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REVIEWS

Human Oocyte Banking and In Vitro Maturation: Aging, Cancer, and Polycystic Ovary Syndrome

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Given the range of fertility issues, oocyte banking and in vitro maturation (IVM) are major advancements for fertility preservation. This literature review studies their applications in ovarian aging, polycystic ovary syndrome (PCOS), and cancer-related infertility.

Oocyte banking and IVM offer solutions for age-related infertility. By cryopreserving oocytes at a younger age, individuals can safeguard their reproductive potential as they age. Improvement of cryopreservation methods and personalized protocols, along with advancements in ancillary procedures like preimplantation genetic testing (PGT) enhance the efficacy of these strategies.

For PCOS patients, IVM offers a safer alternative to in vitro fertilization (IVF) by minimizing the risk of ovarian hyperstimulation syndrome (OHSS) through reduced ovarian stimulation. Advancements in IVM, such as hCG priming and capacitation IVM, have shown improved outcomes, making it a preferable option for PCOS patients seeking fertility preservation.

In cancer patients, cryopreservation before treatment is critical. While IVF with controlled ovarian stimulation (COS) is the standard, IVM provides a faster option for pediatric patients or those needing urgent treatment. Current research aims to expand IVM's uses across different cancers and patient populations.

As these technologies evolve, they provide new avenues for individuals facing infertility challenges, empowering them to continue pursuing their reproductive goals.

Introduction

According to the National Cancer Institute, oocyte banking is a method of fertility preservation in which unfertilized eggs are frozen to be reserved for future use. When the patient is ready to use their frozen eggs, the eggs are thawed and fertilized to make embryos, which are then implanted into the uterus.[1]

In vitro maturation (IVM) of oocytes is a method of oocyte banking that has historically been used for women with polycystic ovaries to prevent ovarian hyperstimulation syndrome (OHSS).[2] OHSS is a common complication of

ovarian stimulation with gonadotropins, specifically with in vitro fertilization (IVF).[3] In IVF, eggs nearing ovulation are removed from the uterus and fertilized in vitro before being implanted. Alternatively, in IVM, mature oocytes are removed from small antral follicles without the extensive hormone stimulation used in IVF, which can help prevent the OHSS seen in IVF.[4]

While IVF has long been the standard option for infertility, IVM rose in popularity during the 1990s when it was discovered that it poses almost no risk for OHSS. IVM has primarily been used for patients with polycystic ovary syndrome (PCOS), but it is also indicated for those who respond poorly to ovarian stimulation and for preservation of fertility caused due to age or disease.[2] Specific instances other than PCOS in which IVM may be used include fertility preservation in patients with cancer, diminished ovarian reserve, and resistant ovarian syndrome.[5] The goal of this review article is to discuss the specific applications and benefits of oocyte banking and IVM in relation to ovarian aging, PCOS, and cancer-related infertility.

Ovarian Aging and Infertility

In recent years, there has been a shift in reproductive patterns, with more women delaying having children.[6] While this trend reflects changing societal norms and increased opportunities for women in education and careers, it also poses significant challenges to fertility. Advanced maternal age is associated with declining quality and quantity of oocytes, leading to decreased fertility and an increase in pregnancy complications.[7] As women age, their oocytes are more susceptible to chromosomal abnormalities, disruptions in meiotic spindle formation, and hardening of the zona pellucida—all of which significantly impact reproductive outcomes.[8]

The decline in fertility with advancing age is well-documented, with spontaneous cumulative pregnancy rates beginning to decline in women aged 31 to 35 years.[9] Around the age of 35 to 39 years, about one-third of women experience difficulties with conception, and by the time they reach 40 to 44 years old, half of all women experience diminished reproductive capacity.[9] These statistics demonstrate the urgent need for effective strategies to address the challenges of fertility preservation in aging oocytes.

Recognizing the impact of ovarian aging on fertility, many people are turning to fertility preservation techniques to enhance their chances of achieving pregnancy in later stages of life. Oocyte banking, also known as *egg freezing*, has emerged as an effective way to preserve fertility in women facing ovarian aging. Oocyte banking involves the retrieval and cryopreservation of oocytes at a younger age, when they are of higher quality and abundance, for future use in assisted reproductive technologies such as IVF and IVM.[10]

