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FERTILITY PRESERVATION: ADVANCES IN CRYOBIOLOGY, REGENERATIVE, AND NANOMEDICINE STRATEGIES – AN OVERVIEW

RUNNING TITLE:

EMERGING TRENDS IN FERTILITY PRESERVATION

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Abstract

The need to preserve fertility has now become a fundamental part of reproductive medicine due to the developments of cryobiology, regenerative medicine, nanomedicine and new biotechnologies. Optimised cryopreservation protocols can improve the viability and preservation properties of gametes and gonadal tissues, and nanotechnology can be used to target the delivery of protective factors and provide real-time monitoring of the reproductive organs. Decellularised scaffolds, 3D bioprinting, and stem cell therapy are regenerative techniques that offer biomimetic platforms that aid in vitro folliculogenesis, spermatogenesis, and tissue regeneration. New biotechnological methods, including CRISPR-based gene editing and in vitro gametogenesis, have the potential to fix genetic infertility and increase the resilience of the germline, but ethical, legal, and societal issues are of high concern. Artificial intelligence and machine learning also maximise fertility by foretelling gamete and embryo quality, personalised treatment direction, and better assisted reproductive technology success rates. The pediatric, adolescent, and transgender populations demand particular attention, and their strategies should consider the development stage, hormone treatment, and specific clinical requirements. Future studies must focus on the following: longitudinal studies, standardisation of technology, translational pathways so as to ensure safety, reproducibility and fair access. The combination of these multidisciplinary innovations alongside patient-centred and ethically-driven solutions can be used to redefine the concept of fertility preservation through the provision of safe, effective, and personalised solutions to individuals at risk of reproductive compromise.

Introduction:

Preservation of fertility has become a dominant discipline in reproductive medicine, where it offers remedies to patients who are in danger of infertility because of medical therapies, genetic susceptibility or old age. Infertility or pregnancy failure is known to affect about 48 million couples worldwide, and hence, there is an increasing clinical need. It is especially required in young patients under treatment with gonadotoxic therapies, including chemotherapy or radiotherapy, which often cause irreversible sterility by destroying the reproductive organs (Antonouli et al., 2023; Rodriguez-Wallberg et al., 2021). The progress in assisted reproductive technologies, with a particular focus on

cryopreservation of gametes and gonadal tissues, has widened reproductive options and spurred new research in cryobiology, regenerative medicine, and nanomedicine, which offer new ways to address infertility. In addition to biological consequences, infertility has great psychological and social impacts, and so, elaborate, patient-based conservation initiatives are very critical (Ataman et al., 2022, Chen et al., 2023)

The availability of superior treatment and a higher survival rate of cancer due to early diagnosis and better treatment methods has increased the focus on the quality of life after treatment, and fertility is one of its components. Systemic cancer treatment and radiation usually introduce gonadotoxicity, which contributes to permanent infertility or premature ovarian failure (Rodriguez-Wallberg et al., 2021; Chibelean et al., 2020). Multidisciplinary care also involves more and more fertility preservation discussions before starting therapy, which reduces the reproductive and psychosocial difficulties. It is estimated that about 5% of cancer survivors are below 40 years of age, which highlights the importance of quick interventions. In addition to the oncology contexts, autoimmune diseases, metabolic disorders, surgical operations, and the development of maternal age require strong fertility preservation plans (Santaballa et al., 2022). Although mature oocyte and embryo cryopreservation is common, there are some clinical conditions where this technique cannot be applied; preparing the patients before puberty or when the patients have an urgent need for treatment, thus, alternative methods of ovarian tissue cryopreservation may be used. Regardless of the advancements in technology, problems are still present. The approaches to cryopreservation that have been in use might not apply to all groups of patients, and the new approaches are unstandardised. Cryopreservation of ovarian tissues is associated with the risks of malignant cell reintroduction in haematological cancer or ovarian metastases, and the outcome is determined by the quality of the frozen tissue and reimplantation effectiveness (Lee et al., 2021; Hu et al., 2023). There are also ethical factors, storage over a long period, price, and fair access that complicate the widespread adoption (Vialle et al., 2025). Age, pubertal status, underlying condition, and emotional stress affect clinical decisions, as they require clear guidance for healthcare providers. The revision presents developments in the field of cryobiology, regenerative medicine, and nanomedicine for the preservation of fertility, focusing on the new tools and strategies to enhance the results, affordability, and reproductive autonomy.

Cryobiology-Based Fertility Preservation:

Oocyte Cryopreservation:

Oocyte cryopreservation, particularly via vitrification, is a well-established method for preserving female reproductive potential. Unlike slow-freezing, which risks ice crystal formation and osmotic damage, vitrification employs ultra-rapid cooling to solidify oocytes without ice crystal formation, markedly improving post-thaw survival and developmental competence (Pai et al., 2021). Clinical outcomes demonstrate fertilisation, implantation, and live birth rates comparable to fresh oocytes, establishing vitrification as a standard, non-experimental procedure (Pawłowski et al., 2023). For patients unable to undergo ovarian stimulation, such as prepubertal girls or those requiring immediate cancer therapy, ovarian tissue cryopreservation provides a crucial alternative. Transplantation of cryopreserved ovarian tissue can restore both fertility and endocrine function, with live birth rates reported up to 33% and spontaneous conception rates around 21% (Fraison et al., 2023). Ongoing research focuses on optimising

cryoprotectant formulations, exposure times, and vitrification protocols to enhance oocyte survival, particularly from compromised ovarian environments (Jones et al., 2020; Smitz et al., 2010).

