVM treatment has been mainly applied to women with PCOS and is not considered to be applicable to all types of infertility with acceptable outcomes. It is clear that IVM treatment is unlikely to replace the current stream of IVF treatments. In 2013, the Practice Committees of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology designated that IVM should be performed only as an experimental procedure estimating both efficacy and safety in carefully chosen patients [8, 24]. As we accrue more experience and outcome data, natural-cycle IVF, mild-stimulation IVF, and IVM treatment

may establish to be not just alternatives to standard stimulation treatments, but also as potentially first-line treatment choices. In the expansion of IVM treatment, one very striking possibility for enhancing successful outcomes is to merge natural-cycle IVF treatment with immature egg retrieval pursued by IVM of those immature oocytes. It has been verified that the exploit of IVM technology can thus be widened to treat women suffering from all types of infertility with adequate pregnancy and live birth rates [25].

IVM of human immature oocytes has developed as a scientific procedure a few decades after the first live birth from IVM oocytes. How so ever, the techniques used for IVM of human immature oocytes fluctuate in protocols, and the clinical definition of IVM treatment also changes from the biologic definition of oocyte IVM. Such differences embrace the source of immature oocytes that may not be at the GV stage owing to patient selections and diverse stimulation protocols. In some cases, the human immature oocytes were gained from follicles that have been aroused for a few days with the use of gonadotropins to sustain moderate follicle growth and triggered with the employ of hCG before oocyte retrieval. A newly proposed clinical definition of IVM is based on the size of follicles during the immature oocyte retrieval, but that recommended definition may be unwieldy and complicated. It has been disparaged that a definition based on the size of follicles is not scientifically acceptable, and such a definition can lead to false results in evaluating the follow-up of children conceived with the exercise of IVM techniques [26].

It is appealing to mention here that the initial reports of pregnancies from IVM oocytes were from kindled cycles where the retrieval of immature oocytes was followed by IVM and IVF, in which the IVM procedure of immature oocytes was not based on the size of follicles. It seems to be tricky to clearly define the clinical meiotic status of oocytes, because there are different situations with patient selections and the sources. Thus, the definition of clinical IVM should be defined in accordance to the origin of immature oocytes to clarify for follow-up the outcomes gained from different sources of immature oocytes. Nonetheless, we think that clinical IVM treatment should be defined as IVM of any immature oocytes regardless of stage, from GV and MI to MII, for quantifiable application, because it involves the procedure of IVM for immature oocytes. It is vital to point out for scientists, especially for basic scientists, that they should distinctly comprehend that the situation of clinical procedures is quite diverse from the laboratory procedures. It is not possible to evaluate the clinical procedures by evaluation of laboratory procedures for IVM of oocytes. The accretion of our combined knowledge is to better comprehend the purpose of performing clinical IVM of oocytes and to use this knowledge for our health care [27].

Overall, IVM of human immature oocytes lingers a relevant and valuable technique in the field of assisted reproduction and fertility conservation. Additionally, progressions in antagonist cycles, GnRH agonist triggering, and voluntary cryopreservation strategies have led many IVF centers to desire easier treatment methods for infertility patients, resulting in a limited number of centers currently performing the IVM procedure [28].

The lower competence of human IVM programs can be featured to the quantity and quality of oocytes gained during IVM cycles. Firstly, the velocity of oocyte retrieval and IVM after in vitro culture is subordinate compared to conventional controlled ovarian hyperstimulation (COH) cycles. Secondly, the on the whole quality of oocytes derived from current IVM culture systems tends to be mediocre to naturally matured oocytes in vivo. Thus, ongoing research and improvements of the IVM program are necessary to offer valuable solutions and additional options to individuals facing fertility challenges [29].

In developed countries in which a restricted number of IVF cycles are allowed and paid for by the government but may engross a long waiting list, the substitute of doing immediate IVM as part of a research protocol emerges to be attractive. In many European countries where there is a mandatory limit to the number of embryos that can be transferred per cycle in an endeavor to curtail multiple pregnancies, IVM appears attractive because it can further trim down costs and threats to the patient, potentially without compromising PRs. In third-world countries, where the entirety cost of ART is less than in developed countries but charges comprise a larger fraction of the patient's earned income, IVM may establish to be more attractive than IVF because more than half of the cycle expense is connected to gonadotropins and GnRH analogues Thus, the universal acceptance and implementation of IVM as a feasible ART option are dependent not only on science but also on manifold worldwide and socioeconomic factors [2, 30]. The updating IVM technique with the incorporation of Artificial intelligence (AI) has been experiencing quick growth in recent years, and abundant applications are improving the single- step efficiency of the whole assisted reproductive technology (ART) procedures like IVF or IVM. Thus apart from improvement of embryo quality, the IVM technique is getting updated with innovative inputs. This can provide noteworthy benefits for infertile couples enduring diagnostic and therapeutic journeys. The calculators for the initiating dose of gonadotropins and the trigger timing during