Optimization of cryopreservation methods is essential to enhancing the efficacy of oocyte preservation and ensuring the long-term viability of cryopreserved oocytes. Different cryopreservation techniques, such as slow freezing and vitrification, have been developed to improve the survival and integrity of cryopreserved oocytes.[10] Vitrification, in particular, has emerged as the best method of preservation due to its ability to minimize ice crystal formation and preserve oocyte integrity.[11] Despite the high toxicity associated with vitrification, due to the high-concentration cryoprotective agents used, it has demonstrated superior preservation rates of ovarian tissue structural integrity compared with slow freezing. Immunohistochemistry analysis also revealed a higher expression of mouse vasa homolog, a marker of germ stem cells, in ovaries subjected to vitrification compared with slow freezing, demonstrating the increased viability of vitrified eggs compared with slow frozen eggs.[11]

Additionally, the cryoprotective agent used for oocyte banking also plays a role in prolonging the viability of the preserved oocytes and the structural integrity of ovarian tissue. Of the popularly used cryoprotectants (glycerol, dimethyl sulfoxide, ethylene glycol, and propylene glycol), the number of antral follicles was significantly higher in ovaries vitrified using ethylene glycol, possibly due to lower embryonic cell toxicity and higher cell membrane permeability of ethylene glycol.[11] Overall, vitrification using ethylene glycol appears to be associated with greater recovery of potentially viable primordial follicles. To maximize chances of pregnancy in regard to oocyte banking, it is also recommended that the oocyte collection occur before the age of 30 years, because the number of oocytes retrieved was highest among women younger than 30 years.[9] By optimizing cryopreservation methods, health care professionals can ensure the preservation of high-quality oocytes for future use, thereby enhancing the reproductive options of individuals facing ovarian aging.

In addition to oocyte banking, IVM techniques offer another path for preserving fertility in aging oocytes. IVM involves maturation of immature oocytes retrieved from unstimulated or minimally stimulated ovaries in the laboratory, followed by fertilization and embryo transfer.[12] Many techniques have been developed to enhance IVM, ensuring the maturation of high-quality oocytes that are able to undergo fertilization and implantation. One key aspect of optimizing IVM is the selection of appropriate culture media and supplements. Research has shown that specific culture media compositions supplemented with growth factors and hormones—such as follicle-stimulating hormone and epidermal growth factor—can significantly improve oocyte maturation rates.[12] This is because follicle-stimulating hormone and epidermal growth factor media mimic the natural ovarian environment, providing the signals needed for oocyte development and maturation.

Furthermore, integrating ancillary procedures, such as preimplantation genetic testing (PGT), into fertility preservation protocols can enhance the selection of high-quality embryos for transfer, increasing the likelihood of successful pregnancies in older women.[13] PGT allows for the identification of chromosomal abnormalities and genetic disorders, enabling the prioritization of genetically normal embryos for transfer. However, it is important to acknowledge that PGT, including techniques such as fluorescence in situ hybridization, has significant drawbacks. Fluorescence in situ hybridization requires cell fixation and can be challenging to use for accurately classifying cells as abnormal, which may impact the effectiveness of the testing.[14] Additionally, advancements in IVM technology, such as the utilization of microfluidic systems and 3-dimensional culture platforms, hold promise for further improving the efficiency of oocyte maturation.[13,14] These innovative techniques provide precise control over the microenvironment surrounding the oocytes, allowing optimal conditions for maturation.

The challenges of ovarian aging showcase the need for effective strategies in fertility preservation in aging oocytes. Oocyte banking and IVM techniques offer promising avenues for fertility preservation, with optimization of cryopreservation methods and personalized approaches enhancing the efficacy of these strategies. By leveraging advancements in assisted reproductive technologies and ancillary procedures, health care professionals can offer tailored solutions for preserving fertility and meeting the reproductive goals of their patients concerned with ovarian aging.

However, it is also essential to delve into the applications of IVM and oocyte banking for special circumstances of infertility, such as those with PCOS or cancer. These populations face unique challenges regarding fertility preservation and reproductive health, necessitating tailored approaches to maximize the chances of successful outcomes.

Polycystic Ovary Syndrome

PCOS is a chronic, incurable endocrine disorder that impacts 8% to 13% of reproductive-age women.[15] This condition is often associated with insulin resistance, hyperandrogenism, β-cell dysfunction, and obesity.[16] There are 4 types of PCOS: insulin resistance, androgen, inflammatory, and post-pill. Insulin resistance PCOS occurs when the body is able to produce insulin but is unable to use it. These patients often have a higher risk of type 2 diabetes and experience symptoms such as high blood sugar levels, weight gain, and darkening of the skin. Androgen PCOS occurs when the ovaries produce excess androgens (male sex hormones), which interferes with ovulation. These patients usually have normal testosterone levels but high amounts of dehydroepiandrosterone. Therefore, they experience symptoms such as irregular menstruation, acne, and hirsutism. Inflammatory PCOS is characterized by chronic inflammation of the ovaries that lead to excess testosterone production. Patients consequently encounter issues with weight

gain, skin rashes, joint pain, acne, and unexplained fatigue. Last, post-pill PCOS happens when an individual has normal periods prior to taking hormonal birth control but later experiences symptoms when stopping it. Unlike the other subtypes, this is usually a temporary condition and irregular periods generally stop 6 to 12 months after stopping contraceptives. The exact cause of these forms of PCOS is unknown, but researchers believe that it is due to a combination of environmental, genetic, and lifestyle factors.[17] In any case, lack of adequate treatment can lead to progression of symptoms and long-term complications such as infertility.

