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Mini-Review Article

Stem-Cell–Based Approaches to Improve Oocyte Quality and Embryo Development

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Abstract

Declining oocyte quality is a major contributor to infertility, diminished ovarian reserve (DOR), and suboptimal invitro fertilization (IVF) outcomes. Recent advances in stem-cell biology and regenerative medicine have introduced novel therapeutic strategies to restore ovarian microenvironmental function, attenuate oxidative stress, and enhance oocyte and embryo competence. Advanced therapeutic modalities, including mesenchymal stem cells (MSCs), perinatal stem cells, induced pluripotent stem cells (iPSCs), and their secretome, particularly extracellular vesicles (EVs), exhibit profound regenerative potential. These therapeutic effects are mediated through paracrine signaling, anti-apoptotic pathways, mitochondrial restoration, and modulation of granulosa–oocyte communication. This review This review summarizes recent mechanistic insights, highlights emerging translational evidence, and proposes future directions for integrating stem cell–based regenerative strategies into reproductive medicinequality. Moreover, we highlight existing challenges, clinical observations, and future directions for integrating regenerative biomedicine into reproductive medicine.

Keywords: Embryo competence, Extracellular vesicles, Mesenchymal stem cells, Oocyte quality, Ovarian aging, Infertility

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Introduction

Oocyte quality is a crucial determinant of female fertility, embryo viability, implantation potential, and pregnancy outcomes(1). Age-related ovarian reserve decline, cumulative oxidative stress, mitochondrial dysfunction, inflammation, decreased ovarian angiogenesis and follicular microenvironmental deterioration negatively affect oocyte maturation and developmental competence(2-4). As the global trend of delayed childbearing increases, clinicians face growing challenges associated with low ovarian reserve, poor responders, and IVF failure(5). On the other hand, classical approaches such as ovulation induction,, antioxidants and IVF cannot fundamentally restore ovarian tissue Concurrently, regenerative medicine has emerged as a transformative field, offering novel therapeutic approaches based on stem-cell biology(6). These cells, which are extracted from the umbilical cord, bone marrow, adipose tissue, and menstrual blood, may help restore ovarian tissue integrity, promote follicular growth, and enhance the formation of high-quality embryos due to their ability to self-renew and differentiate (7). The objective of this review is to analyze recent findings regarding stem cell–mediated enhancement of oocyte quality and embryogenesis, with emphasis on mechanisms, translational achievements, and clinical perspectives.

Methods

To ensure methodological transparency, a structured literature search was conducted using PubMed, Scopus, and Web of Science databases for studies published between January 2019 and February 2026. Search terms included combinations of Medical Subject Headings (MeSH) and relevant keywords such as “stem cells,” “mesenchymal stem cells,” “extracellular vesicles,” “oocyte quality,” “ovarian aging,” “ovarian reserve,” and “embryo competence.” Priority was given to original research articles, systematic reviews, and meta-analyses reporting molecular mechanisms, regenerative pathways, ovarian function restoration, and reproductive outcomes. Articles with insufficient methodological detail or limited relevance to oocyte quality were excluded.

Stem-Cell

Stem cells are characterized by two important indicators, self-renewal, which has the ability to perform mitosis to maintain its population, and differentiation into different cells(8). Stem cells are undifferentiated cells present during embryonic development and adult life that possess the capacity for self-renewal and differentiation into specialized cell lineages(9). In terms of differentiation, stem cells are divided into four groups: totipotent:they have the ability to differentiate into different types of embryonic cells, i.e. the three germ layers of ectoderm, mesoderm and endoderm, as well as extra-embryonic cells and germ cells (gametes), pluripotent : these cells have the ability to differentiate into different types of embryonic cells or three germ layers as well as germ cells (gametes). In other words, all the cells derived from an embryo, except extraembryonic cells, multipotent ;they differentiate only into the types of cells derived from the germ layer from which they originated and unipotent: they only have the ability to produce complete cells similar to themselves(10) (Fig.1). Beyond their potency, stem cells can also be classified based on their

origin and biological source, as illustrated in Figure 2. According to this hierarchical classification, cells are categorized into two primary lineages: Tissue-Specific Stem Cells and Pluripotent Stem Cells. Tissue-specific cells encompass adult stem cells (responsible for tissue repair) and fetal stem cells (involved in development). In contrast, the pluripotent lineage includes Human Embryonic Germ Cells (EGCs), Embryonal Carcinoma Cells (ECCs), Embryonic Stem Cells (ESCs), and Induced Pluripotent Stem Cells (iPSCs). This classification is crucial for determining the most suitable cell type for clinical interventions in reproductive medicine(11) (Fig.2).

