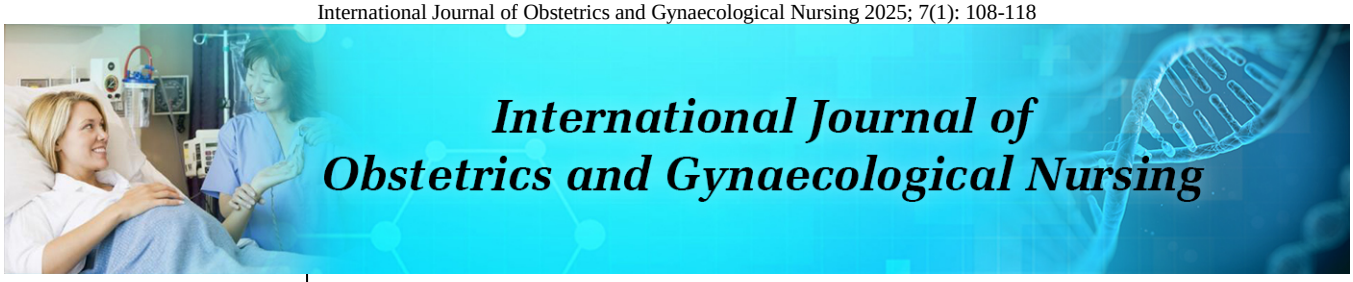

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A review on stem cell therapy for ovarian failure and infertility

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Abstract
Women worldwide face reproductive difficulties including ovarian failure and infertility because of conditions such as premature ovarian insufficiency (POI) and chemotherapy-induced ovarian damage and age-related ovarian reserve decline. The current medical treatments of hormone replacement therapy (HRT) and assisted reproductive technologies (ART) provide relief through symptoms management or reproductive alternatives yet they fail to activate the ovaries' natural operation. Stem cell therapy has recently appeared as a promising regenerative treatment which shows potential to bring back the dual endocrine and reproductive capabilities of damaged ovarian tissue.
The evaluation examines the different stem cell types used for ovarian regeneration including MSCs, ESCs and iPSCs. The article explains how these cells achieve ovarian repair by enabling angiogenesis together with anti-apoptotic effects and immunomodulation and endogenous follicle recruitment. The evaluation examines both positive research results and current study constraints in preclinical and clinical investigations.
The review examines essential ethical matters and safety concerns by studying tumorigenicity and immune rejection and moral issues related to ESC use. The review investigates stem cell research activities across different regions including Arab nations and it outlines future research directions that require standardized methods and extended patient monitoring and regulatory guidelines. Stem cell therapy remains in its initial clinical development yet demonstrates potential to restore fertility while enhancing the quality of life for women with ovarian failure.

Keywords: Ovarian failure, stem cell therapy, ovarian regeneration, reproductive medicine, premature ovarian insufficiency

Introduction
The main issue in reproductive medicine which is primary ovarian insufficiency (POI) leads to infertility problems among women who are of childbearing age. The condition known as POI leads to ovarian dysfunction before age 40 which results in irregular periods or no menstruation and elevated gonadotropin levels and decreased estrogen production [1]. The causes of ovarian failure remain unknown in some cases but medical evidence shows that genetics and autoimmune reactions and iatrogenic treatments like chemotherapy and radiotherapy commonly lead to this condition. The inability to conceive because of infertility produces major psychological and emotional distress and physiological complications in addition to childbearing difficulties. The standard treatments for POI which include hormone replacement therapy (HRT) and assisted reproductive technologies (ART) such as oocyte donation serve to control symptoms or facilitate pregnancy using donor gametes but they cannot bring back natural ovarian function [2].
The field of regenerative medicine has emerged as a promising field which searches for new therapeutic strategies to treat ovarian failure and its associated infertility during recent years. The medical community has focused on stem cell therapy because it demonstrates potential to repair harmed tissues and revive normal bodily operations [3]. Stem cells maintain the dual capability of self-renewal and cell type differentiation which makes them suitable for addressing ovarian insufficiency causes through tissue regeneration or reactivation. Research involving stem cell types such as MSCs ESCs iPSCs and OSCs has been conducted in animal models and human subjects through preclinical and early-phase clinical studies to produce encouraging yet preliminary results [4]. This review aims to evaluate stem cell-based treatments for ovarian failure and infertility by studying their current development and

future prospects to identify potential advancements in fertility preservation for women with these conditions.

Stem Cells

Stem cells constitute a special and highly diverse group of cells distinguished by their capacity to self-renew as well as to develop into multiple specialized cell types (Figure 1). Stem cells differ from typical somatic cells because they exhibit endless replication and generate progenitor cells that lead to tissue and organ formation in the human body [5]. Their exceptional features position stem cells at the core of developmental biology research as well as regenerative medicine and cellular therapy. Stem cells exist in three main categories: embryonic stem cells (ESCs) which derive from blastocyst inner cell masses and develop into all three germ layers (ectoderm, mesoderm and endoderm) and adult or somatic stem cells such as mesenchymal stem cells (MSCs) that have multipotency to repair tissues within their lineage and induced pluripotent stem cells (iPSCs) which convert adult somatic cells into pluripotent cells like ESCs while bypassing ethical concerns about embryonic sources (Figure 2) [6]. The source of stem cells depends on therapeutic goals since they can originate from bone marrow adipose tissue umbilical cord blood and dental pulp. The regenerative properties of stem cells are under investigation for treating premature ovarian insufficiency and endometrial dysfunction and low sperm count in men within reproductive medicine. Stem cells exhibit therapeutic strength mainly through their ability to repair damaged tissue by direct differentiation and their paracrine mechanisms that produce cytokines and growth factors to activate endogenous repair systems in neighboring cells [7]. Research now indicates stem cells may use mitochondrial transfer as a mechanism to restore energy production and decrease oxidative stress in damaged cells. The combination of stem cells with engineered tissues and gene editing tools allows researchers to develop functional three-dimensional tissue structures using scaffolds and biomaterials [8]. Stem cells will act as essential therapeutic tools in medical fields because they overcome various challenges regarding safety duration and clinical protocol standardization and tumor prevention [9].