controlled ovarian stimulation make clinical management more proficient. Infertility treatments by IVF of IVM are assisted by several algorithms that improve the efficiency of each procedure step, making ART program's management easier [31]

REVIEW OF LITERATURE

The concept of In Vitro Maturation (IVM)

In 1935, Pincus and Enzmann [32] stated that immature rabbit oocytes eradicated from their natural ovarian environment were able of undergoing spontaneous maturation and fertilization in vitro. Comparable observations were seen later in human beings in another study by Edwards in 1965 [33]. This knowledge was first applied in the clinical setting as an attempt to release and use immature oocytes that were gained from stimulated IVF cycles. Veeck *et al*. [34] permitted immature oocytes that were retrieved from mounting follicles exposed to in vivo gonadotropin stimulation to impulsively mature in the laboratory. It then was revealed that these immature oocytes not only were skilled of reaching maturation and fertilization in vitro but also of embryonic development and assembly of live offspring in human beings.

The oocyte is a matchless cell in a woman's body, owing to its special structure, function, and undergoing meiosis. Meiotic progression in the oocyte can be defined as the oocyte maturation from reinitiation of the first meiotic division to the metaphase II (MII) stage followed by cytoplasmic maturation to successfully organize the oocyte for fertilization and early embryonic development. In vivo meiotic recommencement in the oocyte is initiated in response to the pre ovulatory surge of LH. The LH surge activates oocyte maturation from the germinal vesicle (GV) stage to MII. For infertility treatment with the employ of IVF technology, the patients are given hCG to persuade the completion of oocyte meiosis in the follicles to retrieve mature MII oocytes 36 hours after hCG injection. Devoid of hCG injection in IVF treatments, most of the retrieved oocytes would be at an immature GV stage [38].

Human immature GV-stage oocytes can be matured artlessly to MII in vitro when they are confiscated from the antral follicles and cultured in the proper culture media. This can be the biological definition of oocyte IVM. Competent oocyte development needs careful harmonization between nuclear and cytoplasmic maturation. Nuclear maturation contains of germinal vesicle breakdown, recommencement of meiosis, extrusion of the first polar body, and seize at the MII stage. Although these steps are not the outcome of oocyte competence, they are necessary for fertilization. Unlike nuclear maturation, cytoplasmic maturation is much more complicated to assess microscopically, and its insufficiency tends to present later in development as damaged embryo cleavage or implantation failure. Thus, competent maturation of retrieved immature oocytes necessitates both nuclear maturation and exposure of these oocytes to the apt signals for synchronous cytoplasmic maturation [39].

The apparatus obligatory for an oocyte to achieve nuclear and cytoplasmic maturation is acquired gradually through its growth phase. The human oocyte attains its mature size of around 100–120 μm at the antral stage, whereas the follicle itself is only a fraction of its concluding ovulatory diameter. The capability of the oocyte to resume meiosis appears to be gained when follicular size is only 10 percent of the presumed ovulatory diameter or approximately 2 millimeters. Thus, in theory, it appears as though immature oocytes retrieved from very tiny antral follicles of size 2–5 mm already possess the machinery required to undergo full maturation. In actual practice, it has been found that the minimum follicular diameter to produce a proficient oocyte is around 5 mm. Although the real signal cascade that prompts maturation of these retrieved immature oocytes is unidentified, the harmonious activation of nuclear and cytoplasmic maturation for oocyte competence is liable to be highly dependent on the timing and size of the follicle from which the oocytes are rcovered [43, 44].

In vitro maturation needs the maturation of oocytes in the laboratory for 24 hours before insemination. It still is mysterious what constitutes a nurturing medium for in vitro oocyte

maturation. Many diverse types of IVM media have been portrayed in the literature, with few studies evaluating the contribution or comparing the unswerving effect of a particular medium on IVM success. There are other characteristics of IVM that still are in the process of standardization. Some of them are patient selection, follicular priming, endometrial preparation and support, method of insemination like IVF vs. intracytoplasmic sperm injection [ICSI]), and timing of Embryo Transfer [16].