Stem-Cell Types Involved in Enhancing Oocyte Quality

Mesenchymal Stem Cells (MSCs)

MSCs derived from bone marrow, adipose tissue, umbilical cord, and Wharton's jelly are the most studied stem-cell type for ovarian regeneration. Recent evidence further supports the therapeutic efficacy of MSCs and MSC-derived exosomes in restoring ovarian function and improving reproductive outcomes in various models of female reproductive dysfunction(12). MSCs secrete angiogenic, anti-apoptotic, and antioxidant factors including insulin-like growth factor (IGF-1) , hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF) , basic fibroblast growth factor (bFGF), and transforming growth factor-β (TGF-β). which respectively causes support of folliculogenesis and Promotion of folliculogenesis and increased antral follicle count(13), enhance of angiogenesis and restore ovarian blood flow(14), reduce inflammation and apoptosis within ovarian tissue(15). It has been shown in a research that these factors help in reducing ovarian atrophy(16). Also, studies have shown that this type of stem cell causes restoration of ovarian stromal architecture(17), decreased apoptosis of granulosa cells(18), improved mitochondrial activity and adenosine triphosphate (ATP) availability(19) enhanced meiotic progression to MII oocytes(20), increased estradiol and anti-Müllerian hormone (AMH) levels in animal models(21). Treatment with mesenchymal stem cells (MSCs) has been associated with increased oocyte yield, embryos, and expanded blastocysts in acute ovarian lesions caused by ovum pick-up (OPU)(22). In 2024, it was shown that adipose-derived mesenchymal stem cells (ASCs) increased the number of oocytes and ovulation in the ovaries AMH levels, as well as leading to improved oocyte quality and increased fertilization and blastocyst formation rates in older women(23). Park et al. reported in 2023 that MSCs lead to fertility restoration and increased fertility rates in individuals with Primary ovarian insufficiency (POI), which could be a treatment option for restoring ovarian function for these individuals(24). A number of studies on mesenchymal stem cells are listed in Table 1.

Perinatal Stem Cells (Placental, Amniotic, and Umbilical Cord Cells)

Perinatal tissues are rich in immunomodulatory stem cells that have a higher proliferative potential than mature mesenchymal stem cells(25). The characteristics of these cells include low immunogenicity(26), high performance and non-invasive collection(27), and their strong

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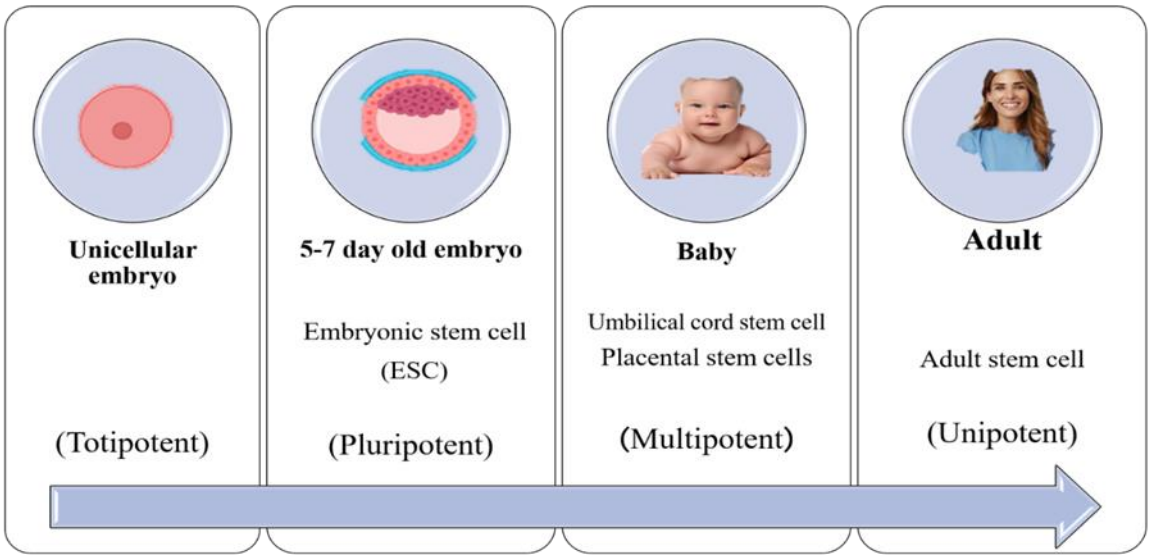