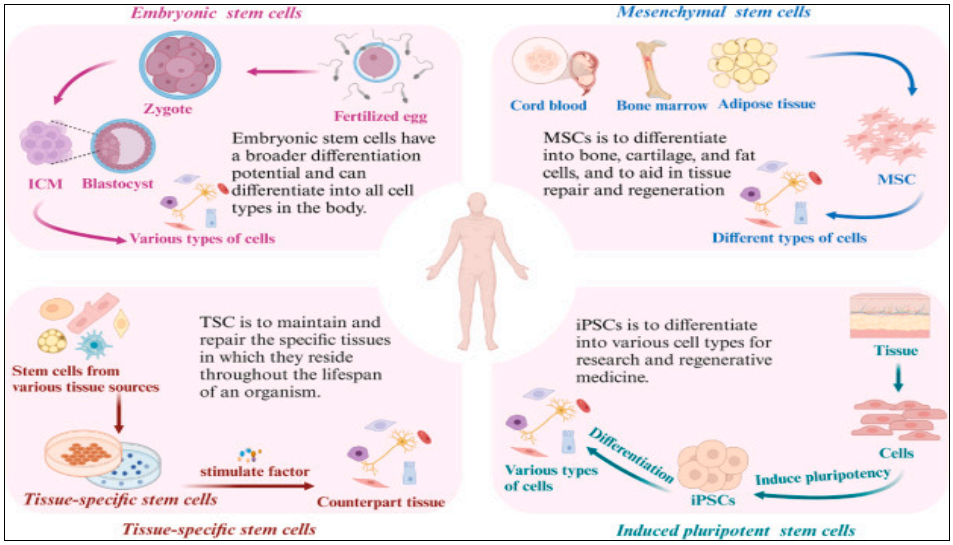

Fig 1: Stem cell types

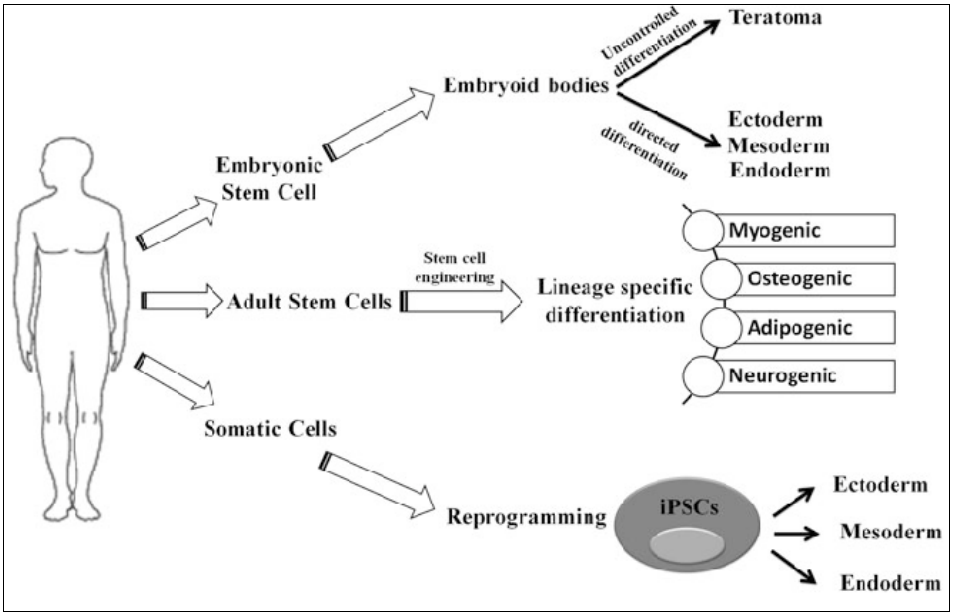

Fig 2: Adult stem cells with their differentiation capacities.

Mechanisms of Stem Cell Therapy in Ovarian Function

The treatment of ovarian failure with stem cells depends on multiple biological processes which work together to bring back ovarian function. The complex mechanisms consist of multiple steps which include direct cell-to-cell interactions and indirect molecular signals. The comprehension of these mechanisms enables better therapeutic protocols and improved results and risk reduction [10].

The main way stem cells help ovarian regeneration involves their transformation into cells resembling ovarian tissue (Figure 3). Stem cells including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) exhibit the capability to develop into granulosa-like cells and other ovarian cell types during laboratory experiments. The differentiated cells can substitute damaged or depleted cell populations in the ovary by replacing granulosa cells which help oocyte maturation and produce estrogen. Stem cell integration into ovarian tissue for supporting folliculogenesis remains a major scientific hurdle although researchers have demonstrated some follicular development support [11].

The paracrine signaling mechanism plays a crucial role through growth factors and cytokines and extracellular vesicles (exosomes) secretion by transplanted stem cells. The secreted bioactive molecules function independently of stem cell differentiation or structural integration into ovarian tissue. The secreted molecules activate resident ovarian cells while enhancing local vascularization and minimizing apoptosis and controlling the ovarian microenvironment [12].

