

REVIEWS

Review of minimally disruptive in vitro fertilization (IVF) approaches as a strategy for assisted human conception

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As a type of assisted reproductive technology (ART), in vitro fertilization (IVF) has been available for more than 4 decades, with the first successful birth using conventional IVF (C-IVF) occurring in 1978. C-IVF has become increasingly available and accessible over the years and is currently a widely used alternative treatment option for prospective parents experiencing infertility. In addition, science and technological advancements have given rise to other IVF techniques that allow families to choose the ART that best fits their personal and unique needs. Among the other IVF techniques, natural cycle IVF, mild stimulation IVF, and in vitro maturation are notable for being less disruptive to the female body and are referred to as minimally disruptive ARTs (MDARTs). However, deciding which MDART to choose is a complex and daunting task that precedes an already emotionally, financially, and physically taxing process. This review explores these modern ART strategies, including protocols, advantages, and limitations, as well as provides the MDART decision matrix that translates these considerations into a practical decision-making guide for patients seeking IVF.

Introduction

The first successful human born of in vitro fertilization (IVF) is now a 46-year-old English woman with 2 children of her own. A reproductive biologist named Robert Edwards began pioneering IVF as a strategy for assisted human conception in 1965 after the successful in vitro maturation of the human oocyte following its release from the ovary. Edwards published 2 studies that year that accurately outlined the time course associated with human egg meiotic maturation, the challenges he experienced with in vitro egg maturation, and the potential that exists for reducing inheritance of genetic diseases.^{1,2} By 1968, Edwards' collaborations with gynecologist Patrick Steptoe saw success in laboratory-based human egg fertilization as they attempted to promote a new method for addressing infertility.³ Today, IVF is used as a treatment option for those with infertility, and advancements in technology have given rise to many different IVF techniques, which accommodate broader diversity of needs for modern family planning. This review provides an initial overview of conventional IVF (C-IVF) and delves into the advantages and disadvantages of the 3 minimally disruptive assisted reproductive technology (MDART) protocols descendent from the original

technique. Then, using the advantages and disadvantages of each of the 3 MDARTs, we present a tailorable model that patients can use to perform their own needs assessment and better understand which protocol is more suitable for them.

Conventional IVF

It took about 13 years after Edwards' pioneering publication on the successful in vitro maturation of the human egg to achieve a successful live birth using IVF in 1978.⁴

The objective of C-IVF is to retrieve high-quality oocytes capable of successful fertilization, maturation, and eventual replantation into the prospective mother. To achieve this, the prospective mother is administered high doses of gonadotropins and other drugs to promote uterine stimulation and increase the total number of retrieved oocytes. This high-dose stimulation of the ovaries induces development of multiple follicles so that the quantity of eggs retrieved is maximized to improve the chances of obtaining viable embryos that can be transferred into the uterus. Despite this high-dose stimulation process and potential uterine burden, C-IVF continues to be a treatment option for families with infertility due to the increased chance of success from the greater number of retrieved oocytes. While patients seeking C-IVF may be those that experience lower pregnancy rates, Gershenson et al⁵ noted that patients' expectations for efficiency of treatment and successful pregnancy were inversely high, potentially in response to the prohibitive costs and other stressors.⁵

C-IVF Protocol

C-IVF is composed of 5 major steps: (1) ovarian stimulation, (2) egg retrieval, (3) insemination and fertilization, (4) embryo culture, and (5) embryo transfer.

Ovarian stimulation: The C-IVF protocol begins with ovarian stimulation using purified human menopausal gonadotropin (hMG) and/or follicle-stimulating hormone (FSH) by subcutaneous administration for approximately 8 to 10 days. Doses of both hMG and FSH range from 150 to 450 IU, with hMG doses containing a 50/50 preparation of FSH and human chorionic gonadotropin (hCG). Dosage is dependent on patient age and ovarian reserve with higher doses reserved for patients who are older, have decreased capacity to produce fertile eggs, or have medical conditions such as polycystic ovary syndrome (PCOS). Once initial stimulation is complete, patients typically begin a 2-week course of gonadotropin-releasing hormone agonist to suppress ovulation; however, if the initial ovarian response is suboptimal, additional stimulation may be applied. Estradiol levels are checked after the completion of the course to confirm downregulation.