In fact, more than 80% of individuals who have anovulatory infertility—a condition ih which ovaries fail to release an egg during the menstrual cycle—have PCOS.[15] Moreover, the oocytes produced by women with PCOS are often of lower quality. This leads to lower fertility rates, lower embryo quality, and lower implantation rates compared with women without PCOS. The hormonal imbalances associated with this condition also contribute to higher rates of miscarriages, so the average overall live birth rate after a woman with PCOS becomes pregnant is around 37%, even after involving different hormonal interventions and assisted reproduction techniques.[18] Therefore, not only is it difficult for a woman with PCOS to get pregnant, but it is also a challenge to carry the fetus to term.

Given this uncertainty, some women with PCOS opt for oocyte banking at a younger age to optimize their chances of having a child in the future. Although egg freezing does not alleviate PCOS-related symptoms, eggs frozen at a younger age are often of higher quality and quantity so it can provide options for future family planning. For women who opt out of oocyte banking, there is generally a 3-step treatment plan recommended by physicians for infertility.[15,16,19] The first pertains to lifestyle modifications because factors such as smoking habits and weight negatively contribute to anovulation. Second-line treatment is laparoscopic ovarian drilling or ovarian induction with gonadotropin. This involves the use of lasers to remove ovarian cysts and drugs such as clomiphene citrate and letrozole to induce ovulation. If more conventional fertility methods did not work, the status quo for third-line therapy is IVF.

Although it has an appreciable success rate (49.3% live birth rate), IVF in women with PCOS can lead to OHSS, a condition characterized by having ascites with severe abdominal pain and blood loss.[20] In fact, the risk of getting OHSS is 3% to 8% higher in women with PCOS who undergo IVF than women without PCOS.[16] OHSS can lead to significant complications. Some of these include blood hypercoagulability, intravascular blood loss, severe cardiopulmonary dysfunction, life-threatening thrombosis, hypovolemic shock, electrolyte imbalance, and impaired kidney and liver function.

Given the risk associated with IVF, IVM emerged as an alternative third-line option in 1990. IVM involves harvesting oocytes from antral follicles from unstimulated or minimally stimulated ovaries.[16] Oocytes are retrieved in metaphase I and they are matured in vitro until they reach metaphase II. These mature oocytes are then fertilized before being implanted into the mother. The primary difference between IVF and IVM is that IVM is performed "without" ovarian stimulation before egg retrieval. *Without* is in quotes because the literature disagrees on what level of ovarian stimulation yields the best results for IVM.[16,19] Regardless, IVM prevents the occurrence of OHSS, which remarkably reduces complications and cost. Because initial studies have shown significantly lower birth rates in IVM than IVF, more recent ones have focused on human chorionic gonadotropin (hCG) priming and adding periods of minimal ovarian stimulation. This has significantly improved oocyte competence and live birth rates, while still eliminating OHSS.[19]

For example, in a study involving 159 IVM cycles, 2064 oocytes were collected after hCG priming.[19] In these oocytes, the maturation rate was 49%, the total fertilization rate was 38.9%, and 235 total embryos were transferred into 159 patients (no cryopreservation).[19] The clinical pregnancy rate was therefore 44.7%, the live birth rate was 34.6%, and no OHSS cases were detected. The study also found a negative correlation between infertility duration and chance of live birth; a 1-year increase in duration correlated with a 10% decrease in chance.[19] It also found a positive correlation between the number of oocytes retrieved and live birth rates. Although the study was retrospective, the researchers found that infertility duration, oocyte number, and embryo cell number were the greatest predictors of live births in women with PCOS who underwent IVM. This statement agrees with many other studies that additionally reported that race had no effect on IVM.