Sperm Cryopreservation:

Sperm cryopreservation, widely employed in male cancer patients, individuals undergoing vasectomy, or those with declining sperm quality, typically utilises slow freezing or rapid freezing techniques. Vitrification is emerging as a promising method, yielding higher post-thaw motility and functionality (Chen et al., 2022). Cryopreservation effectiveness depends on factors such as cryoprotectant selection, freezing/thawing rates, and protocol optimisation to minimise oxidative stress and DNA damage (Hughes et al., 2022). Despite advances, only approximately 50% of spermatozoa retain viability post-thaw, highlighting the need for improved cryoprotective strategies and novel approaches to reduce cryoinjury (Sharafi et al., 2022).

Embryo Cryopreservation:

Vitrification of embryos has become an essential part of assisted reproductive technologies, and slow-freeze methods have been substituted by vitrification because it is more effective at avoiding the formation of ice crystals and increasing the survival of frozen embryos. Vitrified embryos have similar implantation and live birth rates to fresh embryos and make it possible to transfer electively single embryo electively and minimise multiple gestation risks. The use of the freeze-all approach also maximises the results as it prevents the emergence of supraphysiological hormonal conditions during ovarian stimulation and prevents ovarian hyperstimulation syndrome (Nagy et al., 2020). Recent reports have shown that human cleavage stage embryo vitrification is currently being used in ART laboratories, and post-thaw survival and implantation rates are equivalent to fresh embryos. Continued research is trying to streamline carrier systems, warming, and closed vitrification in order to reduce the risk of cryo-damage and contamination, and long-term follow-up evaluates the risk of epigenetic and developmental effects (Gualtieri et al., 2021; Roelens et al., 2025).

Ovarian and Testicular Tissue Cryopreservation:

Cryopreservation of gonadal tissues offers fertility preservation systems to prepubertal patients and patients who are not able to generate mature gametes. Ovarian follicles, which consist of primordial follicles, are normally frozen by slow freezing or by vitrification to retain the endocrine functionality and reproductive capability (Sharafi et al., 2022). Among the major issues are ischemic injury to the graft, loss of follicles and the possibility of reintroduction of malignant cells. Innovations are centred on crystallised cryoprotectant formulations, perfusion method and elimination of cancer cells before transplantation. Cryopreservation of testicular tissues is aimed at spermatogonial stem cells (SSC) in prepubertal boys; however, clinical translation remains experimental because of difficulties in transplantation of SSC and their differentiation into mature sperm. In vitro spermatogenesis provides a solution in the future because mature sperm can be obtained by means of cryopreserved tissue, although challenges that need to be overcome, such as meiotic competence and genetic integrity, must be solved first before clinical implementation is possible (Practice Committees of the American Society for Reproductive Medicine, 2020; Hosseini et al., 2014).

Cryoprotectants and Tissue Engineering:

Recent developments are directed towards improving post-thaw viability by using new

cryoprotectants, including synthetic ice blockers and osmolytes, which reduce the formation of ice and osmotic pressure (Huang et al., 2025). The survival and functionality of the cell is aided by tissue engineering methods: biomimetic scaffolds and bioreactors, which enable structural and metabolic integrity following the cryopreservation of cells. In vitro maturation of follicles can be induced in bioengineered ovarian microenvironments, and the decellularised scaffolds can offer regenerative platforms to ovarian graft reconstruction, enhancing engraftment and minimising immunogenicity (Taylan et al., 2018). The combination of innovative cryoprotectant techniques with the fundamentals of tissue engineering will be highly determinant in maintaining complex multicellular assemblies as well as long-term physiological recovery. Table 1 represents the summary of fertility preservation strategies.

Table 1: List of Fertility Preservation Strategies

Strategy	Target	Method / Approach	Advantages	Limitations / Challenges	Clinical / Research Status	References
Oocyte Cryopreservation	Female gametes	Vitrification / slow freezing	Established, high survival & pregnancy rates	Limited for prepubertal girls; requires ovarian stimulation	Widely used clinically	Antonouli et al., 2023
Sperm Cryopreservation	Male gametes	Freezing with cryoprotectants	Simple, non-invasive, long-term storage	Quality decline post-thaw; limited in azoospermia	Standard clinical practice	Abtahi et al., 2023
Embryo Cryopreservation	Fertilized embryos	Vitrification	High survival and pregnancy success	Ethical concerns: requires fertilisation before freezing	Routine clinical use	Antonouli et al., 2023
Ovarian / Testicular Tissue Cryopreservation	Gonadal tissue	Slow freezing/ vitrification	Option for prepubertal patients; fertility restoration	Experimental in males; tissue reimplantation risks	Experimental/clinical trials	Abtahi et al., 2023
Stem Cell-Based Regeneration	Ovary, testes	MSCs, iPSCs, SSCs	Potential to restore gametogenesis	Safety, tumorigenicity, and ethical concerns	Preclinical/early clinical studies	Antonouli et al., 2023; Abtahi et al., 2023
Artificial Ovaries and Folliculogenesis	Ovarian follicles	3D scaffolds, in vitro follicle maturation	Avoids reintroducing malignant cells	Complex culture systems; limited success	Preclinical / early translational	(Abtahi et al., 2023
Uterine Transplantation	Uterus	Surgical transplantation/tissue engineering	Can restore fertility in uterine factor infertility	Immunosuppression, surgical risk	Clinical (select centres)	Nair et al., 2024;