Clinical features of IVM

Patient Selection

Various publications have depicted the utilization of IVM in women with PCO. These studies have comprised women with irregular menstrual cycles caused by polycystic ovary syndrome or PCOS and those with regular cycles but multifollicular

ovaries on the basis of ultrasound appearance or PCO. The palpable reasons for choosing women with PCO and PCOS as a target for IVM technology is the better number of antral follicles available per ovary. Since women with PCO or PCOS are more prone to experience OHSS, they also are the ones most probable to benefit from IVM [17, 18]. IVM also has been employed in women with regular menstrual cycles and normal appearing ovaries. The rationale for via IVM in this group of patients is to endeavor a less costly and less challenging treatment for infertility as compared with COH-IVF. Until more comparative studies are accessible, it makes clinical sense to apply IVM to women at risk for side effects from gonadotropins and who have plenty ovarian reserve as assessed by history and by standard tests like antral follicle count, age, basal FSH, and basal inhibin B levels [20].

In vitro oocyte maturation

The traditional approach to IVM involves culturing immature COCs from the Prophase-I to reach the metaphase II (MII) stage devoid of the administration of any gonadotropins. Nevertheless, in clinical human IVM programs, it is frequent to use in vivo stimulation with gonadotropins to augment the quality and quantity of oocytes. This stimulation can contain a few days of gonadotropin (FSH) treatment, a single ovulatory dose of human chorionic gonadotropin (hCG), or a mishmash of FSH and hCG [13].

FSH Priming

Ovarian stimulation with hardly any days of FSH priming is frequently used in clinical IVM programs. Animal studies have prompted that in vivo FSH priming improves follicular development and the meiotic and developmental competency of immature oocytes and reduces the time required to reach the MII stage. Similarly, in human IVM programs, FSH priming has been found to progress oocyte yield and maturation rates, ensuing in more mature oocytes. The grounds for pre treating a patient with FSH is that human follicles with a diameter of 2–6 mm have a lofty expression of FSH receptors, and FSH supplements follicular growth and estradiol production [5]. As FSH priming does not persuade oocyte meiotic resumption in vivo, immature compact COCs are gained after oocyte retrieval (Figure 1A). There is no agreement, however, on the dose and duration of FSH priming in IVM cycles. Wynn *et al*. [22] proposed that a short course of FSH treatment, improved the oocyte maturation rate in vitro. In a small, randomized study in sevaral women with PCOS, the percentage of oocytes reaching the MII stage was significantly higher in women who had undergone FSH priming compared with the non-primed group. [23].

hCG priming before oocyte retrieval

Researchers have prompted that hCG may promote the commencement of oocyte maturation in vivo and get better the maturation rate of IVM oocytes, thereby improving pregnancy rates. The incorporation of hCG priming in IVM cycles aims to mimic the conditions seen in conventional IVF cycles, where expanded CCs correlate with better maturation rates. Various studies have described hCG eliciting combined with FSH priming in IVM cycles with inconsistent outcomes. Lin *et al*. [27] did not examine any additional advantage from FSH priming in hCG-primed IVM cycles in PCOS women.

Timing of oocyte retrieval

Selection of the ideal day for oocyte retrieval in IVM cycles fluctuates widely between groups. Whilst some investigators have suggested waiting for the leading follicle to reach 10 mm, others considered that this would be unfavorable and proposed cancelling the cycle. Researchers have also advocated that extending the period of hCG priming time from 35 to 38 hours for immature oocyte retrieval endorses oocyte maturation in vivo and augments the IVM rate of immature oocytes.