Figure 1. Stem cell classification based on differentiation

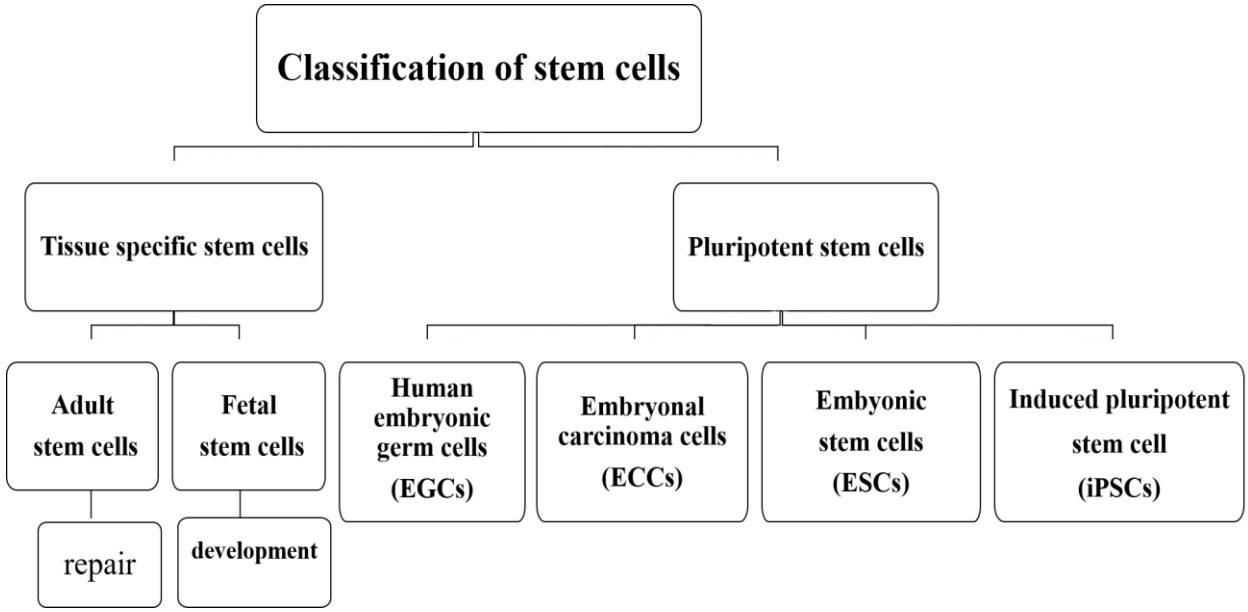

Figure 2. Stem cell classification based on origin

paracrine anti-aging effects(28). studies showed the improvement of ovarian index, increase in fertility rate and population of follicles in different stages in premature ovarian failure (POF) mice using mechanisms of human amniotic mesenchymal stem cells (hAMSCs)(29, 30). In terms of clinical translation, perinatal-derived stem cells (such as those from the umbilical cord, placenta, and amniotic fluid) present a superior profile compared to induced Pluripotent Stem Cells (iPSCs). While iPSCs offer remarkable differentiation potential, they are hindered by significant safety concerns, including genetic instability and the risk of tumorigenicity. Conversely, perinatal cells exhibit low immunogenicity, high proliferative capacity, and a robust

paracrine secretome, positioning them as the most viable candidates for immediate regenerative applications in reproductive medicine These findings position perinatal stem cells as a prime candidate for clinical translation(31). A summary of the study can be seen in Table 1.