The tissue repair and angiogenesis in ovarian tissue receives major support from vascular endothelial growth factor (VEGF) alongside insulin-like growth factor-1 (IGF-1) and basic fibroblast growth factor (bFGF). MSCs achieve better tissue repair through their anti-inflammatory and immunomodulatory properties which create a favorable immune environment while reducing local inflammation [13].

Stem cell therapy has the ability to activate endogenous ovarian stem cells when they exist especially in the ovarian surface epithelium. Research on adult women's ovarian stem cells shows conflicting results about their existence and functional importance but some studies indicate that external stem cells can activate inactive follicles and enhance the growth and differentiation of remaining germline stem cells. The reactivation process has the potential to bring back some ovarian function in women who have POI [14].

Stem cells promote angiogenesis which involves the development of new blood vessels as a fundamental biological process. The blood supply deficiency in damaged ovarian tissue accelerates follicular atresia. Stem cells promote new blood vessel formation through VEGF and related signaling molecules which leads to proper tissue recovery and follicular development by establishing sufficient oxygenation and perfusion [15].

The last proposed mechanism of action involves mitochondrial transfer (Figure 4). New research demonstrates that stem cells can transmit functional mitochondria to damaged somatic cells through tunneling nanotubes or microvesicles. The mitochondrial transfer process enhances metabolic function in ovarian cells especially in tissues that have aged or been damaged by chemotherapy [16].

The therapeutic value of stem cells for ovarian failure extends beyond basic cell replacement because of these mechanisms. The regenerative power of stem cells stems from their complex relationships with ovarian tissue microenvironment and their secreted factors and their capacity to activate the body's natural repair processes [17]. The development of safe clinical applications for infertility and hormonal dysfunction treatment requires complete understanding and effective utilization of these pathways [18].

Types of Stem Cells Used in Ovarian Regeneration

Researchers have investigated different stem cell types for ovarian regeneration purposes while studying their distinct features and benefits and constraints. The scientific community has extensively researched mesenchymal stem cells (MSCs) because these adult stem cells possess multiple differentiation potential to become osteoblasts adipocytes chondrocytes and granulosa-like cells under particular conditions. MSCs derive from bone marrow adipose tissue and umbilical cord tissue because they show low immunogenicity and simple isolation methods and strong paracrine signaling activity.