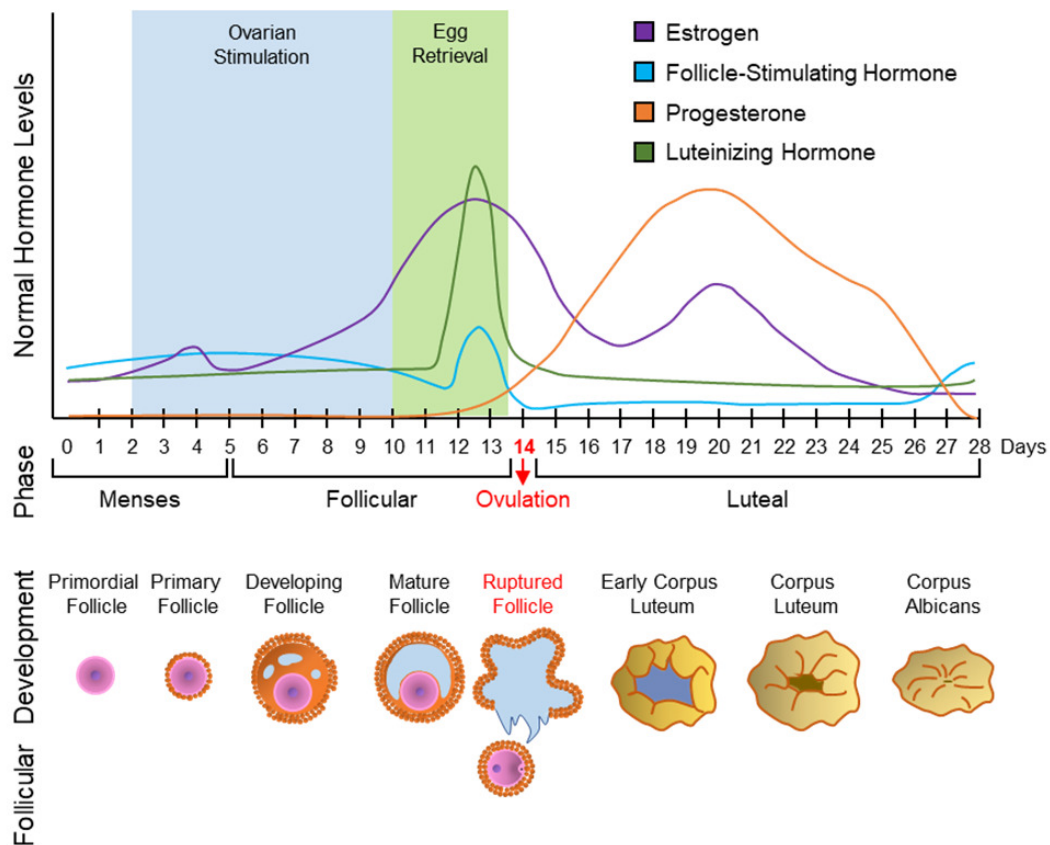


Figure 1. Alignment of the C-IVF protocol to a typical ovarian cycle.

A typical ovarian cycle lasts approximately 28 days. Normally, the ovarian cycle initiates with a primordial follicle arrested in Meiotic Prophase I responding to the cyclic release of follicle-stimulating hormone (FSH). In the C-IVF protocol, ovarian stimulation begins a few days into menses. The primordial follicle develops a single layer of granulosa cells to become a primary follicle. Continuing to grow its granulosa cell layers, the primary follicle develops its theca interna and externa layers and creates an antrum from a hyaluronic acid-rich fluid called follicular fluid. The follicle progresses into Meiotic Prophase II and the oocyte meiotic inhibitor (OMI) found in follicular fluid causes the oocyte to arrest at Meiotic Prophase II. Next, the innermost layer of granulosa cells forms the corona radiata and the outermost layers of granulosa cells become the cumulus oophorus. A surge of luteinizing hormone (LH) causes the final maturation of the follicle and the follicle ruptures leading to ovulation. The C-IVF protocol focuses on retrieving the mature oocyte via transvaginal ultrasound aspiration prior to ovulation.

Patients that have estradiol levels less than 50 pg/mL may now begin gonadotropin stimulation therapy while continuing to suppress ovulation using gonadotropin-releasing hormone agonists.⁵

Egg retrieval: Egg retrieval occurs when there are at least 2 mature follicles found on ultrasound at 18 mm with an appropriate increase in estradiol levels. As depicted in [Figure 1](#), eggs are mature and ready for extraction starting at approximately 10 days and retrieval is conducted prior to ovulation. At this point, a dose of hCG between 5000 to 10000 IU is administered and transvaginal ultrasound aspiration is performed on the sedated patient 34 to 36 hours later to retrieve the mature eggs ([Figure 2](#)).⁵ This technique involves the use of an ultrasound probe to identify the follicles and an aspiration needle that penetrates the vaginal wall and mature follicles to retrieve eggs via suction.

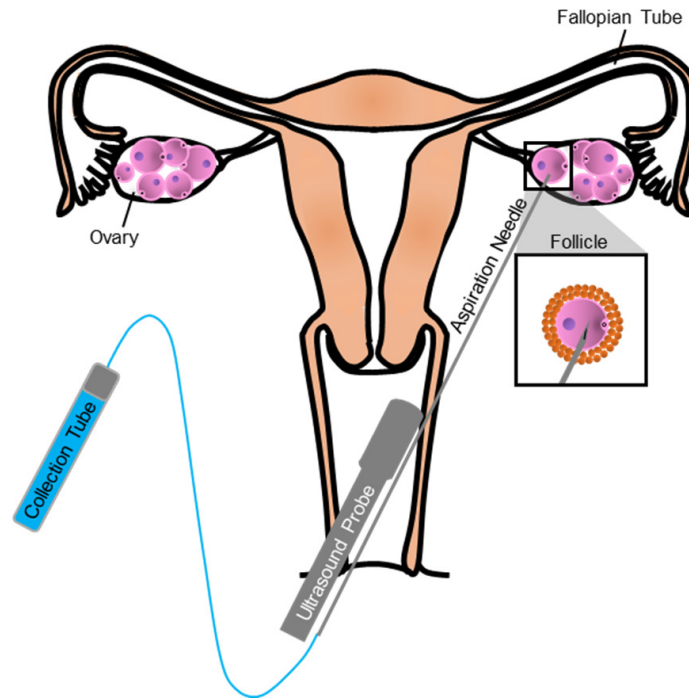


Figure 2. Egg retrieval by transvaginal ultrasound and aspiration.

An ultrasound probe is inserted into the vagina to identify and locate mature follicles within the ovaries. Once mature follicles have been properly identified, a needle is guided past the vaginal wall and into the mature follicle to remove eggs by suction.

Insemination and fertilization: The retrieved eggs are then exposed to a sperm sample using 1 of 2 methods: (1) insemination by microdroplet containing tens of thousands of sperm or (2) the direct injection of a single sperm into the egg using a micropipette—a technique called *intracytoplasmic sperm injection* (ICSI). Approximately 60% to 70% of mature oocytes fertilize with insemination by microdroplet when using highly motile sperm for the first method, while the second ICSI technique was designed to help less motile sperm with successful fertilization. The second ICSI method is found to be particularly effective for potentially low motile sperm or low sperm count situations resulting in low fertilization rates⁵ and allows for individual sperm selection for microinjection into the mature oocyte, with inspection for fertilization occurring 12 to 18 hours later.