						Brownell et al., 2022
Mitochondrial Transfer	Oocytes	Cytoplasmic/mitochondrial injection	Improve oocyte quality	Ethical concerns, limited evidence	Experimental / research	Morimoto et al., 2023
Nanoparticles for Drug Delivery	Gonads	Targeted delivery of gonadoprotective agents	Reduce toxicity, enhance efficacy	Safety, biodistribution, regulatory hurdles	Preclinical / early translational	Girase et al., 2023
Nanomaterials & Scaffolds	Ovarian/testicular tissue	3D hydrogels, biomimetic scaffolds	Tissue support, enhanced follicle survival	Biocompatibility, standardisation	Preclinical studies	Nair et al., 2024; Quan et al., 2020
Nanosensors & Imaging	Ovarian function/oocytes	Biosensors, nano-imaging	Real-time monitoring, early detection	Technical complexity, cost	Experimental	Shea et al., 2014

Regenerative Medicine Approaches:

Stem Cell-Based Therapies:

Stem cell therapies hold revolutionary promise in fertility preservation, regenerative capabilities of damaged reproductive tissues and the production of gametes using pluripotent stem cells. Induced pluripotent stem cells (iPSCs) can differentiate to functional germ cells, whereas mesenchymal stem cells (MSCs) aid in ovarian repair and folliculogenesis (Wu et al., 2023). Autologous stem cell treatment modalities minimise the chances of immune rejection and permit personalised therapy. The ovarian stromal cell and follicle-like scaffolds decellularised and recellularized with decellularised ovarian scaffolds yield functional bioengineered ovaries with up to 70 to 80 per cent of hormone release and follicle viability following transplantation, with few risks of transmitting malignancy to the patient (Alshaikh et al., 2020). Regeneration of testes with spermatogonial stem cells is being researched, and preclinical trials have involved partial restoration of spermatogenesis in experimental animals using spermatogonial stem cells, with male infertility being one area the conventional cryopreservation has not been successful (Parte et al., 2013).

Artificial Ovaries and *In Vitro* Folliculogenesis:

The synthetic ovaries use the isolation of ovarian follicles and their culture in supporting scaffolds to revive fertility without introducing malignant cells. These systems stimulate primordial follicles, and research demonstrates that follicles survive and produce follicle support hormones, which provide therapeutic agents in premature ovarian insufficiency or ovarian reserve (Yoshimatsu et al., 2022). The development of bioengineered three-dimensional models of the ovary, such as artificial ovaries and ovarian organoids, is becoming useful in the field of studying ovarian physiology and pathology, thus providing solid platforms in the management and reproduction of the female body (Del Valle et al., 2023). Decellularised extracellular matrix (dECM) scaffolds maintain the original ovarian structure, promoting follicular growth and vascularisation, but there is a limitation in 3D bioprinting usage (Hassanpour et al., 2018).

Uterine Transplantation and Regenerative Strategies:

Uterine transplantation is a treatment for absolute infertility of the uterine factor, but it is invasive and involves lifelong immunosuppression. Plausible solutions to recreating functional uteri or endometrial tissues with lesser risk include regenerative approaches, such as tissue engineering, 3D bioprinting and organ-on-a-chip models (Brownell et al., 2022; Deng et al., 2024). Moreover, the complex microenvironment of endometrium-on-a-chip models can precisely replicate the microenvironment of the endometrium, which consists of individual layers of epithelial, stromal, and endothelial cells in a 3D extracellular matrix (Ahn et al., 2021). The innovation makes it possible to study the process of endometrial repair and regeneration, which, in turn, opens the door to the study of such conditions as Asherman syndrome (intrauterine adhesions) and infertility and creates an arena where new therapeutic interventions can be developed (Hu et al., 2020).

Mitochondrial Transfer and Oocyte Quality Enhancement:

Mitochondrial transfer, which is the transplantation of healthy mitochondria into damaged oocytes, is intended to enhance fertilisation and embryo growth in age-related infertility or recurrent implantation failure; fertilisation rate increases by almost 45% to

60% in clinical trials (Ahn et al., 2021). Ovarian and endometrial functioning is improved with complementary treatment (platelet-rich plasma (PRP) and exosomes containing stem cells) that contribute to angiogenesis, tissue regeneration, and follicle development. In 2022, Parvanov et al were able to show that Ovarian PRP treatment consisting of autologous ovarian PRP in women with poor ovarian response resulted in significant improvement in ovarian reserve, oocyte, and embryo quality. The average count of Day-5 embryos improved to 2.19, and about three out of every four patients reported better quality of oocytes/embryos. PRP treatment can thus increase IVF success rates among poor responders, and the guideline can be regularly used in fertility clinics (Parvanov et al., 2022). MSC transplantation aids endometrial receptivity and ovarian regeneration, enhancing endometrial thickness and follicular maturation and therapeutic application is further optimised by engineered secretory improvements (Bajpai et al., 2023).

Nanomedicine in Fertility Preservation:

Nanomedicine has already become an innovative platform in fertility preservation, pluming on nanoscale materials to deliver drugs to target locations, to diagnose and regenerate tissue and organs. Engineered nanomaterials can be used to promote ovarian and endometrial regeneration, as well as gametogenesis, through imitating the extracellular matrix and supplying tissue engineering scaffolds to improve reproductive performance and provide less invasive solutions compared to traditional fertility preservation techniques. The latest developments also allow preserving gametes against chemotherapeutic or environmental losses and enhance the efficiency of cryopreservation (Jiang et al., 2024). Moreover, nanoplatforms can be used to monitor the reproductive tissues in real-time, which offers personalised and more effective fertility preservation plans. Figure 1 shows the nanotechnology approaches to fertility preservation strategies.