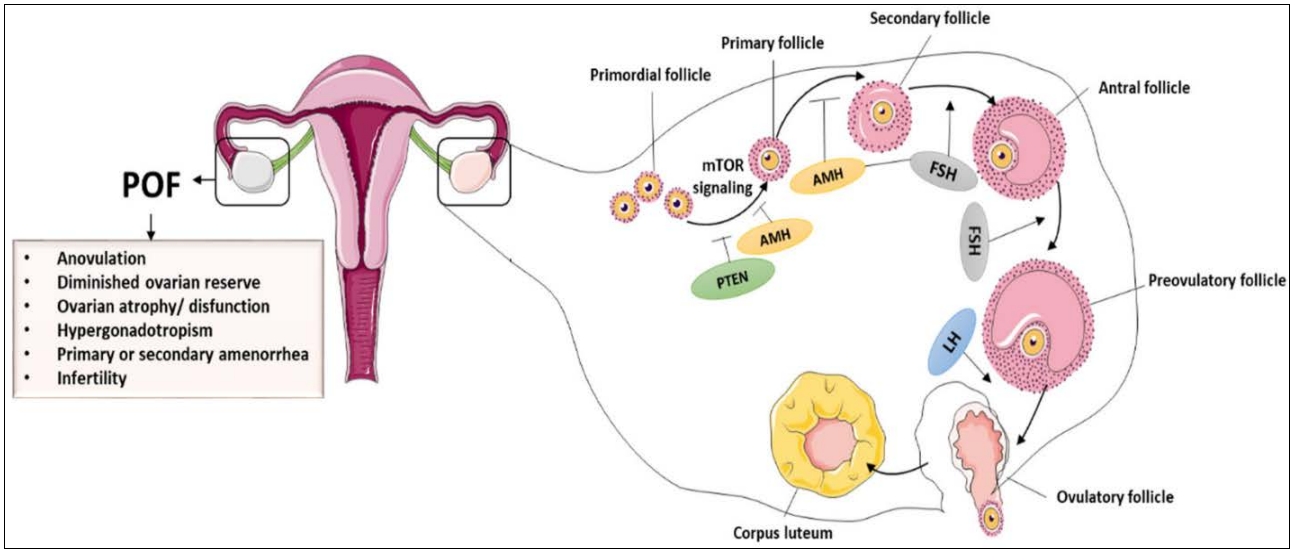

Fig 3: Stem Cell Mechanisms in Ovarian Regeneration

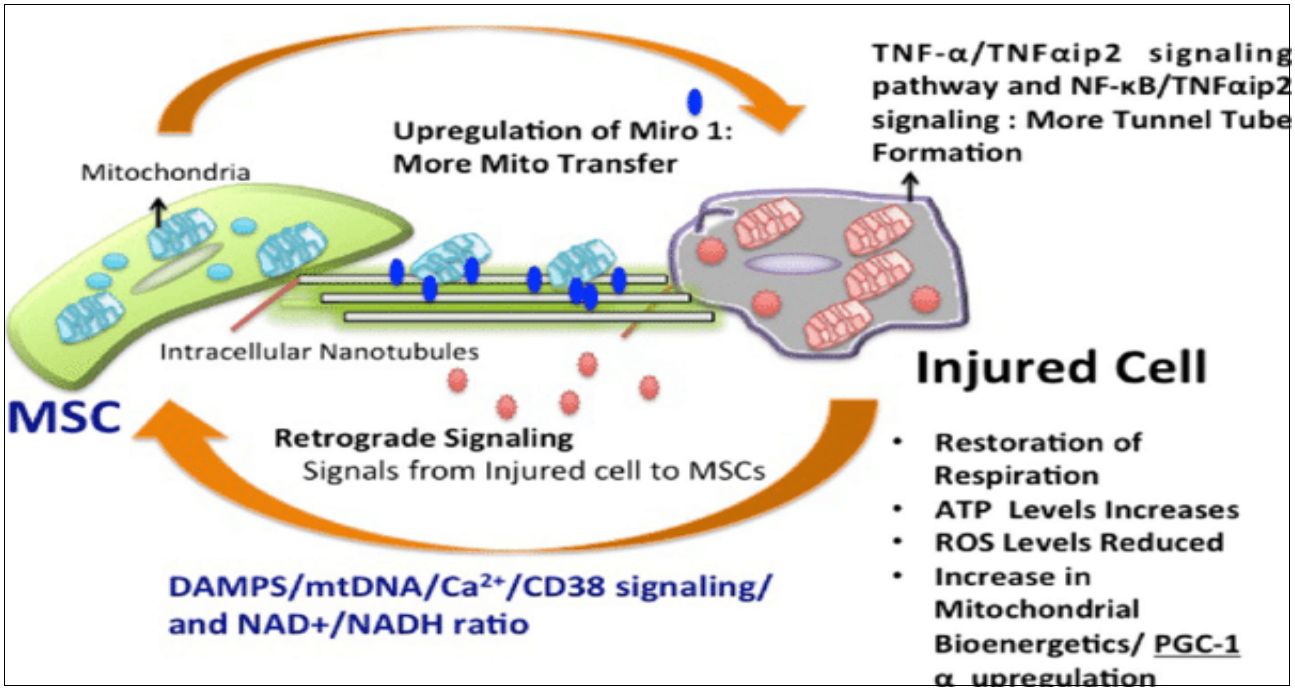

Fig 4: Mechanism of Mitochondrial Transfer

The secreted cytokines and growth factors from these stem cells support tissue regeneration and inflammation suppression while stimulating angiogenesis and potentially activating dormant follicles [20]. The pluripotent state of induced pluripotent stem cells (iPSCs) allows these genetically reprogrammed somatic cells to develop into almost any cellular type including ovarian cell types. The ability of iPSCs to produce granulosa-like cells and oocyte-like cells in laboratory settings makes them a promising yet complex and ethically sound choice compared to embryonic stem cells [21].

The inner cell mass of blastocysts provides embryonic stem cells (ESCs) which demonstrate true pluripotency while researchers use them to create ovarian structures and oocyte-like cells in experimental models. The implementation of these cells remains disputed because of moral issues and the danger of developing teratomas. The scientific community has recently started discussing ovarian stem cells (OSCs) which are believed to exist within the ovarian surface epithelium [22]. The existence of adult human ovarian stem cells remains unclear but researchers have discovered cells with germline potential which show promise as a natural source for ovarian regeneration [23]. The different stem cell types bring forth distinct difficulties and possibilities. The current clinical use of MSCs stands as the most practical and safest option because of their established safety profile and anti-inflammatory properties even though iPSCs and ESCs provide wider regenerative capabilities but encounter technical and ethical challenges [24]. Additional comparative research must be conducted to determine which stem cell source will provide the most effective and safe treatment for clinical ovarian restoration.

The Historical Development of Stem Cell Use in Reproductive Medicine

Stem cells have undergone significant development as medical tools in reproductive medicine since the beginning of the twenty-first century. The scientific community started exploring stem cell regeneration for damaged reproductive tissues during the early 2000s when the field first emerged as a theoretical concept. Scientists demonstrated the first major breakthrough in 2004 when they proved that bone marrow-derived cells migrated to ovarian tissue while showing the ability to integrate within it (Figure 5) [26]. The groundbreaking discovery triggered numerous animal-based studies that demonstrated MSCs along with stem cells could enhance ovarian structure and function in premature ovarian failure caused by chemicals. The advancement of molecular biology techniques during 2006-2007 resulted in the creation of induced pluripotent stem cells (iPSCs) through somatic cell reprogramming which provided scientists with an ethically sound replacement for embryonic stem cells [27]. The *in vitro* creation of oocyte-like cells from both ESCs and iPSCs became a major breakthrough in cellular therapy potential for infertility when scientists reported this achievement in 2010 [28]. The human clinical study by Weiss *et al.* (2013) introduced autologous stem cell ovary injections that led to initial indications of menstrual returns and follicle development [29]. The experimental research showed that cell-based therapies demonstrated potential to restore ovarian endocrine and reproductive function while supporting its use for restoration purposes [30]. Research on ovarian stem cells (OSCs) reappeared after 2015 when Heldman *et al.* suggested adult ovaries might contain dormant germline stem cells that could become reactivable through external stimuli or cellular therapies. The theory about OSCs remains disputed but expanded the range of potential regenerative targets [31]. The development of stem cell therapy within reproductive medicine shows a fast-paced transition from laboratory research to clinical practice which advances because of medical requirements and technological developments. Current clinical trials continue to assess safety and efficacy while striving to establish new standards for infertility treatment [31].