Embryo culture: Three days after egg fertilization, embryos enter the cleavage stage and are assessed by their morphology, symmetry, and embryo fragmentation for potential embryo transfer.⁵ The Society for Assisted Reproductive Technology's Clinic Outcomes Reporting System is used as a predictor of embryo quality based on morphological features seen under microscopy. A study that leveraged the Society for Assisted Reproductive Technology's Clinic Outcomes Reporting System found that embryos with fragmentation of 10% or more from dividing embryonic cells creating extracellular debris had a correlation with lower live birth rates.⁶ In addition, Ziebe et al⁷ found no significant difference in fragmentation patterns and cleavage rates between embryos from natural cycles and stimulated cycles.

These findings suggested that hormonal stimulation increases the likelihood of achieving viable eggs by increasing the number of oocytes retrieved. Therefore, embryo quality should mainly be used to differentiate between the embryos that will be transferred into the mother.⁷ Embryo culture can continue into day 6 with the increasingly improved quality of culture media.⁵

Embryo transfer: The American Society for Reproductive Medicine has published guidelines to help determine the number of embryos to transfer and implant into the prospective mother because this decision is key to optimizing the success rate while reducing the chance of multiple pregnancies. During the embryo transfer, patients are awake and ultrasound-guided catheters are used to guide the precise placement into the uterus. The embryo is loaded into this catheter, which is guided by ultrasound providing real-time imaging and inserted through the cervix for embryo deposition. Transfers performed on the third day after aspiration may use assisted hatching, a procedure that uses acid or laser to breach the embryo's zona pellucida, to improve implantation success rates and clinical pregnancy rates in older women and those with unexplained IVF failures. However, assisted hatching does not increase live birth rates.⁵ Excess embryos not transferred during this process may be cryopreserved using vitrification, an ultrarapid freezing method.

Since Edwards' initial breakthroughs in the 1960s, more than 8 million babies have been born from assisted reproduction.⁸ During this time, variations and advancements to IVF have been made to diversify treatment options available to families dealing with infertility. These advancements also include a more comprehensive understanding of infertility, including discovery of infertility challenges related to the prospective father's sperm. For example, given that fertilization is highly dependent on the motility of sperm to reach the egg, established methods for insemination by microdroplet of immotile sperm may not result in successful fertilization of the egg. These conclusions led to fertilization method expansion such as ICSI described above, which has not been determined to produce better fertilization rates than by microdroplet but addresses the issues caused by low-motility sperm, meaning it requires evaluation of the father's sperm. Deciding on the right type of treatment requires personalization, a balance of medical history, religious and cultural beliefs, risk tolerance, affordability, and long-term family planning.

Natural Cycle IVF

Natural cycle IVF (NC-IVF) was designed to avoid the use of ovarian stimulation drugs by relying on a woman's natural menstrual cycle to retrieve a single egg; Louise Brown became the first documented child successfully conceived by this method in 1978.⁹ No hormonal injections are used to stimulate multiple eggs to develop, which is an important protocol distinction because this reduces the risks of adverse effects associated with IVF medications. Because only a single egg is retrieved per cycle, pregnancy rates

tend to be lower than with C-IVF, but this technique remains a good option for patients with a strong ovarian reserve seeking to avoid the costs and risks associated with ovarian stimulation.¹⁰

NC-IVF Protocol

NC-IVF begins on day 2 of the menstrual cycle with ultrasound monitoring of the follicle growth. Once the follicle has reached a certain size, the prospective mother is injected with hCG to stimulate ovulation. The egg is retrieved 36 hours later, fertilized in the laboratory using C-IVF techniques, and then transferred back to the mother's uterus.¹⁰

Also referred to as the “drug-free IVF,” NC-IVF serves as a viable option for families with financial constraints as well as for prospective/hopeful mothers who require treatment without hormone therapy due to other health constraints or who are in their advanced reproductive years because of the reduced medication burden and allows for a more natural and individualized treatment. However, NC-IVF also has notable limitations such as single egg retrievals per cycle, leading to lower pregnancy rates and a longer time to achieve pregnancy.

NC-IVF Advantages

The most significant advantage of undergoing NC-IVF is the minimal use of fertility drugs. A reduction in prescribed medication confers other benefits such as decreased financial costs and less risks of medication adverse effects, drug interaction, and complications. Von Wolff et al¹¹ showed that modified NC-IVF, which involves the administration of low doses of clomiphene citrate, an affordable selective estrogen receptor modulator that induces ovulation, resulted in a 15% reduction in total costs per cycle compared with conventional gonadotropin-stimulated cycles. A prospective randomized clinical study by the Tehran University of Medical Sciences investigated the difference in pregnancy outcomes between natural cycle frozen-thawed embryo transfer (NC-FET) cycles and artificial cycles in 170 patients at the Shariati Hospital in Tehran, Iran.¹⁰ This study further demonstrated that while NC-FET entails little to no medication, no adverse effects, and significantly reduced costs, there were no differences in successful clinical pregnancy between NC-FET and artificial cycles.¹⁰ In addition, NC-IVF is a viable option for older women for whom C- IVF was not successful. A case report originating from Tokyo, Japan, by Matsuura et al¹² covered 3 successful cases of dominant follicle extraction during the natural cycle in patients of advanced age (37 to 41 years of age). This study demonstrated successful pregnancies in women of advanced ages with regular menstrual cycles (26- to 34-day cycles) who had experienced repeated unsuccessful attempts with stimulated IVF.¹²

Keller et al¹³ also demonstrated the differences in the psychological effects on couples undergoing NC-IVF vs C-IVF. The authors conducted psychometric tests and found that couples who underwent NC-IVF experienced lower psychological distress and increased treatment-related satisfaction and quality of life. The authors speculated that the factors accounting for this difference include the lack of the following requirements in NC-IVF: daily injections, anesthesia for oocyte retrieval, embryo selection, and embryo freezing. Furthermore, because NC-IVF creates only a single embryo for implantation, multiple pregnancies rarely occur. Gonadotropin stimulation drugs used in ovary stimulation to produce large numbers of embryos can also lead to a complication called *ovarian hyperstimulation syndrome* (OHSS), a condition that causes ovaries to swell due to overstimulation by drugs. This results in fluid leaking into the abdominal region and may cause abdominal bloating and pain. Gonadotropin stimulation drugs are not used in NC-IVF, meaning the risk of OHSS is also eliminated. Because these potentially anxiety-provoking procedures are not part of NC-IVF, couples may mentally fare better than couples undergoing C-IVF.¹³