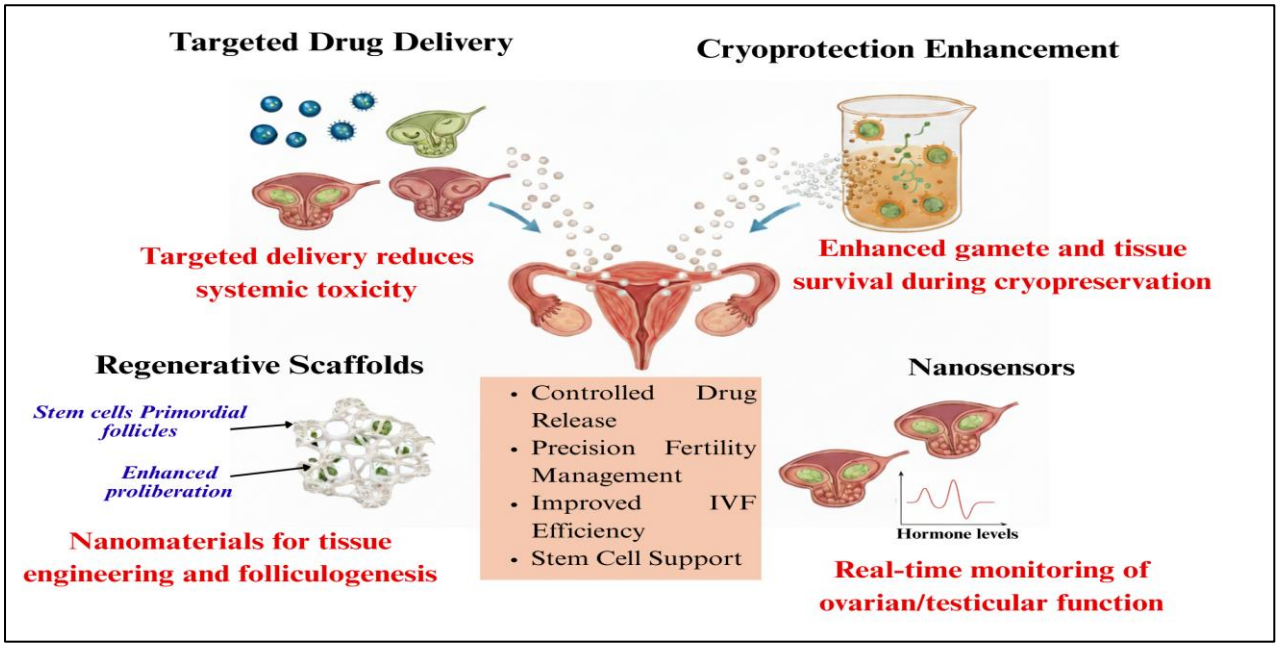

Fig 1. Nanotechnology-based strategies for fertility preservation.

Nanoparticles for Targeted Gonadal Drug Delivery:

Nanoparticles offer an accurate targeting of the ovaries and testes to increase the bioavailability of drugs and avoid the off-target cytotoxicity of gametes (Jiang et al., 2024). They have the capability of wrapping hormones, growth factors and gene-editing tools to optimise the gonadal microenvironment. In animals, nanoparticles enhance their fertility by targeting hormones or genes to support effective and sustainable reproductive control. In human beings, these formulations can be used to complement ovulatory disorders such as clomiphene citrate, whereby their formulations guarantee the best site-specific drug concentrations (Girase et al., 2023). Nanoparticles selectively coated to shield follicles in the ovaries against cytotoxic treatments and to deliver RNA-lipid therapeutic agents with reduced systemic consequences RNA-lipid therapeutic agents (Nomani et al., 2025). Stealth and imaging capabilities permit real-time detection of the treatment response and disease progression to develop precision medicine in fertility preservation. Polymeric nanoparticles and liposomes provide physicochemical control of release and cellular uptake, which is tunable to provide a wide range of customisation in terms of cargo and delivery routes in human and animal reproductive health. This accuracy is especially essential in maternal-fetal medicine, which minimises the risks of both mother and fetus (Hanassab et al., 2024). The kinetics available with nanoparticles, including long-release, allow therapeutic concentrations to be maintained longer, with the resultant decrease in administration frequency and an increase in compliance in chronic fertility therapies (Rather et al., 2013).

Nanomaterials for Scaffolding and Tissue Engineering:

Nanomaterials have offered biomimetic systems of artificial gonads and artificial folliculogenesis in vitro, which contribute to the growth and proliferation of germ cells. The Decellularised extracellular matrix scaffold mimics the natural microenvironment of tissues, which leads to the growth and differentiation of cells to form functional ovarian or testicular tissues. These scaffolds augment oocyte and spermatogonia development, and provide solutions to fertility rehabilitation in gonad damaged patients (Taylan et al., 2018; Quan et al., 2020). Micro/nanorobotics also enhances in vitro fertilisation because it allows specific manipulation of gametes under a complicated biological system (Benhal et al., 2024). Tunable nanomaterials with high surface area support 3D architectures that facilitate cell-cell interactions, nutrient exchange, and functional tissue development. The combination with stem cell therapy permits targeted delivery and imaging, which enhances cell isolation, controlled differentiation, and regenerative performance (Aswini et al., 2024).

