

What are the applications of stem cell therapy for infertility? A literature review

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Abstract

Background/Aim: Stem cell therapy, also known as regenerative medicine, offers great promise in treating a variety of diseases that do not respond to conventional treatments. This systematic literature review aims to critically examine the latest scientific findings on the applications of stem cells in reproductive medicine. It also explores the various types of stem cells discovered to date, highlighting their advantages, disadvantages, and associated ethical considerations.

Methods: Multiple databases, such as PubMed, Google Scholar, grey literature, and the Cochrane Library, were searched for topic-relevant studies within the past 15 years. The search was restricted to the English language. However, literature from all countries was considered, provided it met the inclusion criteria.

Results: The progress of using stem cells in reproductive medicine varied from pre-clinical experiments to clinical stages in varying aspects of male and female infertility-related diseases.

Conclusion: This review highlights the remarkable advancements in the field of reproductive regenerative medicine. Large-scale randomized clinical trials are urgently needed to evaluate the safety and efficacy of stem cell therapies, particularly mesenchymal stem cells (MSCs), which have shown encouraging clinical outcomes. Additionally, MSC-derived extracellular vesicles (EVs) present a promising cell-free therapeutic strategy for infertility, warranting further research to fully explore their potential applications.

Keywords: Stem cells and infertility, reproductive medicine, stem cell therapy applications, subfertility, male infertility, female infertility, types of stem cells, stem cell advantages and disadvantages, clinical use of stem cells in infertility, stem cells and endometriosis, stem cells and non-obstructive azoospermia, stem cells and thin endometrium

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Ethics Committee Approval

This review does not involve any studies with human or animal subjects performed by the author, and therefore, the Faculty Ethics Sub-Group at the University of South Wales granted a low-risk ethical approval for the review process according to the World Medical Association's (WMA) declaration of Helsinki.

Conflict of Interest

No conflict of interest was declared by the authors.

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Introduction

Stem cell therapy, also known as regenerative medicine, offers great promise in treating diseases in the medical field that conventional methods cannot address. Stem cells, the body's raw materials, are the basic building blocks of organs, tissues, blood and the immune system [1, 2]. Under specific conditions, these cells are capable of self-renewal or differentiation into specialized cells and act as an internal repair system in the body to replace lost or damaged tissues [1].

Stem cell therapy has drawn the attention of many researchers over the past decade due to its potential to transform healthcare. Studies of stem cells enhance understanding of disease mechanisms and enable the generation of healthy cells to replace diseased ones. Additionally, stem cells provide platforms for testing the safety and efficacy of new drugs by differentiating them into tissue-specific cells [1, 2].

Infertility affects approximately 15% of couples worldwide [3]. According to WHO [4], around 48 million couples and 186 million individuals experience infertility globally, which severely impacts psychosocial well-being. Causes include male factors (30%), female factors (55%), combined factors (40%), and unexplained cases (25%) [5].

Assisted reproductive technology (ART) eliminates approximately 80% of cases of infertility; however, a significant proportion remains untreated [3]. Therefore, stem cell therapy has been suggested as an alternative, like using patient-specific gametes derived from pluripotent and induced pluripotent stem cells (iPSCs) to overcome the genetic mismatch of donor gametes [6].

Different strains of stem cells possessing the effect of antioxidation, anti-apoptosis, and angiogenesis have been isolated and cultured to regulate reproductive function and immune balance by releasing cytokines as well as exosomes, to ameliorate the reproductive microenvironment [7].

This systematic literature review aims to examine stem cell research conducted on both human and animal models, highlighting the various types of stem cells discovered to date. It assesses the advantages, disadvantages, and ethical considerations associated with each type. Additionally, the review summarizes current applications of stem cell therapy in reproductive medicine, exploring its future potential, safety, and efficacy in both males and females. Moreover, it critically evaluates the existing scientific literature and identifies key areas that warrant further clinical investigation. The review is organized thematically to enable a comprehensive and in-depth analysis of the selected studies.