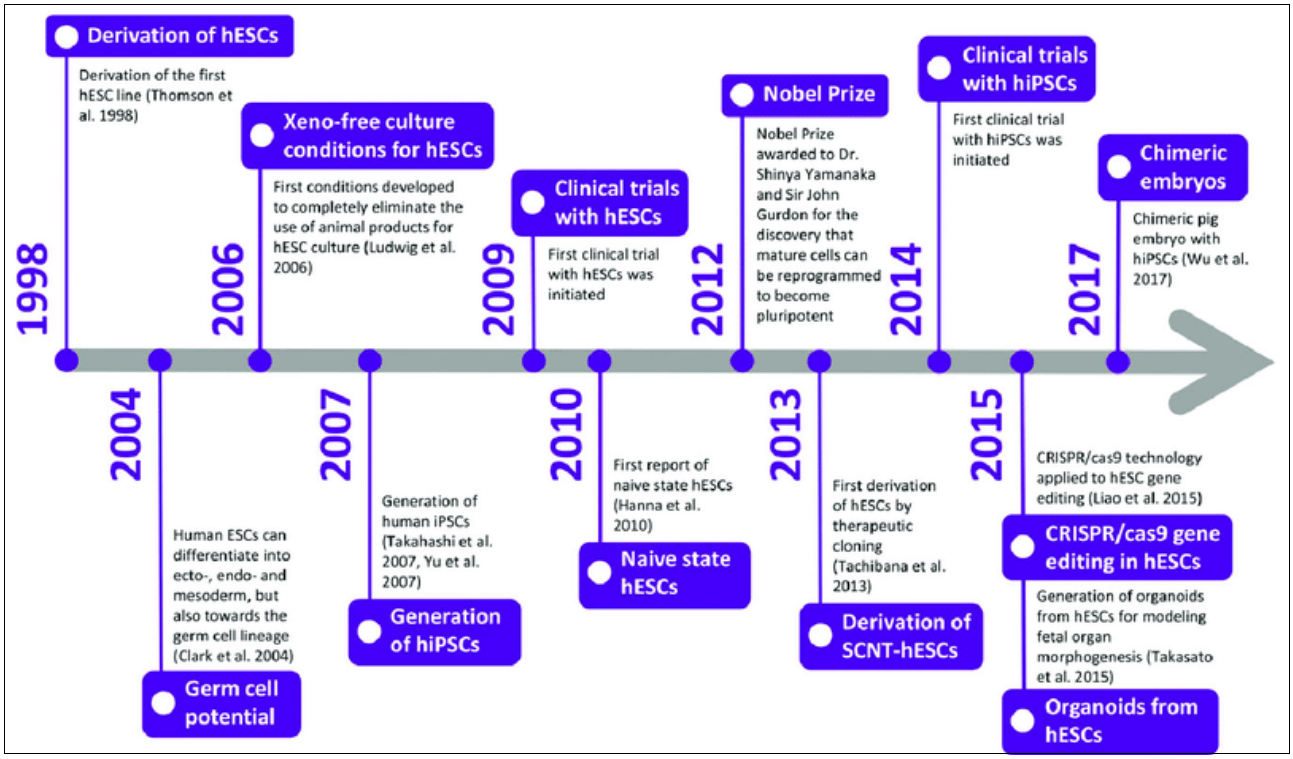

Fig 5: Timeline of Major Scientific Milestones in Stem Cell-Based Reproductive Medicine

Stem Cell Clinics and Research Centers Using Stem Cell Therapy for Ovarian Regeneration and Infertility

Research into stem cell therapy for ovarian regeneration and infertility has expanded in recent years because it shows promise to revive ovarian function and address infertility issues resulting from multiple conditions. Multiple research institutions together with hospitals and clinics worldwide conduct pioneering studies in this field by implementing different stem cell types including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) as well as embryonic stem cells (ESCs) and ovarian stem cells (OSCs). The centers focus on tissue regeneration of damaged ovaries while balancing hormones and enhancing fertility in women who have POI or chemotherapy-induced ovarian failure or age-related fertility decline [33].

The Cleveland Clinic leads the world in ovarian regeneration research through its work with induced pluripotent stem cells (iPSCs). The research at this institution focuses on creating oocytes from iPSCs to assist women without ovarian function to become mothers. The research team investigates the application of adipose tissue-derived MSCs for enhancing ovarian function in models of chemotherapy-induced ovarian failure. The research describes stem cell therapy procedures for ovarian rejuvenation and natural fertility restoration in women with diminished ovarian reserve [34].

The New York Stem Cell Foundation (NYSCF) actively participates in stem cell research for reproductive medicine including ovarian regeneration. They have utilized adult stem cells together with iPSCs to create ovarian tissue while enhancing the quality of oocytes in preclinical models. Their research effectively connects fundamental scientific discoveries to clinical practice for women experiencing infertility because of aging or chemotherapy treatment [35].

Several European research institutions are presently working on the development of stem cell therapy for ovarian regeneration. Instituto Valenciano de Infertilidad (IVI) Spain operates as one of Spain's leading fertility clinics and actively participates in mesenchymal stem cell (MSC) ovarian rejuvenation research. IVI has performed clinical trials using adipose tissue-derived MSCs to treat women with POI. The primary goal aims to trigger ovarian function so women can achieve natural conception. Their primary interest lies in autologous stem cell therapies because they use patients' own cells to prevent immune system rejection problems [36].

The University of Oxford Gynecology and Reproductive Medicine Research Group represents another institution which participates in female fertility stem cell research. They explore stem cell applications for creating oocytes along with restoring the ovarian reserve of women suffering from infertility because of various conditions. The research group focuses on using iPSCs together with MSCs for ovarian function and fertility restoration [37].