Decellularisation of whole-ovary protocols generates 3D bioscaffolds that retain extracellular matrix constituents and ablate cellular content and maintain follicle development, hormone secretion, and immunocompatibility. This is because these bioengineered constructs reduce the chances of tumour cell reintroduction, which is a safer option for oncological patients. The current progress in 3D bioprinting provides ovarian tissue architecture, which can sustain long-term follicle development, steroid production, and transplantation of tumour-free follicles. Optimised decellularised human ovarian scaffolds retain pre-antral follicles functionality and integration, which is a promising

method of fertility preservation (Alshaikh et al., 2020; Hu et al., 2023a; Yin et al., 2025).

Nanosensors for Monitoring Ovarian Function:

Nanomaterials offer biomimetic systems to artificial gonads and in vitro folliculogenesis to promote the development and differentiation of germ cells. Decellularised extracellular matrix scaffolds re-create the native tissue microenvironment to direct cellular growth and differentiation to re-form functional ovarian or testicular tissues. They improve the maturation of oocytes and spermatogonia, and provide options in fertility recovery in patients with gonadal damage (Taylan et al., 2018; Quan et al., 2020). Micro/nanorobotics also enhances in vitro fertilisation by allowing the manipulation of gametes in sophisticated biological conditions (Benhal et al., 2024). Tunable nanomaterials and high surface area are known to promote 3D architecture, cell-cell interactions, nutrient exchange, and functional tissue formation. Combination with stem cell therapy enables local delivery and imaging, which enhances cell isolation, directed differentiation and regenerative findings (Aswini et al., 2024).

Nanosensors make it possible to monitor ovarian biomarkers in real-time and to do it in a very sensitive manner, which allows prompt detection of reproductive diseases and timely intervention (Shea et al., 2014; Yin et al., 2025). They are sensitive devices that monitor changes in hormone levels, inflammatory markers, and gene expression that give a complete understanding of ovarian physiology. Plugging into wearable or implantable systems would enable the collection of continuous data on the use of personalised fertility management and predictive analytics. Non-invasive follicle development and oocyte quality evaluation. Nanosensors work with molecular signatures in follicular fluid or peripheral circulation. They also allow in situ monitoring of ovarian tissue viability following cryopreservation or transplantation, to give essential feedback on graft acceptance, cellular viability, metabolic activity and hormonal production (Jones et al., 2020; Smitz et al., 2010)]. This is necessary because steroid hormones such as progesterone and estradiol exist in ultralow concentrations of picomoles (Meng et al., 2025). More sophisticated electrochemical immunosensors enhance the early diagnosis of gynaecological diseases through cytokine and growth factor detection and can be integrated into fast, home-based fertility devices, which are convenient and offer privacy (Peng et al., 2025).

Nanotechnology in Sperm Preservation:

Nanotechnology also improves sperm cryopreservation through the provision of improved cryoprotectants and delivery systems. The nanoparticles contain cryoprotectants and decrease the toxicity through controlled release and enhance cellular uptake, and reduce osmotic stress (Antonouli et al., 2023). Nanomaterials can also be used as scaffolds to store sperm, which can resist temperature variations, oxidative stress, organelle-specific cryo-injury, and maintain motility and fertilising ability. Nanosensor-based smart cryo-devices can be used to monitor the viability of sperm, their metabolic rate, and membrane integrity in real-time, to optimise preservation procedures (Madrid, 2023).

Microfluidic biosensors are used to select sperm by motility and morphology to assist in reproductive technologies. Antioxidants and protective factors can be delivered by nanoparticles to reduce reactive oxygen species and inhibit DNA fragmentation and chromatin damage, which is essential in fertilisation and embryonic development (Sequeira et al., 2020; Akhtar et al., 2022). Semen analysis based on a home-based nanosensor

provides quick, sensitive, and easy-to-use analysis, as opposed to the methods of the past that were labour-intensive. New omics technologies, such as proteomics and transcriptomics, can be used to determine freezeability indicators and protective proteins to increase the cryo-survival rates, which can inform next-generation strategies to reduce the number of cells damaged by the freezing process and improve the post-thaw sperm functionalities (Khan et al., 2021). These innovations in nanotechnology are critical in enhancing fertility preservation and assisted reproductive success in males.

Special Clinical Contexts in Fertility Preservation:

Individual approaches are needed in fertility preservation in a variety of clinical patient groups, such as pediatric and adolescent cancer patients, patients with premature ovarian insufficiency (POI) or autoimmune diseases, transgender patients, and low-resource patients. These methods need to consider age, comorbidities, and treatment plans and socioeconomic status to maximise reproductive success (Antonouli et al., 2023; Tamburrino et al., 2023; Rodriguez-Wallberg et al., 2021). Children who are not yet mature, lacking gametes, have to depend on at least experimental interventions, including immature gonadal tissue cryopreservation, in vitro maturation, or artificial gonad technologies (Chen et al., 2023). Teens need counselling that covers the risk of fertility as well as the psychological effects of the gonadotoxic treatments (Hussein et al., 2020). Timely referral, preferably prior to the start of treatment, augments the effectiveness of preservation strategies (Rodriguez-Wallberg et al., 2021).