Questions to be addressed in this review are:

- 1- What are the applications of stem cell therapy in infertility?
- 2- What progress has been made in reproductive medicine using stem cells?

Literature Review

Stem cells are undifferentiated cells present in embryos, fetuses, and adults, capable of producing differentiated cells. They originate primarily from early embryonic cells and adult tissues. The zygote, formed by the fusion of an oocyte and spermatozoon, initiates embryonic development. Totipotent cells, such as the

zygote and the first two dividing cells, can form any human cell type, including extra-embryonic tissues. Tissue-specific stem cells arise from differentiated organs postnatally and aid in organ repair. Major stem cell types include: embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), spermatogonial stem cells (SSCs), ovarian stem cells (OSCs), and induced-pluripotent stem cells (iPSCs) [3, 8, 9].

Embryonic Stem Cells (ESCs), which are human ESCs (hESCs), are derived mainly from the inner cell mass of pre-implantation blastocysts, express Oct4 and are pluripotent, forming all three germ layers but not extra-embryonic tissues [6, 10]. First observed in mouse blastocysts in 1981 and isolated from humans in 1998, ESCs can differentiate into primordial germ cells, undergo meiosis, and contribute to gamete formation, with hESCs also supporting endometrial repair [3, 7]. ESC-derived extracellular vesicles enhance ovarian function via the PI3K/AKT pathway in premature ovarian failure [7]. Despite their regenerative potential, ethical concerns over embryo destruction, consent, and donor safety, along with risks of immune rejection, limit clinical application [3, 7, 9].

Mesenchymal Stem Cells (MSCs), first isolated from bone marrow in the 1970s, are multipotent stromal cells capable of differentiating into osteocytes, adipocytes, and chondrocytes, while exerting immunoregulatory and trophic effects that support tissue repair [3, 10, 11]. They can be sourced from bone marrow, adipose tissue, umbilical cord, menstrual blood, amniotic fluid, placenta, and dental pulp [3, 10]. MSCs have been applied for ovarian dysfunction and endometrial disorders, promoting angiogenesis, reducing apoptosis and fibrosis, and modulating immune responses [3, 12]. Fetal MSCs exhibit higher proliferation, differentiation, and immunomodulatory capacity than adult MSCs, expressing pluripotency markers and longer telomeres, offering therapeutic advantages [3, 10].

Spermatogonial Stem Cells (SSCs) are pluripotent cells that sustain lifelong spermatogenesis within seminiferous tubules, including spermatogonia proliferation, meiosis, and spermiogenesis, with defects leading to male infertility [7, 3]. Representing a small fraction of testicular cells, SSCs can be isolated using markers such as Stra8 in mice and Thy-1, CD9, and SSEA4 in humans and rats [3, 13]. Their function depends on the Sertoli cells, and co-transplantation with growth factors, such as LIF, FGF, EGF, and GDNF, which can restore spermatogenesis in KITLG-deficient azoospermia [7, 14, 15]. SSCs can transmit genetic information, generating other tissues, and are generally considered ethically acceptable [9, 13].

Ovarian/Oogonial Stem Cells (OSCs) challenge the long-held view that postnatal mammalian ovaries lack germ cell renewal. Mitotically active germline cells have been isolated from adult ovaries in various species [6, 13, 16]. OSC lines from mouse ovarian surface epithelium express MVH, BrdU, telomerase, Oct4, and Nanog, and can generate functional oocytes in sterilized mice, producing GFP-labeled offspring [3, 7, 13, 16]. In humans, rare germ stem cells (GSCs) expressing Ddx4 can form oocyte-like structures in vitro, suggesting potential neo-oogenesis even in women with diminished ovarian reserve [7, 13]. While encouraging, their physiological role in adult ovarian function remains unclear, and in vitro oocyte maturation techniques require further refinement [16].