NC-IVF Limitations

Due to the single egg retrieval per cycle in NC-IVF, there are significantly lower live birth rates per cycle. Statistically, this translates to overall lower rates of pregnancy and longer average time to pregnancy. Pregnancies took 30% longer in modified NC-IVF compared with C-IVF.¹¹ Another issue with single egg retrieval is that no extra embryos will be available as reserve in case the pregnancy is unsuccessful. The patient will have to undergo another NC-IVF treatment and egg retrieval procedure. Therefore, the lower pregnancy rate associated with the minimal use of fertility drugs in NC-IVF protocols may result in additional treatment cycles, especially in patients with lower responses to fertility drugs. Because NC-IVF is timed with the patient's ovulation cycle, the procedure can conveniently be performed every month if the patient's ovulation cycle is regular.¹² With this consideration, NC-IVF may be difficult to plan around a patient's ovulation cycle if it is irregular.

Mild Stimulation IVF

A significant proportion of women experience a poor response to the C-IVF protocol¹⁴ due to C-IVF requiring high doses of hMG and hCG to maximize the number of oocytes per cycle, leading to increased treatment costs and increased hormonal burden. In 1996, Edwards et al¹⁵ expressed concerns regarding the excessive doses used for ovarian stimulation in C-IVF and called for the use of milder and lower doses to minimize the health risks associated with ovarian hyperstimulation. The need for safer and more patient-friendly protocols along with improvements in laboratory techniques that removed the need for retrieving a large follicular cohort resulted in the development of the mild stimulation IVF (MS-IVF) protocol shortly thereafter. MS-IVF is an alternative protocol leveraging lower doses of hormones, but also

limiting the number of oocytes retrieved.¹⁶ The International Society for Mild Approaches in Assisted Reproduction defines MS-IVF oocyte retrieval to be between 2 and 7 oocytes and C-IVF to be 8 or more oocytes.¹⁷

Smaller doses of exogenous gonadotrophins (<150 IU/day)¹⁷ and limited ovarian stimulation results in better protocol tolerance and potentially lower treatment costs. The main allure of MS-IVF is the promise of a safer, less-intensive IVF treatment option¹⁸ and a delicate balance between IVF success and patient discomfort when developing patient treatment plans. From the patient's perspective, it is imperative to consider all factors including costs, complications, and duration of treatment. MS-IVF is founded on the belief that optimal treatment includes the balance of successful stimulation, treatment outcomes, and minimal rates of OHSS development. Therefore, it is important to consider the main goal of an IVF treatment: to successfully have a singleton healthy gestation.¹⁹

MS-IVF Protocol

With MS-IVF, the prospective mother receives a lower dose of FSH for a shorter duration compared with C-IVF. The retrieved egg is fertilized and transferred back into the woman's uterus after monitoring for a few days. The implantation window is a brief duration of the menstrual cycle when the endometrium is most receptive to a fertilized embryo being implanted and particularly important in MS-IVF, where the hormonal injections are minimized. Properly preparing the endometrium for the implantation by coordinating and balancing the complicated mixture of growth factors, cytokines, and hormones becomes critical. While no prescriptive standard exists for assessing endometrial receptivity, embryologists can leverage several methods including histological evaluation, gene expression analysis, and imaging. The feasibility of leveraging endometrial biomarkers may also provide a more targeted and personalized IVF approach based on a benefits assessment.²⁰

MS-IVF Advantages

MS-IVF involves fewer injections and lower dosages compared with C-IVF, and many of its advantages stem from this distinguishing feature of MS-IVF. Patients who undergo MS-IVF also experience decreased treatment burden and risk of adverse effects. C-IVF protocols lead to an increased incidence of patient discomfort and an increased risk of developing other adverse effects including OHSS. The decreased risk of severe OHSS associated with MS-IVF leads to an improvement in patient comfort and satisfaction.¹⁷ The decrease in complexity of MS-IVF treatment plans, fewer and shorter dosing intervals, and minimized adverse effects also improve patient compliance and outcomes.^{21,22}

Studies have found that ovarian stimulation may affect embryo quality defined by embryo chromosome layout and morphology. This is speculated to be due to ovarian stimulation overriding the natural selection of high-quality oocytes that takes place during a natural physiological cycle. However, MS-IVF closely mimics a physiological cycle, which results in better embryo quality and a higher incidence of euploid embryos compared with C-IVF.²³ Additionally, the overall delivery rate at term over a 12-month period of MS-IVF was found to be the same as C-IVF treatment.²⁴

MS-IVF Limitations

Although initial costs per fresh IVF cycle with MS-IVF are lower,²⁴ long-term costs may accumulate to become greater than with C-IVF: the MS-IVF cost per pregnancy includes the fresh and frozen embryo transfers associated with a single oocyte retrieval, which may exceed costs for C-IVF.²⁵ Long-term costs can also include additional treatments, cryopreservation, and storage.

Previously accepted outcomes of C-IVF assumed that the quantity of embryos retrieved was synonymous with the quality of embryos.²⁶ However, more recent studies have suggested otherwise because retrieving fewer embryos may be associated with higher-quality embryos and, thus, a greater likelihood of implantation and gestation.²³ Fewer egg retrievals also mean limitations in the number of eggs available for cryopreservation.