Multidisciplinary oncofertility teams comprising oncologists, reproductive endocrinologists and specialized nurses that facilitate risk assessment, counselling, and access to preservation procedures. The eligibility of female pediatric patients is based on age, pubertal age, and the type of cancer, and the data of ovarian cortex surface helps to plan surgery to ensure the maximum tissue harvest and minimum intervention (Jaeck et al., 2025).Although it is suggested to implement universal counselling, there are still gaps in the population, particularly with adolescents and young adults, which makes it necessary to develop standardized communication and referral practices. In patients with POI or autoimmune diseases, there are ovarian tissue cryopreservation strategies, hormonal regulation, and in vitro folliculogenesis, depending on the remaining ovarian capacity and the time of treatment. Pre-gender-affirming interventions early counselling and gamete or tissue preservation, are beneficial to transgender patients, and methods are modified to include hormone treatment and surgical planning. Low-resource environments are a challenge to fertility preservation because of the lack of facilities, finances, and qualified people. It is essential to implement flexible, affordable strategies and education programs that would enhance fair access and outcomes (Antonouli et al., 2023; Rodriguez-Wallberg et al., 2021). A number of clinical trials are being conducted to prove the efficacy of fertility preservation approaches, including ovarian tissue cryopreservation and uterine transplantation, regenerative, or nanomedicine-based treatments. Table 2 has compiled some of the registered trials, including their design, sponsors, and target population in fertility preservation.

Table 2. Completed clinical trials on fertility preservation

Clinical Trial Reg. No.	Study Type/ Phase	Sponsor	Condition / Population	Official Title	Ages/sexes eligibility
NCT05372549	Interventional	Clinique Ovo	Fertility Preservation	Correlation of Oxidative Stress and Oocyte Quality in Fertility Preservation	18–37 years, Female
NCT01448460	Observational	University of Louisville	Fertility Preservation	Oocyte Vitrification for IVF Patients and Women With Fertility-Threatening Conditions	14–42 years, Female
NCT00380406	Interventional/ Phase 3	Ottawa Hospital Research Institute	Fertility Preservation, Cancer	PROtecting Ovaries and Fertility During Chemotherapy - The PROOF Trial: A Randomized Controlled Trial of GnRHa for Fertility Preservation in Oncology Patients	18–38 years, Female
NCT02661932	Interventional/ Phase 4	Erasme University Hospital	Fertility Preservation, Breast Cancer	Efficiency and Safety Study of Ovarian Stimulation With Letrozole for Fertility Preservation in Breast Cancer Patients	18–40 years, Female
NCT04992468	Interventional/ Phase 4	Fundación Santiago Dexeus Font	Infertility	Dual Trigger vs. GnRH-a Trigger for Elective Fertility Preservation. A Randomized Controlled Trial	18–40 years, Female
NCT00429494	Interventional/ Phase 2	M.D. Anderson Cancer Centre	Amenorrhea, Premature Ovarian Failure, Ovarian Function Insufficiency	Phase II Study of GnRH Analogue for Ovarian Function Preservation in Hematopoietic Stem Cell Transplantation Patients	Up to 40 years, Female
NCT01035099	Interventional/ Phase 4	Weill Medical College of Cornell Univ.	Breast Cancer, Infertility	A Randomized Open Label Clinical Trial of Fixed Dose Letrozole vs. Titrated Letrozole for IVF With Cryopreservation of Oocytes and Embryos in Breast Cancer Patients	19–45 years, Female

NCT02659592	Interventional/ Phase 3	Sheba Medical Centre	Reproductive performance following ovarian transplantation	Transplantation of Frozen Thawed Ovarian Tissue Demonstrates High Reproductive Performance and the Need to Revise Restrictive Criteria	20–40 years, Female
NCT01160315	Interventional/ Phase 2/3	Erasme University Hospital	Fertility preservation, Lymphoma	A Prospective Open Randomized Trial on the Efficacy of Gonadotropin-releasing Hormone Agonist Depot-Triptorelin to Prevent Chemotherapy Induced Premature Ovarian Failure in Lymphoma Patients	18–45 years, Female
NCT02892942	Interventional/ Phase 4	Assistance Publique - Hôpitaux de Paris	Infertility, good prognosis IVF-ET candidates	An Innovative Controlled Ovarian Hyperstimulation (COH) Protocol That Combines Large Oocyte Availability and Physiologic Estrogenic Environment for Good Prognosis IVF-ET Patients	18–40 years, Female
NCT01696786	Interventional	Weill Medical College of Cornell University	Fertility Preservation	Oocyte Cryopreservation	Up to 42 years, Female
NCT05100498	Interventional	Mackay Medical College	Fertility Preservation, Breast Neoplasm Female	Web-based Oncofertility Support Tool for Reproductive-age Women With Breast Cancer	20–65 years, All sexes
NCT04487639	Interventional	University Hospital, Clermont-Ferrand	Sperm Preservation in Oncological Patients, Fertility, Cryopreservation	Presence of SARS-CoV-2 in Semen: Impact on Fertility Preservation in Male Oncological Patients During the COVID-19 Pandemic	18–60 years, Male
NCT01817296	Interventional	Boston Children's Hospital	Klinefelter Syndrome	Klinefelter Syndrome: Are we Missing the Optimal Time for Fertility Preservation?	12–25 years, Male