Induced-Pluripotent Stem Cells (iPSCs) are somatic cells reprogrammed into a pluripotent state using factors such as Oct4, Klf4, Sox2, and c-Myc, resembling ESCs in morphology, marker expression, and differentiation potential [3, 7, 10]. Derived from sources including fibroblasts and cord blood, iPSCs can be differentiated into haploid gamete-like cells expressing germ cell markers like VASA and DAZL [7]. While iPSC-derived germ cells can integrate into gonadal tissue, complete meiosis remains challenging, with regulators such as SOX17 and BLIMP1 guiding primordial germ cell specification [3, 10]. iPSCs bypass ethical issues of embryo destruction and reduce immune rejection but still require careful oversight regarding potential embryo formation and genomic integrity [3, 10, 14]. Although gametogenesis from iPSCs has been achieved in mice, translating these protocols to humans is limited and requires further validation [3, 9, 16].

Stem cell-based therapies offer significant therapeutic potential but are associated with notable risks that need to be managed carefully. These risks can generally be divided into three categories: those that are intrinsic to the cells, those arising out of manufacturing and handling, or those relating to clinical applications [17].

At the cellular level, immune rejection is a problem to be faced, particularly where sources are allogenic. Stem cells can carry pathogenic traits; the wrong cell type can literally be brought forth from an "unintentional" differentiation. Out-of-control proliferation will displace normal physiological processes with harmful cells and thus increase chances for tumor formation. [17].

During manufacturing and handling, contamination from microbes, prions, or residual chemicals remains a persistent challenge. Variability in donor material, processing errors, incomplete removal of undifferentiated cells, and problems in storage or transport can compromise cell quality and safety. Moreover, hidden viruses in donor cells can be reawakened during culture [17].

In clinical application, patients may experience problems, such as graft-versus-host disease, arrhythmias, inappropriate engraftment, etc. Treatments may not work and can be harmful, while some aspects of the damage that results from them may be irreversible [17].

Infertility affects approximately one in six couples worldwide and is defined as the failure to achieve pregnancy after 12 months of unprotected intercourse. While assisted reproductive technologies (ART) resolve around 80% of infertility cases, many challenges remain, motivating research into stem cell therapies [10, 12, 13].

Stem cell therapies are being investigated for female infertility arising from premature ovarian failure (POF), polycystic ovary syndrome (PCOS), Asherman's syndrome (AS), recurrent implantation failure (RIF), endometriosis, and fallopian tube obstruction.

Premature Ovarian Failure (POF) affects about 1% of women under 40 and is characterized by reduced ovarian reserve and low steroid hormones [7, 11, 18, 19]. Current treatments, including hormone replacement and egg donation, are limited, but MSC therapy, particularly from umbilical cord and amniotic membrane, has shown potential in restoring ovarian function, improving hormone levels, and reducing granulosa cell apoptosis [11, 12, 18]. MSC-derived extracellular vesicles (EVs) further

support angiogenesis, reduce oxidative stress, and modulate immune responses, with early clinical trials reporting spontaneous pregnancies [20].

Polycystic Ovarian Syndrome (PCOS) affects 5–10% of reproductive-age women and accounts for over 27% of infertility cases [10, 18]. MSC therapy has been shown to reduce ovarian inflammation and fibrosis, and MSC-derived EVs, which deliver miR-323-3p, enhance cumulus cell survival [3, 11].

Asherman's Syndrome (AS), caused by intrauterine adhesions, often results in menstrual irregularities and infertility [18]. Stem cell therapies using various MSC sources have improved endometrial thickness, menstrual volume, and pregnancy rates, with EVs promoting angiogenesis and reducing fibrosis through TGFβ1/Smad2 inhibition and VEGF signaling [3, 18-20].

Recurrent Implantation Failure (RIF) and Thin Endometrium present challenges in IVF, with thin endometrium (<7 mm) linked to higher miscarriage rates [18, 19]. Therapies combining endometrial MSCs (em-MSCs) and platelet-rich plasma (PRP) enhance vascularization, promote differentiation, and improve pregnancy outcomes [12].

Endometriosis affects 10% of reproductive-age women, with pathogenesis involving ectopic endometrial growth, immune dysregulation, and genetic factors [3, 18]. While MSC therapy carries theoretical risks of contributing to disease progression, MSC-derived EVs targeting angiogenesis and inflammation have shown potential in preclinical studies [18].