Induced Pluripotent Stem Cells (iPSCs)

iPSCs can be generated from somatic cells and differentiate into granulosa-like cells or primordial germ-cell–like cells (PGCLCs), offering a platform to study ovarian aging and develop synthetic oocyte-supportive cells(32). It has been shown that mouse iPSCs cells, when fused with ovarian somatic cells, behave as primordial germ cells and contribute to maturation and fertilization in vitro(33). It has also been explained in research that these cells rejuvenate the ovarian tissue by producing different paracrine factors(34). However, safety concerns related to tumorigenicity and genetic instability remain significant barriers. Some studies related to the iPSCs are listed in Table 1.

Paracrine Mechanisms Underlying Stem-Cell Benefits

Extracellular Vesicles (EVs) and Exosomes

Extracellular vesicles are considered as a group of structures enclosed in a lipid bilayer membrane that are secreted by most cells into the extracellular space and can contain proteins, lipids and nucleic acids that change the behavior of receptor cells, including the ovary(35). miRNAs are said to play important roles in primordial follicle formation, follicular recruitment and selection, follicular atresia, oocyte-cumulus cell interaction, granulosa cell function, and luteinization(36). So that in a study, the positive regulatory effect of miR- 34 on oocyte maturation , embryo and blastocyte quality has been shown(37). Investigation indicated that miR-21 could inhibit apoptosis of mouse periovulatory granulosa cells(38). It has also been reported that exosomal miRNAs, which are present in ovarian follicular fluid and play a role in the exchange of genetic information between cells, are critical to maintain oocyte quality(39). A recent meta-analysis of animal studies confirmed that stem cell-derived extracellular vesicles significantly improve ovarian reserve markers and follicular development in models of premature ovarian failure(40).

Anti-Oxidative Mechanisms

Oxidative stress causes granulosa cell apoptosis, which causes follicular depletion and accelerates oocyte aging and reduces embryo viability. MSCs secrete anti-apoptotic cytokines such as HGF, IGF,VEGF, which support healthier oocyte maturation(41). MSC-derived cytokines activate phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), *Sirtuin 1* (SIRT1), and AMP-activated protein kinase (AMPK) signaling pathways, which are essential for metabolic and oxidative homeostasis in oocytes(41). The therapeutic efficacy of stem cell interventions is predominantly mediated through the activation of critical intracellular signaling pathways, most notably PI3K/AKT, SIRT1, and AMPK. These pathways play a pivotal role in maintaining metabolic homeostasis within the oocyte by regulating mitochondrial bioenergetics and neutralizing reactive oxygen species (ROS). Specifically, the activation of these cascades enhances ATP

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availability and ensures the structural integrity of the meiotic spindle, thereby preventing chromosomal aneuploidy and improving overall embryo competence(42).

Enhancement of Mitochondrial Function

Healthy mitochondria are essential for oocyte competence and early embryo cleavage. As past studies have shown that mitochondrial dysfunction can lead to oocyte maturation arrest, defective spindle formation and abnormal chromosome segregation, ultimately resulting in embryonic chromosomal aneuploidy (43, 44). In contrast, it is reported that stem-cell–derived EVs have been shown to transfer mt DNA-stabilizing proteins and improve ATP production in oocytes(45). An overview of the mechanisms for improving oocyte quality is given in Table 2. Among the paracrine mechanisms described above, extracellular vesicles (EVs), particularly stem cell–derived exosomes enriched with regulatory microRNAs, appear to be the most strongly supported by current evidence. Increasing experimental and preclinical studies indicate that EV-mediated signaling represents a central pathway through which stem cells exert their regenerative effects on ovarian tissue and oocyte competence. EVs function as key mediators of intercellular communication by transferring bioactive molecules—including proteins, lipids, mRNAs, and microRNAs—to ovarian and follicular cells, thereby modulating cellular signaling pathways involved in folliculogenesis and oocyte maturation. Notably, EV-associated microRNAs have been shown to regulate several reproductive processes, including primordial follicle activation, granulosa cell proliferation, follicular development, and oocyte–cumulus cell communication. In addition, emerging evidence suggests that stem cell–derived EVs contribute to improved mitochondrial activity and cellular energy metabolism in oocytes, partly through enhancing ATP production and supporting mitochondrial DNA stability. These effects may ultimately promote better spindle organization and reduce the risk of chromosomal abnormalities during meiotic division. Therefore, while antioxidative protection and mitochondrial regulation are also important mechanisms, a substantial body of evidence suggests that many of these beneficial effects are mediated through EV-based signaling pathways. These observations are supported by several studies demonstrating the therapeutic potential of stem cell–derived extracellular vesicles in restoring ovarian function and improving oocyte quality in experimental models(46, 47).