In Vitro Maturation

While preliminary work with in vitro maturation (IVM) was being reported in the 1960s by Edwards, it was not until 1994 that Trounson et al²⁷ reported the first successful pregnancy using IVM. IVM involves retrieving immature eggs from the ovaries, maturing them in the laboratory, and fertilizing them with sperm to form embryos that can then be transferred to the uterus. Because egg maturity is not a factor, it does not require high doses of fertility drugs nor other stimulation of the reproductive system and can serve as a less-invasive and much more affordable option than C-IVF.²

IVM Protocol

IVM has 2 major clinical protocols for the preparation and collection of immature oocytes: the ovaries either remain unstimulated or may be briefly primed. The protocol involving unstimulated ovaries uses an ultrasonography-guided needle to extract the immature oocytes and surrounding “nurse cells” via needle insertion through the vaginal wall to the ovaries’ small antral follicles ([Figure 3](#)). These oocytes are matured in vitro for up to 2 days followed by C-IVF procedures in the laboratory setting to generate an embryo that can progress to metaphase II and meets viability standards. This protocol is known as *spontaneous IVM*²⁸ and is less invasive due to the ovaries not requiring stimulation. In situations where the oocyte numbers may need to be increased, short follicular-phase FSH priming is

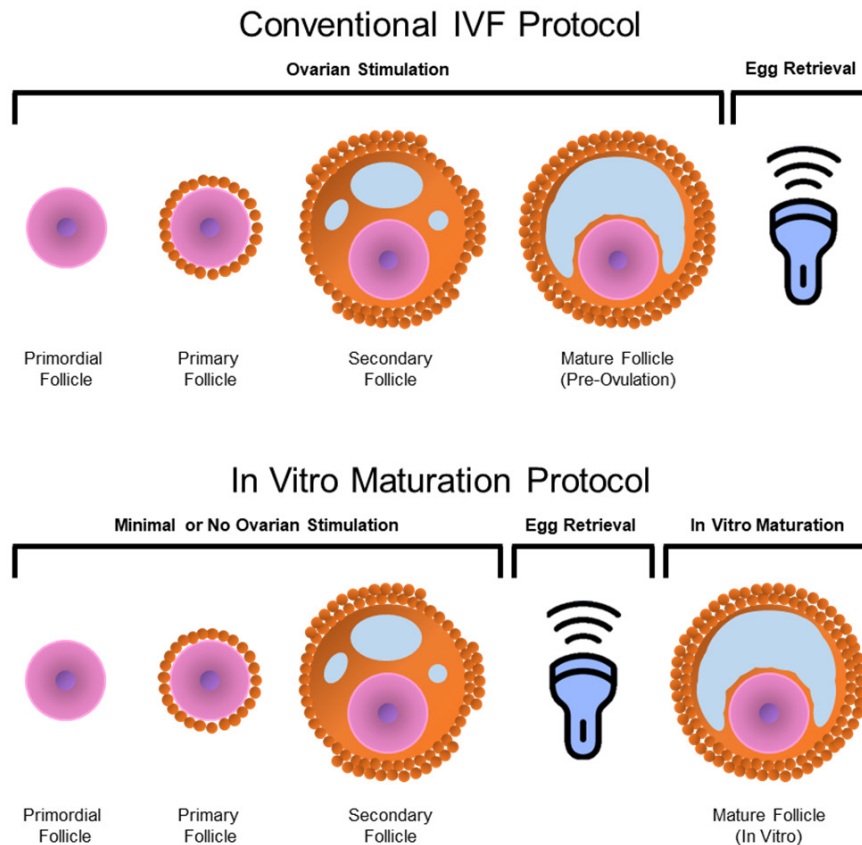


Figure 3. Comparison of conventional IVF and in vitro maturation protocols.

Differences between the protocols for C-IVF and IVM involves the use of hormonal therapy and when egg retrieval occurs. Hormonal therapy is used in C-IVF to stimulate follicle development in the ovaries. Once oocyte maturation is complete, the egg is removed using trans-vaginal ultrasound and aspiration. In IVM, there is minimal to no ovarian stimulation required as oocyte maturation occurs in vitro. Primary follicles develop into secondary follicles upon the development of an antrum formed from hyaluronic acid-rich follicular fluid and these secondary follicles are retrieved using trans-vaginal ultrasound and aspiration.

applied through administration of hCG. The second protocol involves the 1-time administration of 10 000 IU of hCG 36 to 38 hours prior to oocyte extraction. The time required for this protocol is reduced from 36 to 24 hours because oocytes may have already initiated meiotic resumption.²⁸ No development differences were observed between IVF and IVM protocols.

IVM Advantages

One of the most significant benefits of IVM is that it does not rely on managing and administering multiple doses of FSH. Instead, it administers little to no levels of FSH compared with what is seen in C-IVF. Low exogenous gonadotropin hormone levels decrease the risk for the development of OHSS.²⁹ Women with PCOS have a higher risk of developing OHSS, which results in higher rates of termination of IVF embryo transfer cycles.³⁰ However, IVM has helped pave the way as a novel alternative for patients with PCOS.

In a noninferiority randomized clinical trial comparing the outcomes of live birth between IVF and IVM in patients with high antral ovarian follicle counts, there was no statistically significant difference between the number of live births in IVF and IVM after a single cycle in both groups of patients with and without diagnosed PCOS.³¹ This study helped highlight that certain patient populations, such as those with PCOS and high antral follicle counts, now have an alternative in the type of ART they want to use that has been proven not to have an increased risk for developing OHSS, which puts their cycle at risk of termination.³⁰

Not only has IVM alone been studied and proven successful in lowering OHSS risk for patients with PCOS, it has also been studied in conjunction with other ARTs to improve on their efficacy. A prospective study done with 64 patients to improve the efficacy of IVF embryo transfer programs for patients with PCOS included IVM culture followed by IVF and embryo transfer or zygote intrafallopian tube transfer (ZIFT) or both. The study results showed that the combined embryo transfer approach of ZIFT with uterine embryo transfer resulted in the greatest pregnancy rate (37.5%) as opposed to either protocol alone (ZIFT: 0% or uterine embryo transfer: 20.5%).³⁰ This enables improvements to be made to IVM techniques based on patient conditions as well as other protocol combinations.