1. Oocyte retrieval

Unlike in conventional IVF collections, oocyte retrieval in IVM cycles can be more demanding, due to minor follicle sizes and stronger connection of immature COCs to the follicle wall, especially with no ovulatory dose of hCG or GnRH agonist. In the preponderance of IVF centers, the standard needle diameter for puncturing small follicles, which can range from 2 -12 mm in size, is typically between 16 - 21 gauges. Using a thin needle for multiple punctures on tiny follicles, along with lower aspiration pressure, may irregularly result in needle blockage during the procedure [21]. The detection of oocytes from follicular aspirates in IVM cycles can be loomed using two methods: the direct method and the filter method. In the first method, the follicular aspirate is transferred to a Petri dish and scrutinized under a stereomicroscope to detect COCs, similar to the process in traditional IVF cycles. This methodology is employed in both hCG-primed cycles, with or without priming with FSH, as many of the retrieved oocytes have enlarged CCs [11]

Laboratory aspects of IVM

IVM of immature oocytes, culture medium for IVM and supplements

The unprompted maturation of immature oocytes in vitro can lead to unfinished cytoplasm maturation, potentially banging the developmental competence of the oocytes and resulting embryos. To tackle this issue and develop the overall success of IVM programs, some studies have discovered a biphasic IVM approach, which involves 2 phases: pre IVM and IVM. In the pre IVM phase, chemicals like cAMP analogues, kinase inhibitors, otherwise PDE inhibitors are used to holdup or temporarily avert spontaneous oocyte maturation for a short period (habituallyaround 2 hours) [29]. Presently, many IVM protocols involve adding serum, FSH, LH/hCG, or EGF-like growth features to the culture medium based on their role in oocyte maturation in vivo. Cadenas *et al*. [24] verified significant up- regulation of substances such as amphiregulin, inhibin A, inhibin B, and midkine in human follicular fluid and granulosa cells during the final maturation of follicles in vivo. However, additional widespread research is obligatory to determine the optimal combination and concentrations of these supplements in the culture medium to gain improved IVM outcomes.

1. IVM culture time and Insemination

In the early IVM studies, oocyte maturity was characteristically assessed after 48 or 56 h of culture [17]. Conversely, recent researchers have shown that a significant number of MII stage oocytes can be obtained after just one day of culture from GV stage oocytes collected in IVM cycles [11].

2. Culture of IVM embryos, Embryo Transfer (ET) and cryopreservation

After zygotes called fertilized oocytes are generated through IVF fertilization or ICSI within an IVM cycle, the succeeding embryological tasks and methods for ET and cryopreservation closely bear a resemblance to those employed in conventional IVF cycles [11]. Even if the cleavage rate of IVM embryos parallels that of IVF embryos, the blastocyst rate of IVM embryos is normally somewhat lesser than that observed in IVF embryos [20, 21]. In terms of cryopreservation, investigations have exposed favourable survival rates and sensible clinical outcomes when employing vitrification to freeze both cleavage-stage and blastocyst- stage embryos obtained from clinical IVM programs [31].

3. Endometrial preparation and luteal support

In IVM cycles, sufficient endogenous estrogen from the dominant follicle to prepare the endometrial lining is scarce and oocytes are retrieved before the endometrium is fully estrogenised. The progesterone hold up from the corpus luteum is inadequate and can negotiate endometrial receptivity. This asynchronous development between the embryo and the endometrium may clarify the poor implantation rates in fresh transfer IVM cycles [32]. Russell *et al*. [32] published improved oocyte maturation rates and embryo development when exogenous estrogen priming was commenced in the mid-follicular phase versus when estrogen was started early in the follicular phase. More studies are entailed to assess the optimal regimen to harmonize the window of implantation with embryo development in IVM cycles.

Freeze all strategy

In a retrospective case series of seventy nine consecutive PCOS patients undergoing IVM followed by vitrified-warmed ET at cleavage stage over a two year period, the cumulative live birth rate per embryo transfer was 16.2 percent, the cumulative LBR per patient was 21.8 percent and the LBR per retrieved immature oocyte was 1.1 percent [25]. The authors found that the ongoing pregnancy rate in the freeze-only group was considerably higher than that in the fresh embryo transfer group as was the live birth rate [36].

Advantages and Potential Applications of IVM

IVM for PCOS patients

IVM of oocytes has been suggested as a safer alternative to conventional ovarian stimulation (COS) in patients with PCOS as the danger of ovarian hyperstimulation syndrome (OHSS) is minimal. Recently, strategies such as GnRH agonist triggering in combination with a policy of freeze-all embryos have been widened to reduce the risk of OHSS risk [24]. As a result, the fame of IVM of oocytes to treat subfertile women with PCOS has reduced. However, a recent study found that in women with amplified risk of OHSS, women were willing to trade off annulment rate, number of injections, chance of pregnancy and costs for lower risk of OHSS [35]. This prompts that IVM may be a proper substitute in selected patients with PCOS after suitable counseling.