Stem cell research progresses rapidly throughout Asia because numerous clinical trials with stem cells for ovarian regeneration occur in China and India. St. Mary's Hospital in China has utilized bone marrow-derived MSCs to treat women with chemotherapy-induced ovarian failure. Their clinical trials involve stem cell ovarian transplantation for women with ovarian damage from cancer treatments to resume their hormonal function and menstrual cycles. The initial research shows women can recover their ovarian capability to reproduce [38].

Care Clinic in India has been employing adipose derived stem cells to treat premature ovarian insufficiency (POI). The clinic's research includes a clinical trial in which autologous adipose-derived stem cells are injected into the ovaries of women with POI. The goal is to activate the ovarian tissue, normalize the hormonal levels and possibly help these women to get pregnant naturally. Some initial success has been reported by the clinic with patients reporting improved menstrual cycles and ovarian function post treatment [39]. Stem cell therapy for ovarian

regeneration is also being tried in the Arab world, where a number of hospitals and research institutions are carrying out clinical trials and research on stem cells for reproductive health.

The Stem Cell Therapy Center in Dubai operates as a leading UAE clinic which provides stem cell therapy for ovarian regeneration. The center performs clinical trials using adipose derived mesenchymal stem cells (MSCs) to treat women with premature ovarian insufficiency and chemotherapy induced ovarian failure. The procedure starts with stem cell extraction from patient adipose tissue before laboratory processing and ending with stem cell reinjection into ovaries to initiate ovarian rejuvenation. The treatment objective is to restore hormonal equilibrium and reproductive ability in women who experience early ovarian dysfunction [40].

The King Faisal Specialist Hospital in Riyadh performs stem cell research for ovarian regeneration within their facilities. The clinical trials at this hospital include MSC therapies for women who have premature ovarian failure or chemotherapy-induced ovarian damage and infertility. The hospital works with research institutions to evaluate stem cell treatment as a potential solution for restoring ovarian function and hormonal balance and fertility in these patients [41].

The research on stem cell therapy for ovarian tissue repair happens through a partnership between Qatar University and Hamad Medical Corporation. The research team studies how MSCs and iPSCs function to restore ovarian tissue while improving fertility results through this partnership. The research collaboration conducts preclinical and clinical studies to create safe therapeutic interventions for women with ovarian failure caused by different medical conditions [42].

Preclinical and Clinical Studies on Stem Cell Therapy for Ovarian Failure and Infertility: The main evidence for stem cell treatment of ovarian dysfunction is based on preclinical studies that use models of premature ovarian insufficiency (POI) and chemotherapy-induced ovarian damage. Research studies evaluate different stem cell types to determine their capability for ovarian function recovery as well as hormone production enhancement and damaged ovarian tissue rejuvenation [43, 44]. Preclinical research using Mesenchymal Stem Cells (MSCs) in Animal Models has become widespread because MSCs are derived from adipose tissue as well as bone marrow and umbilical cord tissue. MSCs have proven successful in multiple preclinical research studies to bring back ovarian function by releasing growth factors and cytokines which stimulate tissue repair and minimize inflammation. MSCs introduced either through intravenous infusion or direct ovarian injection have shown promise in animal studies which resulted in enhanced ovarian follicle development and restored estrous cycle and hormonal balance. MSC-based therapies show potential for treating ovarian failure that occurs after chemotherapy or radiotherapy according to research findings. Ai *et al.* (2023) employed adipose tissue-derived MSCs in their mouse model study of chemotherapy-induced ovarian failure. The research demonstrated that MSCs enhance ovarian follicle development and bring back estrous cyclicity which indicates therapeutic possibilities for chemotherapy-induced ovarian failure in women [46].

The use of iPSCs alongside ovarian regeneration has attracted notable interest because these cells develop into oocyte-like cells as well as granulosa-like cells when cultured in laboratory settings. Research using adult somatic cell-derived iPSCs has shown that these cells can return to pluripotency before developing into gonadal cells. Animal model research demonstrates that iPSCs can develop into ovarian tissue which shows promise for enhancing ovarian reserves and fertility in aged or chemoterapeutically treated animals. The clinical use of iPSCs remains limited by genetic instability as well as tumorigenic potential that needs additional development for safe application [47]. Takahashi & Yamanaka (2006) performed preclinical research by converting adult mouse fibroblast cells into iPSCs which subsequently produced oocyte-like cells. The implanted cells in ovaries of sterile mouse models brought back ovarian function and enhanced fertility rates [48].