An additional consideration for IVM is the absence of developmental differences in outcomes between children born from IVM and C-IVF. In a follow-up study of a randomized clinical trial involving 546 women evenly split between IVM and C-IVF groups, it was shown that at 6, 12, and 24 months after birth, results from the Ages and Stages Questionnaire (which measures communication, gross and fine motor skills, problem-solving, and personal social skills) were statistically insignificant between the 2 groups. This longitudinal study helped to reinforce several other retrospective studies that have not found increased risks for children conceived from IVM.³²

Cost is another important factor to consider when choosing an ART. C-IVF uses much higher levels of gonadotropin and can become more costly than IVM. Therefore, IVM is more inclusive to couples from different levels of socioeconomic status.²⁹

IVM Limitations

IVM has been shown to have a greater chance of early miscarriage and decreased implantation efficiency.²⁸ There are many possible explanations contributing to this, including that the eggs retrieved may lack the full maturity required for successful fertilization and embryo development, the IVM process may not comprehensively replicate the natural environment and may be subject to suboptimal laboratory conditions, and eggs and embryos may experience alterations that affect development competence and viability. In a randomized clinical trial comparing C-IVF in women with infertility and

high antral follicle count, it was also found that ongoing pregnancy rates at both 6 and 12 months were lower in the IVM group compared with the C-IVF group. Patients with PCOS experienced implantation rates of 9.5% and 17.1%, pregnancy rates of 21.5% and 33.7%, and miscarriage rates of 25.33% and 15.7% for IVM and IVF, respectively. Live birth rates for IVM were determined to be 15.9% for IVM and 26.2% for IVF.²⁸ It also found that the number of high-quality embryos was higher for IVF than it was for IVM. Due to factors spanning from challenges for maturing eggs in vitro to patient self-selection, IVM has been seen to produce half the birth rates compared with IVF, and while not statistically significant, it is important to consider the lower numbers of successful pregnancies.³¹

Accessibility to fertility clinics that offer IVM is another hurdle to cross for families. The lack of a united front to share emerging knowledge and improvements of IVM in humans and other species from research laboratories is a major disadvantage of IVM.³³ This can be seen as a limiting factor in its advancements in the ART market.

Discussion

Improving access to infertility care has become an area of prominent importance as more options become available and advanced. Barriers to ART exist and limit the accessibility for couples to move forward with ART infertility treatment options. One of the most prominent barriers is the high estimated cost. In a cross-sectional survey study completed in 5 different gynecology clinics in Massachusetts, it was deemed that regardless of race, ethnicity, education level, and insurance status, the greatest self-reported barrier to ART was the total cost required. The same study reported that 85.7% of participants believed that access to infertility treatment is a right.³⁴

While a greater issue exists in the health care system to provide equitable access to treatment, costs continue to present challenges even for aspiring parents who may have an opportunity to leverage ART. For patients who have the resources to pursue ART, choosing a treatment plan can be a daunting task that must be delicately balanced against resource limitations, health considerations, and personal beliefs and family goals. It seems almost impossible at times to decide which plan to choose with so many different benefits, downsides, and opinions, especially for prospective parents unfamiliar with ART procedures and impacts. NC-IVF, MS-IVF, and IVM all present a unique set of benefits and challenges that patients should discuss and consider before making a treatment plan decision. [Figure 4](#) outlines the main advantages of each treatment option with the goal of providing a preliminary decision aid for patients. It is important to note that limited information is available on the postnatal outcomes of IVM due to the small pool of IVM children born, which is not enough to calculate absolute risk for specific health abnormalities.³³

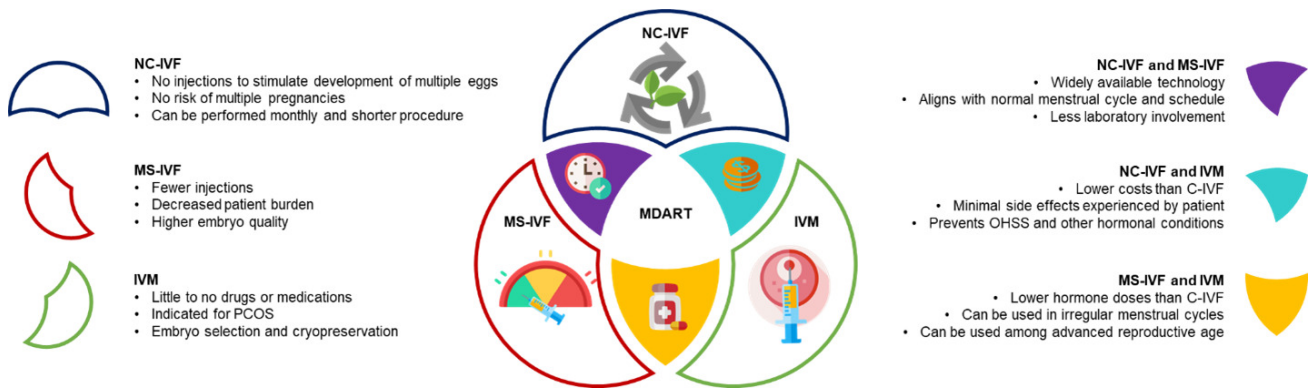


Figure 4. Common and distinguishing advantages across NC-IVF, MS-IVF, and IVM.

The three minimally disruptive strategies of NC-IVF, MS-IVF, and IVM were founded on C-IVF principles and techniques but deviate away from C-IVF to offer more flexibility to meet the patient's needs. While, NC-IVF, MS-IVF, and IVM differentiates themselves from C-IVF by being minimally disruptive to the female body, each technology has its own unique merits with existing overlaps between the technologies. These unique merits and overlaps allow for a multi-faceted patient-centric approach to selecting an MDART that best fits their unique needs and circumstances.