Stem-Cell Effects on Embryo Development

Although oocyte quality is the primary determinant of embryo viability, stem-cell therapies influence embryogenesis indirectly. By reducing DNA fragmentation and supporting spindle integrity in oocytes, stem-cell–derived factors lead to better cleavage rates, higher blastocyst formation, and increased frequency of Grade-A embryos(48).

Challenges and Limitations

Despite the promising potential of stem cell-based therapies in enhancing oocyte quality and ovarian function, several critical challenges and limitations must be addressed before their widespread clinical application. A

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Table 1 . Summary of a comprehensive study reviewing stem cell-based studies in improving oocyte quality

Category	Reference	Mechanism or key factor	Result
MSCs	Mirfakhraie R,et al.,2023	Secretion of anti-inflammatory factors	reducing ovarian atrophy
MSCs	Takehara Y, et al., 2013	Extracellular matrix remodeling	restoration of ovarian stromal architecture
MSCs	Zhang L, et al ., 2023	Inhibition of apoptotic pathways	decreased apoptosis of granulosa cells
MSCs	Mohammadalipour A, et al., 2020	Transfer of mt DNA stabilizing proteins	improved mitochondrial activity
ASCs	Patricia F, et al., 2020	increased estradiol and AMH levels	Increasing fertility in ovarian failure
Prenatal SCs	Liu R , et al ., 2019	Strong paracrine signaling (hAMSCs)	improve the follicular microenvironment to recover ovarian function in POF
iPSCS	Telfer EE, et al ., 2023	Differentiation into germ-like cell (PGCLCs)	Act as primary germ cells in combination with ovarian somatic cells
iPSCS	Wang Y, et al., 2025	Rejuvenating secretory factor	Ovarian tissue rejuvenation

MSCs :Mesenchymal Stem Cells , mt DNA: mitochondrial DNA
hAMSCs :human amniotic mesenchymal stem cells , POF :Premature ovarian failure
iPSCs : Induced Pluripotent Stem Cells , PGCLCs:Primordial germ cell -like cell

Table2. Overview of mechanisms for improving oocyte quality

Mechanism of action	Target Process	Molecular Benefit
Paracrine Secretion	Exosomes /miRNAs	Transfer essential growth factors to the oocyte microenvironment.
Signaling Activation	PI3K/AKT/ SIRT1	Regulates metabolic homeostasis and promotes follicular survival.
Antioxidant Support	Redox Balance	Reduces ROS levels and prevents oxidative damage to oocyte DNA
Mitochondrial rescue	Bioenergetics	Increased ATP production and restores mitochondrial membrane potential.

PI3K/AKT/ SIRT1: phosphatidylinositol 3-kinase/protein kinase B/ *Sirtuin 1*
ROS: reactive oxygen species

primary concern involves the safety profile, particularly the risk of immune reactions or contamination during the cell processing stages. Furthermore, while pluripotent stem cells (like iPSCs) offer significant regenerative capacity, they carry an inherent risk of tumorigenicity and genetic instability. Regulatory and ethical barriers also remain significant, alongside the need for standardized protocols for the production and isolation of extracellular vesicles (EVs). Additionally, the variability in cell sources and culture conditions leads to inconsistent therapeutic outcomes, necessitating further long-term safety evaluations. Importantly, these limitations also reflect substantial knowledge gaps that currently hinder clinical translation. The long-term safety of stem cell–based interventions and extracellular vesicle (EV) administration, including their potential effects on genetic stability, epigenetic regulation, and offspring health, remains insufficiently characterized. Furthermore, variability in stem cell sources, isolation procedures, manufacturing protocols, and culture conditions contributes to inconsistent therapeutic outcomes across studies. The optimal cell type, dosage, route of administration, and patient-selection criteria have not yet been clearly established for different infertility phenotypes. Addressing these challenges will require