4. IVM for fertility preservation

Time to cancer treatment is a grave concern for many cancer patients, as they often cannot afford to delay starting chemotherapy, radiation therapy, or surgery. In such urgent situations, IVM treatment tenders a precious advantage over traditional IVF. IVM can be initiated immediately and at any phase of the menstrual cycle without the need for hormonal

stimulation. This allows cancer patients to preserve their fertility without having to delay cancer treatment, as the IVM treatment cycle can be completed within a short-time frame of 2–10 days. Since IVM oocyte cryopreservation could be undertaken without any need for gonadotropin stimulation, potential side effects such as OHSS can be evaded [26].

IVM is also a feasible option in patients who have absolute contraindications to gonadotropin stimulation. Furthermore, ovarian stimulation is not an opportunity in prepubertal girls. Grynberg *et al*. [37] observed that in breast cancer patients undergoing urgent fertility preservation, there were no much differences in the number of COCs recovered or their IVM rates whatever the phase of the cycle at which oocytes were collected. With regard to these findings, Creux *et al*.[38] appraised the efficacy of IVM when immature oocyte retrieval was performed in the early follicular, late follicular, or luteal phases in cancer patients undergoing urgent fertility preservation. There was no noteworthy difference in the number of oocytes retrieved, maturation rates after 48 hours of culture, fertilization rates, or the total number of oocytes and embryos cryopreserved when immature oocyte retrieval was performed at various times in the menstrual cycle.

IVM techniques can also be combined with ovarian tissue cryo banking for vital fertility preservation. In the near future, it is likely that the application of IVM procedures will expand to include conditions such as thalassemia, sickle cell anaemia and Turner syndrome. In a very recent study, it was seen that the biphasic in vitro maturation system (CAPA-IVM) improved the developmental competence of ovarian tissue oocytes from patients with gynaecological tumours in comparison to the usual IVM method. To develop the viability and developmental potential of cryopreserved oocytes obtained through IVM cycles, additional research is warranted. This quest of improved survival and embryo development holds the potential to broaden the scope of IVM techniques for the rationale of fertility preservation [34, 39].

5. IVM for resistant ovary syndrome and oocyte maturation disorders

Resistant ovary syndrome, which is also called as ovarian insensitivity syndromeor Savage syndrome, is an uncommon endocrine disorder distinguished by elevated endogenous gonadotropin levels and stumpy estrogen levels, primary or secondary amenorrhoea, normal secondary sexual characteristics, usual AMH and antral follicle counts, and a standard female karyotype. For patients with resistant ovary syndrome, IVM is presently the only doable alternative to egg donation. Various live births have been reported following IVM cycles in patients with this condition. How so ever, in patients with deficient oocyte maturation disorders, researchers have suggested disappointing results after IVM treatment, even with enlarged oocyte culture [40, 41].

6. IVM for poor responders

The most favorable management of women who retort poorly to conventional ovarian stimulation remains a challenge. There is a scarcity of data on the use of IVM protocols for poor responders. A small number of researchers have analyzed whether embryo transfers with rescue IVM derived embryos could get better clinical outcomes in poor-responder patients undergoing ovarian stimulation. In a case report, Liu *et al*. [40] reported 3 pregnancies (two live births and an ongoing pregnancy) in eight poor responder patients who underwent in vitro maturation of immature oocytes derived from stimulated IVF cycles before cycle cancellation. In an added study which included 440 poor responder patients, enduring ICSI cycles in which fewer than five MII oocytes and at least one immature oocyte was retrieved, patients were divided into 2 groups based on the injected oocytes' nuclear maturation status. The group where only embryos derived from mature oocytes were injected was compared with cycles in which least one immature oocyte continued in culture for spontaneous maturation and ICSI. Although the rescue IVM group had a greater number of transferred embryos and a lower embryo transfer cancellation rate, there were no significant differences in the clinical pregnancy rate or miscarriage rate between the 2 groups, suggesting that rescue IVM did not provide any additional advantage in poor responder cycles. Some researchers have proposed that natural cycle IVF/IVM may attain improved outcomes in poor responder patients after failure of stimulated cycles [43].