Leveraging the advantages and limitations of NC-IVF, MS-IVF, and IVM found in the scientific literature, we developed a patient-centric decision-making model called the MDART decision matrix to guide families on the minimally disruptive strategy that best aligns with their needs. Designed to prioritize the patient's values and demonstrate how it aligns with observed ART advantages and disadvantages, the MDART decision matrix concisely evaluates all 3 MDARTs to guide the patient in navigating their decision process while respecting patient priorities. The MDART decision matrix uses a simple Likert scale, with 1 representing disagreement, 2 representing neutrality, and 3 representing agreement while measuring the patient's threshold for several common factors related to the decision. These factors are risk tolerance, treatment impacts, medical history, MDART accessibility/availability, and the beliefs and preferences that may affect the patient decision-making process. These factors are categorized across 5 major categories common to the ART selection process and each protocol has been preassigned a decision weight (ie, MDART weight) across these considerations based on observations from scientific review. A weight rationale has been provided to substantiate the preassigned MDART weight. Collectively, these factors contribute to the MDART alignment score, which is represented mathematically by the **Equation** below:

$$\begin{aligned} & \text{MDART Alignment Score} \\ &= \frac{\sum_{i=1}^n (\text{Patient Priority}_i \times \text{MDART Weight}_i)}{\text{Maximum MDART Score}} \times 100 \end{aligned} \quad (1)$$

As shown in the **Equation**, patient priorities are used in conjunction with MDART weights to determine an MDART alignment score. A sample clinical scenario is provided below to demonstrate the application and utility of the MDART decision matrix:

A 38-year-old patient presents to your clinic seeking IVF services after 2 years without success of pregnancy with her husband. The patient's medical history includes irregular menstrual cycles with a confirmed PCOS diagnosis at 16 years of age. Her family history includes irregular menstrual cycles from both her mother and her maternal grandmother, with her grandmother dying of epithelial ovarian cancer at the age of 62 years. Patient intake reveals that she is looking to have a single child due to her career trajectory in management consulting but is worried about the financial impacts that come with pursuing IVF as an infertility treatment option. She expresses concern regarding the accrued costs associated with multiple cycles of IVF due to her past lack of success in becoming pregnant. The patient is also concerned about the potential adverse effects of ovarian stimulation therapy that may occur due to her medical and family history but is willing to compromise on her concerns if drug-induced therapy results in a greater probability of success. She has no religious beliefs that conflict with her decision to pursue IVF but is concerned about passing on congenital issues to her future child due to her medical history and age.

Based on this clinical scenario, [Figure 5](#) illustrates the potential MDART decision matrix results this patient may receive. Given her concerns for costs and desperation for success, factors under Accessibility and Availability as well as Risk Tolerance were marked with a high patient priority value. A single year increase in ovulations has also been associated with a 6% increased risk of developing epithelial ovarian cancer,³⁵ which may potentially put the patient at higher risk for developing a malignancy given her family history for epithelial ovarian cancer and the stimulatory effects on ovulation by IVF treatments. The patient's clinically significant medical history and family history resulted in most factors under Medical History being assigned a high patient priority value. This patient also wishes to address concerns regarding adverse effects but her desire to have a child outweighs these concerns, which earned a lower patient priority score under Impacts of Treatment. She also reports a lower patient priority for Beliefs and Preferences for not being limited by religious beliefs. Overall, this patient receives her highest MDART alignment score of 84.6% for IVM, with NC-IVF coming in second at 84.0% and MS-IVF coming in last at 75.4%. Therefore, this patient would opt for IVM as the treatment of choice due to its best alignment with her individual needs and requirements.

The MDART decision matrix is not intended to serve as a prescriptive recommendation for a patient in lieu of a thorough medical review and consultation. However, it helps simplify current literature into consumable education and guide the patient in better visualizing the tradeoff points