Fallopian Tube Obstruction impairs fertilization and embryo transport; current treatment is primarily surgical. Animal studies indicate that MSC transplantation or MSC-derived EVs can reduce inflammation and promote tissue repair, with cell-free therapies showing promise via macrophage polarization and NF-κB pathway modulation [11, 21, 31].

Male infertility arises from infections, toxins, radiation, drugs, anatomical defects, and endocrine disorders [11]. Current treatments include surgery, hormone therapy, medications, and ART, such as intracytoplasmic sperm injection (ICSI), but challenges including low success rates and lack of functional gametes remain [18]. Stem cell-based approaches include isolation and transplantation of SSCs, generation of SSCs from BM-MSCs and Ad-MSCs, and differentiation of iPSC-derived germ cells. These approaches may restore fertility in men with normal genetics, although genetic defects cannot be corrected; for example, testicular tissue preservation before puberty is recommended in Klinefelter's Syndrome, yielding about 70% sperm retrieval success [18].

Erectile Dysfunction (ED) affects over half of men older than 40 and is often linked to endothelial dysfunction from diabetes, cardiovascular disease, neurological disorders, or drugs [6, 22]. Conventional treatments, including PDE5 inhibitors, provide temporary relief without addressing underlying tissue dysfunction. Stem cell therapies, including umbilical cord, bone marrow, adipose-derived, and placental matrix stem cells, have shown encouraging improvements in penile blood flow, erection quality, and glycemic control in early clinical studies, though larger randomized trials are required to determine optimal cell type, dose, and safety [22].

Materials and methods

Inclusion Criteria: This study included all published and unpublished articles containing information on types of stem cells in both human and animal models, as well as the application of stem cell therapy for infertility in males and females. Additionally, articles involving infertile couples of reproductive age, regardless of whether the cause of infertility was known or unknown, were included if stem cell therapy was considered a potential treatment option.

Exclusion Criteria: Articles were excluded if they focused on the use of stem cells in medical fields other than reproductive medicine, were published more than 15 years ago, or were not written in English.

Outcome Measures: The primary outcomes included the identification of all stem cell types isolated, cultured, and applied in animal or human models. The study also evaluated the advantages, limitations, and ethical considerations associated with each type of stem cell. Furthermore, a comprehensive summary of current applications of stem cell therapy in reproductive medicine was developed, emphasizing accuracy, quality, and safety. Future perspectives and areas necessitating further research were also delineated.

Search Strategy: Multiple databases, including PubMed, Google Scholar, grey literature, and the Cochrane Library, were systematically searched for relevant studies published within the last 15 years. The search was restricted to English-language literature from any country. Keywords used encompassed terms such as stem cells and infertility, reproductive medicine, stem cell therapy applications, subfertility, male infertility, female infertility, types of stem cells, stem cell advantages and disadvantages, clinical use of stem cells in infertility, stem cells and endometriosis, stem cells and non-obstructive azoospermia, and stem cells and thin endometrium [8, 23].

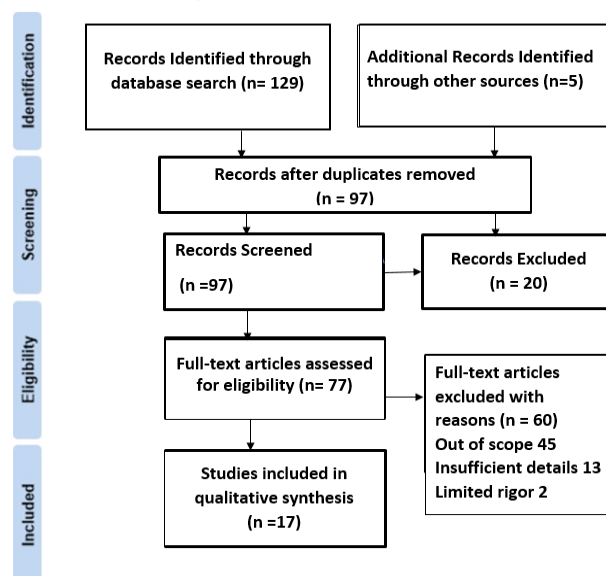
The selected studies underwent critical appraisal to eliminate irrelevant or weak evidence, reduce information overload, and ensure the inclusion of relevant, reliable, and valuable studies while identifying potential biases. As detailed in Table 1, quality assessment employed the Critical Appraisal Skills Programme (CASP) qualitative checklist tool, involving screening of titles, abstracts, and other metadata, followed by full-text article evaluation [15, 24, 25].