Limitations and Key Challenges of IVM

While IVM presents several advantages over conventional IVF, it is important to recognize that IVM also comes with its challenges. Performing an IVM cycle demands more time and expertise compared to conventional IVF cycles [41]. Additionally, the overall efficiency of IVM tends to be lower than that of IVF cycles. In standard human IVM programs, the procedure for attaining immature oocytes closely look likes that of standard IVF. As previously stated, this can present confronts for clinicians in terms of visualizing and aspirating immature oocytes during ultrasound guided retrieval.

Besides, diverse pre-treatment methods, such as FSH- or hCG-priming before oocyte retrieval, have been utilized. As a result, the techniques used in clinical IVM can display substantial variability across different clinics. These variations in protocols and methods can blow the effectiveness and success rates of IVM cycles, delaying the establishment of a optimized procedure.

Another dispute in IVM cycles is the lack of standardized commercial media and consensus protocols for media preparation. Consequently, each laboratory must prepare its own culture medium, leading to deviations in the composition of the medium between different laboratories. Hence, ongoing research is essential to identify critical factors that influence the quantity and quality of oocyte maturation. These factors cover the composition of the culture medium, the timing and extent of culture, as well as the incidence of supportive factors. Through the identification and standardization of these elements, standardized and effective culture conditions for IVM can be established [30].

Other problems associated with IVM comprise cycle cancellation, poor embryo quality, low implantation rates and high miscarriage rates. Addressing these challenges and refining the oocyte retrieval procedure within IVM cycles will play a crucial role in enhancing on the whole efficiency and success rates of IVM programs. By devising focused techniques and protocols adapted to IVM oocyte retrieval, clinicians can augment the outcomes of IVM programs [42].

SUMMARY AND FUTURE OUTLOOK OF IVM

Modern published studies give credibility to the fact that IVM technology rapidly is raising in the clinical field of ART, with ever-improving triumph rates. In spite of significant clinical improvement, pregnancy, implantation, and unprompted abortion rates are not reliable or reproducible among studies. This likely can be a result of the divergences in clinical practices with regard to the population of patients, perfect timing of oocyte retrieval, nurturing conditions of the lab media, and grounding of the endometrium rather than the technique itself. The standardization of IVM is ongoing and appears to be highly reliant on the competence of the immature oocyte retrieved. Further research and perceptive of the human oocyte within the immature follicular environment is vital for the advancement of IVM technology and its relevance to a broad range of patients. Nevertheless, IVM already has widened its clinical reach to infertile patients, irrespective of diagnosis [43]. The amendments of IVM technology can include letrozole use for early antral follicle development, quick clearing of the collection system to minimize the time between the oocyte parting the ovary and its identification by the embryologist, and the employ of FET to control and optimize embryo transfer for IVM derived blastocysts results in adequate indicators of oocyte competence hard to distinguish from IVF derived oocytes. More blastocysts were generated from women with a high antral follicle count using IVF than using IVM, recommending the full cohort of IVM-derived oocytes was less proficient than the cohort of IVF-derived oocytes. How so ever, the best IVM-derived blastocysts emerged to function as well as the best IVF-derived blastocysts. Expectantly, the ideas used in this IVM series will be combined with other new looms to advance the evolution of IVM-technique [10, 11].

Ongoing research is indispensable to identify decisive factors that influence the quantity and quality of oocyte maturation. These factors include the composition of the culture medium, the timing and interval of culture, as well as the charisma of supportive factors. Through the identification and standardization of these elements, optimized and effective culture conditions for IVM can be established. Two main hypotheses can be proposed as an explanation that includes firstly the embryo quality, which can be patient-determined or as a result of the process of in-vitro oocyte maturation and culture and secondly the endometrial quality, which can also be patient-determined or a result of asynchronous steroid hormone preparation. The continued spread of IVM as a real substitute to conventional IVF will only be possible if it proves to have analogous outcomes. Thus, we must decide how to improve implantation rate following IVM. Albeit encouraging successes have been illustrated for the last four indications, the small number of pregnancies makes these arguably anecdotal. On the contrary, PCOS patients represent the huge majority of women who undergo IVM and also for that reason the mainstream of clinical pregnancies and live births follow IVM to women with PCOS [44]. The decisive goal of the any ART procedure is to help patients execute their most basic desires of reproduction and continuity, using expertise that was only imaginary not long ago. These techniques are not yet faultless and may be linked with taking some gauged risks and gutsy decision making, without which we would never have been capable to rally round so many people and craft so many cheerful families.

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