i	Description	Patient Priority	NC-IVF	MS-IVF	IVM	
		1 = Disagree, 2 = Neutral, 3 = Agree	Weight	Weight	Weight	Weight Rationale
1	Cost is an important factor. I must take affordability concerns into consideration.	3	3	1	3	Given that the patient does not need to pay for ovulation stimulation medication with NC-IVF and IVM, it is cheaper than other techniques such as MS-IVF.
2	It is important for the assisted reproductive technology to be available locally to me.	3	3	3	1	Not all fertility clinics offer IVM due to its specialized nature which limits the accessibility of the technology to patients and their families. There is also a lack of a united front in sharing emerging knowledge and improvements of IVM from research laboratories.
3	Time is critical – I am looking for the quickest option for a successful pregnancy.	3	1	1	3	MS-IVF and NC-IVF treatments follow the ovulation cycles of women. There is time involved with egg maturation and ovulation. IVM has a reduced timeline as extracted eggs are immature eggs. Maturation is completed in vitro and eggs may have already initiated meiotic resumption. However, IVM has lower success rates and therefore may require additional cycles which would increase time before successful pregnancy.
4	Cost coverage must exist in full or partial coverage within my current care plan.	3	1	1	1	Insurance coverage for IVF is dependent on the state. Some states have laws requiring insurers to cover some or all parts of treatment. However, not all patients are eligible for coverage. Please consult your state's coverage laws and your insurance provider to determine whether your insurance will cover treatment.
	Medical History	1 = Disagree, 2 = Neutral, 3 = Agree	Weight	Weight	Weight	
5	I have irregular menstrual cycles. I want to ensure a greater chance in a successful pregnancy given my condition.	3	2	1	3	Patients with irregular menstrual cycles would benefit most from IVM due to leveraging immature eggs taken from the small antral follicles in the ovaries. This decouples the process from the menstrual cycle and embryo maturation can now occur outside of the woman's body.
6	I am of advanced reproductive age. I want to ensure a greater chance in a successful pregnancy.	1	3	1	3	Studies have shown that NC-IVF and IVM are good alternatives for patients of advanced reproductive age due to elimination of ovarian side effects from stimulation.
7	I have gone through cycles of stimulated IVF in the past and I am considered as a poor responder to treatment.	3	2	1	3	For patients that do not respond well to ovarian stimulation medications, NC-IVF and IVM are the better options. Between NC-IVF and IVM, IVM may be a better option despite studies showing both as viable options for poor responder patients due to the fact that IVM can use immature eggs extracted from the mother.
8	I have a medical history of PCOS complications or other similar conditions.	3	2	1	3	In NC-IVF, there are no injections used to stimulate the development of multiple eggs. However, there is a large bolus injection of hCG to induce ovulation. This bolus is administered one day prior to egg extraction. In IVM, egg maturity is not a factor and does not require high doses of fertility drugs nor reproduction stimulatory drugs. While IVM has a protocol that uses follicular-phase FSH priming, there is also the spontaneous IVM protocol that does not stimulate the ovaries at all. Therefore, IVM gets the higher weight over NC-IVF.
9	I have immediate family members that currently has or have had cancer diagnoses.	3	3	1	3	Ovarian stimulation drugs may increase the number of ovulations per cycle and there may be an associated risk of ovarian cancer from a longer lifetime of ovulation ³⁵ . Therefore, this risk can be mitigated by treatments that minimize exposure to ovarian stimulation drugs: NC-IVF and IVM.
10	I have been found to be genetically predisposed to conditions such as cervical cancer or other similar conditions.	3	3	1	3	Ovarian stimulation drugs may increase the number of ovulations per cycle and there may be an associated risk of ovarian cancer from a longer lifetime of ovulation ³⁵ . Therefore, this risk can be mitigated by treatments that minimize exposure to ovarian stimulation drugs: NC-IVF and IVM.
	Risk Tolerance	1 = Disagree, 2 = Neutral, 3 = Agree	Weight	Weight	Weight	
11	The efficiency of the process is important. I'd like to reduce the treatment cycle times even if higher risk to quality of eggs is implied.	3	2	3	1	Additional cycles expose the patient to treatments for longer periods of time. This can lead to clinical complications and financial burden. MS-IVF uses minimal ovarian stimulation drugs to help increase chances of a successful pregnancy. Studies have also shown that IVM has the lowest success rate comparative to other IVF techniques.
12	Guarantee for success is critical to me. I need live birth rates above all else.	3	2	3	1	MS-IVF uses minimal ovarian stimulation drugs to help increase chances of a successful pregnancy. Studies have also shown that IVM has the lowest success rate comparative to other IVF techniques.
13	Improving the chance of success through investment in quality is important. I want to maximize quality and quantity of eggs retrieved.	3	1	3	1	MS-IVF uses minimal ovarian stimulation drugs to help increase chances of a successful pregnancy. NC-IVF and IVM do not rely on ovarian stimulation to increase the number of eggs.
	Impacts of Treatment	1 = Disagree, 2 = Neutral, 3 = Agree	Weight	Weight	Weight	
14	My personal health and safety is important. I prefer to minimize the amount of side effects.	2	2	1	3	MS-IVF uses minimal ovarian stimulation drugs and expose patients to hormones which can lead to complications. In NC-IVF and IVM, there are no injections used to stimulate the development of multiple eggs. However, there is a large bolus injection of hCG to induce ovulation. This bolus is administered one day prior to egg extraction. In IVM, egg maturity is not a factor and does not require high doses of fertility drugs nor reproduction stimulatory drugs. The spontaneous IVM protocol does not stimulate the ovaries at all, and therefore, IVM may be the best option for personal health and safety concerns.
15	I plan to grow my family. It's important that the process does not limit my future success in having more children.	1	3	1	3	The use of ovarian stimulation medication in MS-IVF may lead to ovarian hyperstimulation syndrome and other clinical complications. NC-IVF and IVM minimizes exposure to reproductive stimulation drugs.
16	I plan to grow my family. Maximizing the quality and number of eggs retrieved is essential so I can leverage them in the future.	1	1	3	2	MS-IVF leverages ovarian stimulation medication which can increase the number of eggs in development. NC-IVF does not use ovarian stimulation medication and results in one egg extraction at a time. IVM has access to more eggs than NC-IVF as it uses the immature eggs stored within the mother's body.
	Beliefs and Preferences	1 = Disagree, 2 = Neutral, 3 = Agree	Weight	Weight	Weight	
17	I want to respect certain constraints from my religious faith or belief system. The process should be as natural as possible.	1	3	2	1	NC-IVF, MS-IVF, and IVM require varying levels of clinical assistance and are ranked based on the degree of scientific intervention beyond the prospective mothers' natural biological processes for a natural conception.
18	It is critical to test and screen for genetic conditions diagnoses in the embryo prior to continuing with embryonic implantation.	2	3	1	3	Prenatal genetic screening presents ethical and religious challenges as testing results may lead to a difficult decision to abort a fetus. While all IVF and IVM treatments are able to utilize prenatal genetic screening, IVM and NC-IVF tests the one egg extracted per cycle while MS-IVF may result in more testing overall due to the increased number of eggs from ovarian stimulation.
MDART Alignment Score			84.0%	75.4%	84.6%	

Figure 5. Using the MDART Decision Matrix to identify a patient's preferred IVF strategy.

The MDART Decision Matrix uses patient priorities that have been measured on a Likert scale to evaluate the IVF strategies that best align with the patient's needs and address the patient's concerns.

via a chart. By providing prospective mothers and their families with a framework that enables them to prioritize factors as it pertains to their family planning and can be flexible to accommodate new scientific advancements, we empower patients to feel more comfortable in engaging in these decisions and enable physicians to facilitate better outcomes through patient collaboration. Given the intent of MDART as a patient education and choice tool, future improvements can be made based on patient feedback of its application and the tool's ability to meet decision needs.

Conflicts of Interest Statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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SUPPLEMENTARY MATERIALS

MDART Decision Matrix

Download: <https://gmr.scholasticahq.com/article/117697-review-of-minimally-disruptive-in-vitro-fertilization-ivf-approaches-as-a-strategy-for-assisted-human-conception/attachment/230526.xlsx>