Another multicenter retrospective study involving 374 women (368 with successful embryo transfers, 98.4%) assessed live birth rates in women with PCOS or high antral follicle count who underwent IVM with a prematuration step, known as *capacitation IVM*.[21] This involved the use of a C-type natriuretic peptide to inhibit meiosis in the prematuration process in order to prevent spontaneous resumption of meiosis during IVM. This method resulted in a 31% live birth rate after embryo transfer.[21] Amphiregulin, a growth factor, was then added to the second phase of the protocol to improve oocyte maturation. The combination of these methods allowed for synchronized cytoplasmic and nuclear maturation of oocytes. This change resulted in an oocyte maturation rate of 63.2%, cumulative pregnancy rate of 60.4%, and ongoing pregnancy rate of 43.6%.[21] No OHSS cases were recorded and the 24-month cumulative live birth rate for capacitation IVM was 38.5%.

Although IVM is associated with a lower number of available mature oocytes, fertilization rates, embryo formation rates, and live birth rates (30%-39%) compared with IVF (49.3% live birth rate), it is still the most advantageous assisted reproduction method for women with PCOS because it uses lower amounts of gonadotropin for ovarian stimulation, uses minimal ovarian stimulation, eliminates OHSS risk, involves lower cost, and does not involve physiological levels of gonadal steroids.[19,20] In fact, patients with PCOS are arguably the most ideal candidates for IVM because of the systemic concerns regarding OHSS and patient safety. Therefore, this technique should become the preferred third-line therapy, a trend that is slowly being observed across the US. That being said, it is imperative that research still be done on how best to alter the IVM protocol to achieve the highest live birth rates possible. Many patients take the additional risk of IVF because their desire to have a child is above all else, regardless of the consequences. If the success rate of IVM equals or surpasses that of IVF, a shift in the status quo will be seen on a systemic level as more patients elect for and more physicians recommend IVM. Until then, it is best to be reminded that the most successful protocol modifications to date have involved hCG priming and a short period of minimal ovarian stimulation.

Cancer-Related Infertility

Cancer treatments, such as chemotherapy and radiation, often impair fertility, leading many patients to consider fertility preservation before starting treatment. A common method is IVF with controlled ovarian stimulation (COS), wherein the ovaries are stimulated to produce mature eggs for extraction. However, this method may not be suitable for all patients, particularly those with contraindications to ovarian stimulation, such as patients with hormone-sensitive cancers, as well as those who are prepubertal or require immediate cancer treatment. For these individuals, IVM of oocytes followed by their banking presents a viable alternative.

One consideration is the effectiveness of IVM compared with IVF with COS. A previous study showed that while the maturation rate was significantly higher in IVF with COS cycles compared with IVM cycles, the fertilization rate between the 2 was not significantly different, suggesting that while more oocytes mature in stimulated cycles, it does not necessarily translate to higher fertilization success.[22] In addition, while oocyte morphology was generally better in the stimulated cycles—suggesting a higher quality of oocytes due to stimulation—there were no significant differences in the spindle visualization or zona pellucida birefringence score between the 2 groups, indicating similar oocyte structural integrity in both IVF with COS and IVM cycles. It is important to note that the results of this study focus on fertilization rate, which does not necessarily equate to the rate of healthy live births. Another study showed that IVF with COS resulted in live births for 5 of 15 patients with cancer (33%), while IVM resulted in live births for 3 of 25 patients with

cancer (12%).[23] These preliminary findings suggest that IVF with COS may be more effective in producing live births compared with IVM. However, this study was small, and future studies with larger sample sizes are warranted.

Researchers have suggested that an important use of IVM is in patients who require urgent cancer treatments and do not have time for the COS protocol.[24] In contrast, one study found that COS for oocyte vitrification should not postpone the start of neoadjuvant chemotherapy (ie, chemotherapy conducted before moving onto other treatments such as surgery) for patients with breast cancer compared with IVM.[25] The authors suggested that neoadjuvant chemotherapy should not be considered a barrier to urgent COS for fertility preservation in patients with breast cancer.[25] Based on these perspectives, the debate seems to center on balancing the urgency of starting cancer treatment with the effectiveness and timing of fertility preservation techniques. While IVM offers a faster route to preserving fertility, COS might provide better outcomes in terms of oocyte maturation and chances of live birth.

Another key consideration for patients with cancer considering IVM is the quality of ovarian reserve because quality is a critical factor in the success of fertility preservation methods. A previous study showed that there was no significant difference in ovarian reserve or response to ovarian stimulation between *BRCA* gene carriers, regardless of their cancer status, and noncarriers.[26] These data suggest that the presence of *BRCA* mutations alone does not adversely affect the ovarian reserve, providing reassurance to carriers about their potential responses to fertility treatments. In patients who have already undergone chemotherapy, IVM for fertility preservation is still a viable option. A study showed that while chemotherapy may reduce the number of retrievable oocytes, it does not affect the maturation ability of the ones that can be retrieved.[27] The study also found that a patient's age, rather than chemotherapy exposure, was a more important factor for influencing the success of IVM, with younger, premenarche patients showing worse outcomes than middle-aged patients.[27] These findings further highlight the importance of considering individual patient characteristics when planning fertility preservation strategies.