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standardized protocols, rigorous safety assessments, and well-designed multicenter clinical trials with extended follow-up to ensure the efficacy, reproducibility, and long-term safety of these emerging regenerative therapies. The major challenges and current limitations are summarized in Table 3.

Future Perspectives

Looking forward, the integration of regenerative medicine into reproductive clinical practice is expected to shift toward personalized therapy, where stem cell applications are tailored to a patient's specific ovarian profile and age. One of the most promising frontiers is the bioengineering of MSC-derived EVs with targeted miRNA cargo to maximize their regenerative potential while minimizing cellular risks(49). Furthermore, the development of synthetic ovarian niches using biomaterials aims to provide a controlled environment that mimics the natural follicular microenvironment. Combining stem cell therapies with mitochondrial replacement or advanced antioxidant strategies could also offer a multi-faceted approach to reversing age-related oocyte decline. Ultimately, large-scale clinical trials adhering to FDA/EMA (Food and Drug Administration/European Medicines Agency) guidelines will be the final hurdle to establishing these therapies as a standard of care for infertility.

These large-scale clinical trials should be designed to address specific knowledge gaps, including the precise mechanisms of action in vivo, optimal dosing and delivery methods for EVs and stem cells, long-term safety assessments, and the health outcomes of offspring. Furthermore, establishing standardized endpoints and harmonized protocols across multi-center studies will be crucial for generating robust and comparable clinical data. Future research should also focus on developing patient stratification strategies based on individual ovarian profiles to maximize the likelihood of success in specific subgroups, such as poor responders or women of advanced maternal age. These are serious prospects for infertility treatment in the next decade. It can be seen summarized in Table 4. Future clinical translation will also require carefully designed clinical trials to determine the optimal therapeutic protocols for stem cell–based interventions. Critical factors include the selection of appropriate cell sources, dosing strategies, delivery routes (such as intraovarian or systemic administration), and patient selection criteria. In addition, standardized outcome measures—including improvements in ovarian reserve markers, oocyte quality, fertilization rates, and live birth outcomes—should be incorporated into future studies. Addressing these aspects will be essential for establishing the efficacy, safety, and reproducibility of stem cell–based therapies in reproductive medicine.

Integrating Cell-Free Therapies and Artificial Intelligence

To fundamentally bypass the biosafety risks associated with live cell transplantation—such as tumorigenicity, vascular occlusion, and long-term immunogenicity—future research directions are increasingly shifting toward cell-free therapeutics. This approach focuses entirely on engineered, cell-free embryonic or mesenchymal extracellular vesicles (EVs). By pre-loading these nano-shuttles with synthetic, high-potency microRNA (miRNA) sequences designed to

Table 3. Summary of Challenges and Limitations

Category	Specific challenge/limitation	Impact on clinical application
Safety & Biological Risks	Risk of immune reaction or contamination	May cause adverse inflammatory responses in patients.
Pluripotency Concerns	Risk of tumorigenicity and genetic instability (especially in iPSCs)	Limits the use of certain stem cell type due to cancer risk.
Technical standardization	Need for standardized EV production and isolation protocols	Leads to variability in potency and therapeutic dosage.
Procedural Variability	Variability in cell source and culture condition	Makes it difficult to replicate results across different clinics.
Long-term Evaluation	Long -terms safety not fully established	Requires extended follow -up studies on offspring health.
Legal & ethics	Regulatory and ethical barriers	Slows down the transition from bench to bedside.

iPSCs : Induced Pluripotent Stem Cells , EV: Extracellular Vesicles

explicitly block granulosa cell apoptosis and enhance mitochondrial respiratory chain complexes, clinicians may enable a highly predictable and risk-mitigated therapeutic profile.Furthermore, integrating Artificial Intelligence (AI) and machine learning algorithms into the manufacturing pipeline represents a paradigm shift in reproductive biology. AI-driven deep learning models can be utilized to analyze donor cell secretomes and EV surface marker profiles in real-time(50). This predictive modeling ensures the screening and selection of ultra-pure, high-potency EV batches optimized for intraovarian micro-injection based on individual patient stratification. By merging AI-targeted bio-selection with standardized cell-free matrices, future clinical translation may facilitate the transition from proof-of-concept studies toward routine and automated clinical implementation for ovarian rejuvenation.