NCT01645241	Interventional	Fundacion Dexeus	Infertility, Fertility Preservation, Ovulation Induction, Vitrification, Oocyte Donation	Evolutive Potential of Embryos Obtained From Oocytes After Luteal Phase Ovarian Stimulation	18–35 years, Female
NCT04268004	Interventional	Leena Nahata, Nationwide Children's Hospital	Infertility, Male, Fertility Preservation, Cancer	Optimizing Fertility Preservation and Decision Quality in Male AYA With Cancer: A Family-centered Intervention	12–25 years, Male
NCT01918280	Interventional	Hospices Civils de Lyon	Klinefelter Syndrome, Male Infertility	Fertility Preservation in Cases of Spermatogenesis Failure: Prospective Study for Klinefelter Syndrome With Non-mosaic Karyotype (47, XXY, Homogeneous)	15–55 years, Male
NCT04002414	Interventional	University of California, San Francisco	Female Infertility	Physical Activity and Fertility Care Study (PACE)	18–43 years, Female
NCT02678910	Interventional	Vlad Radulescu	Cancer, Hematologic, Rheumatologic Disorders, Infertility	Ovarian Tissue Freezing For Fertility Preservation In Women Facing A Fertility Threatening Medical Diagnosis/ Treatment	12–41 years, Female
NCT04602910	Interventional	Mackay Medical College	Breast Cancer Female	Developing a Web-based Shared Decision-making Tool for Fertility Preservation Among Reproductive-age Women With Breast Cancer: An Action Research Approach	22–65 years, All sexes
NCT00852306	Interventional	Northwell Health	Infertility	A Comparison of Two Freezing Techniques	21–50 years, Female

Emerging Strategies and Future Directions:

CRISPR-Based Gene Editing:

CRISPR-Cas9 has a transformative potential in the correction of genetic malfunctions causing infertility, the prevention of reproductive disorders that are inherited, and the improvement of the viability of germline cells (Jaeck et al., 2025). It allows focused editing of oocytes, sperm, and early embryos and can treat single-gene diseases and potentially provide resistance to gonadotoxic treatment of cancer patients. It can also be used in in vitro gametogenesis and somatic gene therapy in reproductive tissues, including enhancing uterine receptivity or remediating genetic factors responsible for endometriosis (Böttcher et al., 2021). Nevertheless, it requires strict preclinical studies and social discussions of ethical and safety issues, such as the off-target effects, mosaicism and hereditary modifications of the genome, before clinical use.

3D Bioprinting of Reproductive Tissues:

It is possible to recreate more complex reproductive tissues, such as artificial ovaries and testes, using 3D bioprinting and with a high level of spatial organisation, which can be used to support in vitro gametogenesis and hormone production (Felgueiras et al., 2020). Combination with microfluidic systems offers dynamic nutrient supply and waste elimination, which improves tissue survival and performance (Sequeira et al., 2020). They can be used to repair the endocrine activity and fertility of patients with gonadal dysfunction or in gonadotoxic treatments and as platforms specific to the patient, in drug discovery and in personalised treatment (Sen et al., 2024). Bio-printing (4D/5D) can also enhance the complexity and functionality of human tissues, which could result in bioprosthetic ovaries and organoids with maximised implantation durations (Žiaran et al., 2025). The emerging strategies in fertility preservation are illustrated in Figure 2.

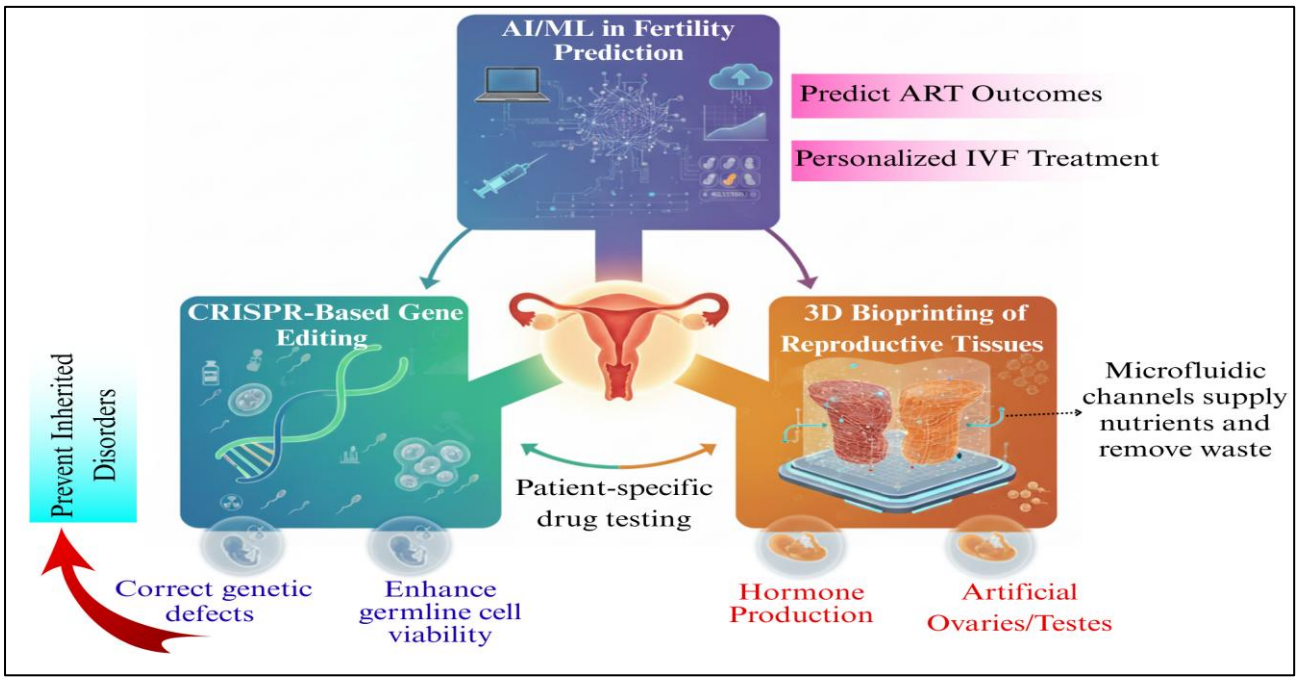

Fig 2. Emerging strategies in fertility preservation and reproductive medicine.