Nevertheless, several types of cancer and their treatments, particularly those involving the pelvic organs or those requiring very aggressive chemotherapy or radiotherapy, have been shown to significantly impact ovarian function in some cases.[28] While our literature review found many articles detailing the quality of ovarian reserve in patients with cancer, the response to IVM in different types of cancers are lacking in existing literature, representing a notable gap in the field. This gap in knowledge limits the ability to provide accurate counseling and tailored treatment plans for many patients with cancer. Understanding how various cancers impact the effectiveness of IVM could lead to more personalized and effective fertility preservation strategies.

In patients with pediatric cancer, IVF with COS is not an option because the injection of hormones is contraindicated in this age group. An alternative for preserving fertility is the cryopreservation of ovarian cortical tissue, which can later be reimplanted through autotransplantation. However, this approach carries the risk of reintroducing malignant cells into the patient. IVM of oocytes presents a safer alternative for these patients. Research supports the viability of a dual strategy involving the cryopreservation of both IVM oocytes and ovarian tissue, potentially broadening the spectrum of fertility preservation options available to these pediatric patients.[29] Another study also underscored the benefits of combining the following techniques: (1) ovarian tissue cryopreservation, (2) oocyte retrieval from ovarian tissue, and (3) oocyte aspiration followed by IVM. They found that this combination technique resulted in a significantly higher yield of oocytes, more metaphase II oocytes, improved maturation rates, and an increased number of cryopreserved oocytes.[30] This multifaceted approach seems particularly promising because it maximizes the chances of future fertility while also minimizing risks.

IVM of oocytes represents an emerging alternative for fertility preservation among patient with cancer, particularly for those who face limitations with traditional IVF and COS due to contraindications, urgent treatment needs, or pediatric status. However, the effectiveness of IVM in terms of live birth outcomes and its suitability across various cancer types and patient demographics still requires more robust research. Advancing this research is crucial to improve and expand fertility preservation options for patients with cancer.

Conclusions

The various uses of IVM represent large-scale advances in the field of assisted reproductive technologies and offer hope to patients facing fertility-related challenges. In this review, we discussed the range of functions offered by IVM in several different clinical contexts, including ovarian aging–related infertility, PCOS, and cancer.

IVM has been promising for ovarian aging and age-related infertility. Through the use of oocyte cryopreservation at a young age, individuals can potentially protect their reproductive capabilities from the inevitable decline in fertility that comes with age. Developments in IVM and ancillary procedures, such as PGT, have further enhanced IVM outcomes, thus offering better solutions for individuals facing ovarian aging.

For patients with PCOS, the hormonal imbalances that correspond with the disease often lead to infertility. IVM serves as a promising alternative to IVF by preventing the development of OHSS for patients with PCOS by minimizing ovarian stimulation. As a result of this, IVM offers a safer and more cost-effective option for fertility preservation for patients with PCOS.

Although initial studies showed lower rates of live births compared with IVF, new advancements in IVM, such as hCG priming and capacitation IVM, have demonstrated improvements in outcomes, thus making IVM a better choice for patients with PCOS.

Focusing on fertility preservation for patients with cancer before beginning treatment is important given the impact that cancer therapies can have on reproductive functions. Although IVF with COS is still the best option for most patients with cancer, its efficacy is limited for pediatric patients and those requiring urgent treatment. In these cases, IVM provides faster fertility preservation, albeit with lower birth rates in comparison with IVF. As discussed above, future research within this field aims to improve IVM techniques and expand its range of applications across different cancer types and patient populations. This trajectory strives to make biological parenthood possible for a wider patient population regardless of prior medical issues such as cancer treatment or PCOS. Some challenges to furthering this field of study include overcoming societal and legal hurdles including the ever-changing legislation surrounding IVF and its morality.

In conclusion, the diverse uses and potential of IVM and oocyte banking in addressing a variety of infertility issues emphasize their importance in modern reproductive medicine. As these technologies continue to improve, they offer new opportunities for individuals hoping to realize their reproductive goals despite many differing obstacles. By embracing both innovation and personalized care, health care professionals can also empower individuals to navigate their fertility preservation journeys with confidence and optimism through IVM.

Conflict of Interest

None reported.

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