Proposed Conceptual Framework of Stem Cell–Mediated Oocyte Rejuvenation

Based on the current body of evidence, stem cell–mediated enhancement of oocyte quality may be conceptualized as a three-level regenerative framework. The first level involves restoration of the ovarian microenvironment through angiogenic, anti-inflammatory, and anti-apoptotic signaling. The second level focuses on cellular rejuvenation via reduction of oxidative stress and improvement of mitochondrial bioenergetics, resulting in enhanced ATP production and preservation of meiotic integrity. The third level encompasses the direct enhancement of oocyte developmental competence through extracellular vesicle (EV)-mediated communication, including the transfer of regulatory microRNAs and other bioactive molecules that support folliculogenesis, granulosa-cell function, and embryo development. This integrated framework provides a unifying perspective for understanding how different stem cell–based interventions converge to improve reproductive outcomes and may serve as a basis for future translational and clinical studies.

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Table 4. Future Perspectives

Strategy	Future Direction & Mechanism	Goal Reproductive Medicine
Precision Medicine	Patient- specific stem cell profiling based on ovarian reserve	Achieving higher success rates in "Poor Responders".
Cell – free therapy	Engineering Exosomes with specific miRNA(e.g.,miR-21)	Reducing risks of tumorigenicity and immune rejection.
Tissue Engineering	Scaffolds ad synthetic ovarian niches	Supporting follicular growth an artificial environment
Combined Therapies	Stem cells + Mitochondrial transfer + Antioxidants	Synergistic restoration of oocyte quality in aged ovaries
Regulatory Maturation	Standardizing protocols for FDA/EMA compliance	Facilitating the transition from research to clinic

FDA/EMA : Food and Drug Administration/European Medicines Agency

Table 5. Final summary

Section	Key Takeaway
Core Problem	Decline in oocyte quality & ovarian reserve
Main Solution	Stem cells (MSCs , iPSCs) & their secretome
Mechanisms	Anti-oxidation , mitochondrial recovery , & P13K/AKT signaling
Outcome	Higher fertilization rate & improved embryo competence
Future Tasks	Standardization of EV protocols & clinical safety trials

MSCs :Mesenchymal Stem Cells , iPSCs : Induced Pluripotent Stem Cells
P13K/AKT : phosphatidylinositol 3-kinase/protein kinase B
EV: Extracellular Vesicles

Conclusion

In conclusion, declining oocyte quality remains a primary obstacle in reproductive medicine, particularly in cases of advanced maternal age and diminished ovarian reserve. This review highlights that stem-cell-based approaches, ranging from Mesenchymal Stem Cells (MSCs) to induced Pluripotent Stem Cells (iPSCs), offer transformative potential for ovarian rejuvenation and improved embryo development. The therapeutic benefits are largely driven by paracrine signaling, specifically through the action of extracellular vesicles (EVs) and exosomes, which mitigate oxidative stress, restore mitochondrial function, and enhance the follicular microenvironment. While preclinical evidence is compelling, clinical translation faces hurdles such as the need for standardized protocols, long-term safety assessments, and ethical considerations. These challenges reflect fundamental gaps in our current knowledge regarding the long-term safety of stem cell–derived products, the reproducibility of EV-based interventions, and the identification of reliable biomarkers to monitor therapeutic response. Addressing these issues through well-designed clinical

trials and international collaboration will be essential to move from proof-of-concept studies toward routine clinical implementation. Future research should focus on bioengineering cell-free therapies and personalized regenerative strategies to establish these novel interventions as a safe and effective reality in fertility clinics. Table 5 summarizes the major findings discussed in this review.

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