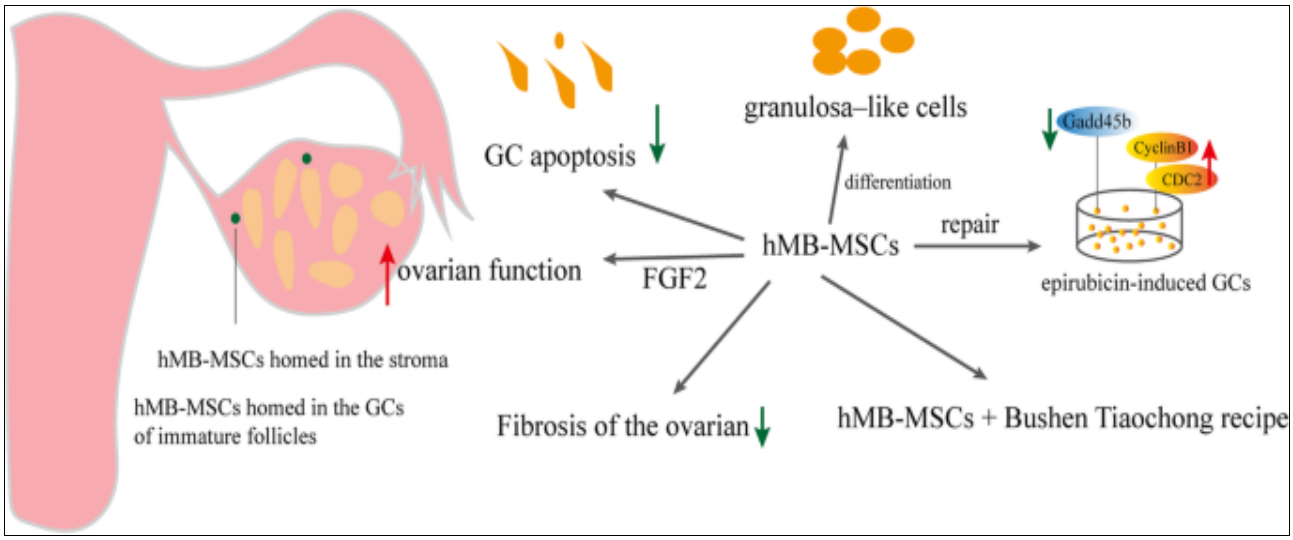

Fig 5: Mesenchymal Stem Cell Therapy for Ovarian Regeneration

Ethical and Safety Considerations in Stem Cell Therapy for Ovarian Failure and Infertility: The implementation of stem cell therapy for ovarian failure and infertility requires thorough evaluation of ethical and safety aspects to establish treatment feasibility and patient acceptability. The evolution of stem cell research and clinical applications requires thorough examination of potential risks and benefits together with ethical implications for responsible use in reproductive medicine [49].

The ethical issues surrounding stem cell therapy for ovarian regeneration stem mainly from the potential modifications to human reproductive abilities and the utilization of human biological resources including eggs embryos and stem cells. The following ethical concerns are particularly important:

The ethical debate surrounding embryonic stem cells (ESCs) emerges from their need to derive them from human embryos. The procedure to obtain ESCs leads to embryo destruction which creates moral conflicts about embryo status and life rights. Different cultural and religious groups across the world present varying perspectives about embryo sanctity because some people deem embryo destruction to be unethical. The ethical discussions about ESCs frequently shape both regulatory frameworks and public policies that govern their medical research and therapeutic applications. Various nations have implemented legal restrictions that limit the creation along with research activities involving embryos. Stem cell-based ovarian regeneration faces especially sensitive ethical challenges because of embryonic stem cells [50].

Consent and Autonomy in Donating Oocytes or Gametes

The derivation of stem cells for ovarian regeneration in some stem cell therapies might require egg or gamete donations from donors. The ethical concerns about women's autonomy and informed consent when donating their eggs become a major issue. Women who provide oocytes for stem cell research or therapeutic purposes need complete knowledge about the potential dangers together with the research goals and extended consequences. The ethical problem of commercial exploitation exists when human biological material such as eggs becomes subject to market activities. The ethical concern about human gamete commodification and exploitation risks harming economically disadvantaged communities requires thorough evaluation. The ethical guidelines must protect women from being forced to donate eggs for research purposes that generate profits [51].

Germline Modification and Genetic Engineering

Stem cell therapy presents genetic modification risks to reproductive cells through germline modifications particularly when using induced pluripotent stem cells (iPSCs) or ESCs to create oocytes. Stem cell genetic modification capabilities create designer baby concerns because they allow parents to choose or alter specific genetic traits before birth. Although germline modification has not become standard in stem cell therapy for ovarian regeneration it presents a potential risk which requires strict regulatory oversight. The practice of genetic engineering in human embryos or germline cells for fertility enhancement and disease elimination creates substantial ethical challenges. The possibility of unanticipated genetic mutations together with genetic discrimination exists as concerns for future generations [52].

Reproductive Autonomy and Social Justice

Stem cell therapy may be able to restore fertility in women who have developed ovarian failure because of age, medical treatments, or disease. However, access to these therapies may not be equitable, and there may be concerns about social justice. These therapies are often expensive, and the availability of stem cell treatments could be limited to affluent populations, leaving others with less access to this potentially life changing technology. It is an important ethical challenge to ensure that stem cell therapies are made accessible to a diverse population of women, regardless of socioeconomic status. Policy makers and clinicians must strive for equitable distribution of medical treatments [53].

Safety Considerations in Stem Cell Therapy for Ovarian Failure: Stem cell therapy safety stands as the main priority in clinical practice because stem cells can produce adverse effects when improperly managed. Patients who receive stem cell treatments for ovarian failure need protection from the following safety concerns to maintain their health and well-being.

Tumorigenicity and Cancer Risk

The main safety issue with stem cell therapy for ovarian failure is the development of tumors. Stem cells, particularly induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), are pluripotent and can develop into different types of tissues. However, this characteristic also implies that they can develop teratomas (tumours with a variety of cell types) if the differentiation process is not fully controlled [54]. In animal studies, iPSCs and ESCs have been observed to develop teratomas when grafted into tissues or organs. Tumour formation is one of the major challenges to their application in human clinical practice [55, 56].

Immune Rejection and Graft-versus-Host Disease (GVHD): The use of allogeneic stem cell transplants which involve stem cells from donors instead of patient cells presents immune rejection as a significant safety issue. The use of stem cells that are not autologous (patient-specific) creates a risk that the immune system will identify the transplanted cells as foreign leading to graft-versus-host disease (GVHD). MSCs offer low immune rejection risk because of their immunomodulatory capabilities yet this risk persists. Research has demonstrated that patients who get stem cells from another donor might develop GVHD symptoms which range from mild to severe based on the degree of immune system mismatch between donor and recipient [57].