Data Analysis: This review followed a thematic analysis process comprising six steps: familiarization, coding, generating themes, reviewing themes, defining and naming themes, and writing up the findings. This approach was crucial in minimizing confirmation bias, which is the tendency to selectively acknowledge information that supports pre-existing beliefs while ignoring contradictory evidence. The results were summarized, with selected data presented in tabular form. Conclusions were drawn through careful interpretation of the findings [8].

Research Method: This study employed a systematic literature review design to identify, select, and critically appraise relevant literature to answer the formulated research questions. Due to its rigorous methodology and reliance on filtered, critically evaluated data, a systematic review is considered the highest level of evidence in the research hierarchy [14, 26]. The systematic review process followed the PRISMA 2020 guidelines, as

illustrated by the PRISMA flow diagram (Figure 1) [27, 28]. As the study is qualitative, the grounded theory approach was employed to analyze and categorize the data, allowing for the collection of rich, detailed information on the topic [8, 30].

Figure 1: PRISMA Flow Diagram [28]



Results and Discussion

Most of the characteristics of stem cells used in stem cell-based therapies for infertility are summarized in Table 2.

Worldwide, there are a growing number of human clinical trials investigating stem cell treatments for infertility, reflecting the hopeful results obtained from various animal studies. The application of stem cells in reproductive medicine ranges from preclinical experiments to clinical stages, targeting multiple male and female infertility-related conditions.

This review highlights remarkable ongoing progress in the field of reproductive medicine. It brings attention to the advantages, limitations, and ethical concerns associated with different types of stem cells. Mesenchymal stem cells (MSCs) have received significant attention, as they can be derived from numerous abundant and accessible sources and possess favorable biological properties. These factors include the multipotent differentiation potential, secretory activity, mitochondrial transfer, immunomodulatory and anti-inflammatory properties and their low immunogenicity – especially when dealing with autologous MSCs. Furthermore, MSCs pose minimal ethical or moral concerns, which facilitates their adoption in the field of cellular therapy.

Further clinical evaluations are needed to obtain definitive evidence supporting the effectiveness and safety of stem cell therapy in infertility. MSCs have shown promising clinical results in common male and female infertility disorders, including premature ovarian failure (POF), polycystic ovary syndrome (PCOS), Asherman's syndrome (AS), recurrent implantation failures (RIFs) endometriosis, fallopian tube occlusion, azoospermia as well as erectile dysfunction. In addition, MSC-derived EVs, which release biologically active molecules consisting of nucleic acids, lipids and proteins, are involved in several physiological and pathological processes. Cell-free treatment options using EVs for infertility also appears to be a positive approach, which could have a wide range of applications, but this needs further investigation.

Table 1: Quality assessment by using CASP qualitative checklist tool [15]

Studies	1. Was there a clear statement of the aims of the research	2. Is a qualitative methodology appropriate?	3. Was the research design appropriate to address the aims of the research?	4. Are the study's theoretical underpinnings clear, consistent and conceptually coherent?	5. Was the recruitment strategy appropriate to the aims of the research?	6. Was the data collected in a way that addressed the research issue?	7. Has the relationship between researcher and participants been adequately considered?	8. Have ethical issues been taken into consideration?	9. Was the data analysis sufficiently rigorous?	10. Is there a clear statement of findings?	Score out of 10
1-[19]	Yes	I can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
2-[7]	Yes	I can't tell	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	9
3-[9]	Yes	I can't tell	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
4-[6]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	8
5-[11]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
6-[12]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
7-[10]	No	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6
8-[20]	Yes	I can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
9-[16]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
10-[13]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
11-[29]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
12-[18]	Yes	I can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
13-[3]	No	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6
14-[31]	Yes	I can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
15-[21]	Yes	I can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
16-[22]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7
17-[17]	Yes	I can't tell	Yes	Yes	Yes	Yes	No	No	Yes	Yes	7