Artificial Intelligence and Machine Learning in Fertility Prediction:

Machine learning and AI can be used to improve predictive performance, optimise treatment regimes, and enhance diagnostic accuracy in reproductive medicine. Algorithms are used to process large datasets to forecast the outcome of ovarian stimulation, individualise drug doses, select embryos, and standardise sperm and oocyte tests (AlSaad et al., 2024; Orovou et al., 2025). The machine learning models, such as Logistic Regression, SVM, MLP, KNN and ensemble models that achieve better IVF outcome predictions than the traditional methods (Sadegh-Zadeh et al., 2024). Such instruments enable personalised treatment design, optimize oocyte availability and quality and decrease the adverse events, which is a paradigm shift towards data-driven assisted reproduction. The use of neural networks and advanced AI models also supports clinical decision-making by incorporating multidimensional data about a patient to provide individual fertility care. The use of machine learning (ML) to predict the results of assisted reproductive technology (ART) has significantly increased. In 2025, Dehghan et al conducted a systematic review on 27 studies and found 107 predictive features where female age was the most prevalent. The majority of the studies employed supervised ML, especially support vector machines. Mainly, the evaluation of model performance was based on the AUC and then accuracy, sensitivity, and specificity (Dehghan et al., 2025). Also, ML has the potential to enhance ART decision-making, but valid models require careful selection of features and techniques.

Translational Roadmap:

To facilitate the gap in laboratory innovations and clinical use, a systematic translational roadmap is essential. These involve strict clinical trial design, standardised protocol, regulatory approval, cost-effective implementation and long-term outcome monitoring. AI incorporation into the process of embryo quality control and sperm selection can increase the success of IVF and minimise human error (Hew et al., 2024). Clinician and patient education, strategic collaboration, and equal access are critical to ensuring that the effects of emerging technologies are maximised. Constant review of effectiveness and safety is a way to ensure that new interventions promote the responsible and effective fertility preservation (Siristatidis et al., 2021)

Ethical Considerations in Fertility Preservation:

Fertility preservation is based on autonomy and informed consent, where patients must be made aware of the benefits, risks, and experimental nature of the new interventions, like CRISPR-based gene editing and mitochondrial transfer. The patients should be completely informed about the possible long-term consequences on their health, genetic issues, and the uncertainties of the success rates of these advanced reproductive technologies. They should also reflect on the future applications of stored gametes or embryos, especially where there is a change of relationship or the death of patients, which in most instances leads to a complicated legal and ethical dilemma (Hudson et al., 2017). Technological change is often occurring at a very fast pace, and thus there is a lack of clarity regarding ownership, disposition, and inheritance of cryopreserved reproductive resources, with the most effective solution to this issue being to unify legal rules and establish a balance between personal autonomy and social standards (Shah et al., 2011).

Ethical issues in vulnerable groups, such as children with cancer and transgender patients, are unique due to the changing decisional capacity and reproductive intentions (ESHRE Guideline Group on Female Fertility Preservation, 2020; Lambertini

et al., 2016). Storing gametes and embryos over long periods of time brings forth other issues of time, cost, and handling of unclaimed or lost samples. Moreover, there is the recent change in the society and in the law, like the reversal of Roe v. Wade, has provoked the reconsideration of the legal personhood and the rights to constitute and reproductive rights, which may influence the work of IVF and frozen embryos (Letterie et al., 2023). These developments demonstrate the necessity of constantly revising the ethical guidelines and legal regulations to protect patient autonomy and access to care. Artificial intelligence implementation into embryo selection also gives rise to other ethical issues, such as transparency in algorithms, bias, data privacy and the possibility of contributing to increased social inequalities (Aufieri et al., 2025). Disparities are further increased by financial barriers and unequal access to fertility preservation, especially among the lower socioeconomic populations (Daar, 2009). Ethical, legal, and social issues should be approached comprehensively to make advanced fertility preservation technologies responsible, equitable, and patient-centred.

Conclusion and Future Prospects:

This review outlines the fast-paced development of fertility preservation, including the development of cryobiology, regenerative medicine, nanomedicine, and novel biotechnologies, along with raising ethical, legal, and societal concerns. This has the potential to enhance the reproductive outcomes of varied groups of people, including cancer patients, those with premature ovarian insufficiency, and transgender patients, utilising customised, patient-centred care. Longitudinal studies should be considered as a priority in future to determine the long-term effectiveness, safety and functional outcomes of the new fertility preservation methods. The industry requires interdisciplinary collaboration to help fill reproductive biology gaps, enhance technological integration, and personalise care to patients. Laboratory innovations must be strictly verified, standardised, and regulated in translation to clinical practice in order to guarantee consistent results. Further investment in basic research is essential as a way of creating superior cryoprotectants, bio-inspired scaffolds that mimic the native reproductive micro-environment and enhanced gametic and tissue preservation methods. A special focus should be on the populations with specific issues, such as pediatric, adolescent, and transgender patients, whose needs must be met with specific strategies to support the continuous development, hormone treatments, and gender-affirming procedures. CRM of ovarian tissue and sperm by the use of optimised cryoprotectants, microfluidic sorting, and predictive models of gamete and embryo quality is promising to enhance success. All in all, the combination of modern biotechnologies, moral principles, and patient-based clinical interventions can reshape fertility preservation, providing safe, effective, and equal ways to people who are at risk of reproductive impairment.

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