Genetic Stability of Stem Cells

The genetic stability of stem cells is another important factor in their safety. During the process of culturing and differentiating stem cells, genetic mutations or chromosomal abnormalities may occur. Such genetic alterations may pose a higher risk of cancer or other health issues if the stem cells are to be used for transplanting into a patient. It is important that researchers should select stem cells that are genetically stable for clinical use. It has been observed that stem cells cultured for a long time may acquire genetic mutations that may affect their ability to differentiate into ovarian tissue and may also affect the therapeutic efficacy [58, 59].

Long-term Effects and Follow-up

Stem cell therapies for ovarian failure remain in their early stages so researchers have not gathered sufficient long-term data about their safety and effectiveness. Scientists have not yet fully understood the long-term consequences stem cell therapy has on fertility and ovarian function and overall health outcomes. The potential adverse effects of stem cell treatments require ongoing monitoring through comprehensive follow-up studies to detect possible tumor development and immune responses and unanticipated side effects in treated patients. Clinical trials must perform extended follow-up procedures to evaluate the results of stem cell therapy [60]. Hu *et al.* (2024) conducted research on MSC therapy for ovarian failure which demonstrated encouraging short-term results but emphasized the need for ongoing long-term evaluation of treated women's reproductive health and overall safety [61].

Challenges and Future Directions in Stem Cell Therapy for Ovarian Failure and Infertility

The clinical use of stem cell therapy for ovarian failure and infertility requires multiple challenges to be addressed before it can be used widely. The challenges range between scientific-technical hurdles and ethical and regulatory hurdles. The major hurdle in stem cell therapies is to establish their efficacy and safety levels. The current understanding of long-term treatment outcomes from stem cell therapy remains limited even though some preclinical and clinical investigations have demonstrated promising results. The ability to safely use stem cells for ovarian tissue regeneration while restoring fertility alongside hormonal function remains a critical issue because it must avoid adverse effects including tumor formation and immune rejection [62].

Standardization of stem cell protocols presents another important hurdle in the treatment process. Research studies produce inconsistent outcomes because stem cell sources differ from culture conditions to administration methods. Standardized treatment protocols must be developed through collective effort to maximize stem cell therapy results while enabling study result comparison. The supply and production capabilities of stem cells for medical applications require resolution. Using stem cells from patients' bodies (autologous stem cells) decreases immune rejection risks but the process of collecting and expanding these cells proves difficult and time-consuming for many patients [63].

The ethical debate about stem cell usage particularly focuses on embryonic stem cells. Human embryo creation regulations and human gamete commercialization need thorough development to prevent exploitation while protecting patient consent rights. The development and implementation of stem cell therapies for ovarian failure will be shaped by existing ethical and regulatory standards [64].

The future of stem cell therapy for ovarian failure and infertility will advance through better stem cell technologies which include induced pluripotent stem cells (iPSCs) along with gene editing and 3D tissue engineering approaches. The ethical problems linked to embryonic stem cells become irrelevant with iPSCs because they allow customized treatments. The CRISPR-Cas9 gene editing system together with other editing methods enables scientists to repair genetic flaws while improving stem cell regeneration abilities. Three-dimensional ovarian tissue models together with organoids create superior *in vitro* testing systems which help evaluate stem cell therapy safety and efficacy before human application [65].

Conclusion

Stem cell treatment for ovarian failure and infertility is considered one of the most promising and innovative approaches to solve the problems of reproductive health. In this review, stem cell therapy is presented as a potential treatment for women with POI, chemotherapy induced ovarian failure, and other forms of infertility with the goal of regeneration of ovarian tissue, restoration of hormonal balance, and consequently, improvement of fertility. Within the last ten years, stem cell research has made great progress, especially with regard to MSCs, iPSCs, and germline stem cells which have provided positive preclinical and early clinical data. These therapies may offer hope for women who have few reproductive options because of ovarian dysfunction.

Nonetheless, there are still some important challenges that have to be faced. However, there are still many problems that have to be solved. Stem cell therapies are significant issues that need to be controlled in both preclinical and clinical studies. To be effective and safe stem cell therapies need to go through strict testing and continuous post-market surveillance for detecting adverse effects. Other ethical issues, such as the use of embryonic stem cells and genetic modification and informed consent for gamete donation, are also major challenges that need to be addressed in order to ensure that treatments are conducted with complete ethical integrity.

These therapies need standardization of stem cell protocols to be successful and the origin of stem cells, differentiation of stem cells, and route of administration are important. Autologous stem cells are preferred because they have a lower risk of immune rejection but they are limited by availability and scalability. Also, the tumorigenic potential and genetic instability of iPSCs need to be solved before their clinical use can be generalized.

Stem cell therapy for ovarian regeneration could potentially change the field of reproductive medicine in the future. CRISPR-Cas9 gene editing technologies could potentially fix genetic defects, 3D tissue engineering and organoid development could provide more accurate models to test the safety and efficacy of stem cell therapies. Also, personalized medicine approaches like the use of iPSCs-derived patient-specific stem cells could provide a more personalized treatment with less risk and better benefit.

Conclusion: Although stem cell therapy for ovarian failure and infertility is in its infancy in terms of clinical application, it holds great promise. To overcome the problems of safety, efficacy, ethical issues, and regulatory problems, further studies are required. Thus, the future direction will require a balanced strategy of scientific advancement with ethical considerations and regulatory supervision to guarantee that these therapies will be able to be used safely and effectively to restore fertility and enhance the reproductive health of women worldwide. Therefore, further innovation and refinement of stem cell therapy may offer a solution to the growing global problem of infertility in the future.

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