Table 2: Characteristics of Stem Cells Used in the Treatment of Infertility

Topics	Descriptions	References
ESCs	• ESCs Pluripotent: can differentiate into 3 germ layers (not extraembryonic). • Source: Derived from the inner cell mass of blastocyst/morula; expresses Oct4. • Germline potential: The capacity to form primordial germ cells and gametes (in vitro). • Therapeutic implications: Promote endometrial restoration, hESC-EVs modulate PI3K/AKT, and hopes for POF treatment. • Limitations: Not immune-privileged; ethics restrict clinical utility	[3, 6, 7, 9, 10]
MSCs	• Multilineage: Can give rise to mesodermal cells (bone, adipose tissue and cartilage). • Labelling (ISCT): Plastic-adherent; expression of CD105, CD73 and CD90, lack of expression of CD45, 34 (CD45RA), CD11b or CD14, CD19 or HLA-DR and cultured to chondrogenic differentiation. • Sources: Marrow, adipose tissue, menstrual blood, umbilical cord and matrix amniotic fluid and membrane, placenta/trophoblasts, salivary gland and dental pulp. • Fetal MSCs (FMSCs): Multiply more and differentiate better, display greater telomerase activity and have stronger immune modulating potential than adult MSCs. • Biological functions: Differentiation, secretion of bioactive factors, mitochondrial transfer, balanced immunomodulation, and anti-inflammation. • Ethical: Fewer ethical constraints than ESC and more widely accepted in clinical trials. • Applications: Widely studied testing for preclinical and clinical trials, such as therapies for ovarian dysfunction and endometrial disorder.	[3, 9, 10, 11, 20]
SSCs	• Nature: Pluripotent stem cells that differentiate into spermatogenic cells and undergo self-renewal throughout the life span of a male. • Isolation: Was improved by species markers; SSEA4 and GPR125 were the markers used for human SSCs. • Genetic tools: CRISPR can repair KITLG mutations (supportive cells), but not AZF region mutations (germ cells). • Application: Possible future auto-transplantation, and of promise in both fertility treatment (e.g. pre-pubertal male post chemo/radiotherapy). • Function: Transfer father's genes to his offspring. • Ethics: Not associated with additional substantial ethical requirements.	[3, 7, 9, 13, 16]
OSCs	• Discovery: Identification of germline stem cells (GSCs) in adult ovaries challenged the concept that female germ cells are non-renewable. • Significance: Recovers the idea of neo-oogenesis, offers hope for cancer patients with ovarian insufficiency (i.e., fragile X-associated and otherwise idiopathic POF, iatrogenic POF, age-related infertility). • Challenges: The technical and conceptual challenges in clinical translation are numerous • Ethics: No ethical concerns with its use.	[3, 6, 7, 13, 16]
iPSCs	• Source: Initially derived by inducing mouse fibroblasts with transcription factors; a landmark for cell therapy. • Indications: It may achieve spermatogenesis and oogenesis recovery, even in the presence of chromosomal anomalies. • Pros over ESCs: Adult-derived cells, no embryo, less chance of being controversial, and lower risk of the immune system rejecting them. • Limitations: Informed consent is required; clinical utility under evaluation.	[3, 7, 9, 10, 29]

ART: Assisted Reproductive Technology, **MSCs:** Mesenchymal Stem Cells, **MSC derived EV:** Mesenchymal Stem Cell-derived Extracellular Vesicles, **WHO:** World Health Organization, **iPSCs:** induced Pluripotent Stem Cells, **ESCs:** Embryonic Stem Cells, **SSCs:** Spermatogonial Stem Cells, **OSCs:** Ovarian Stem Cells, **hESCs:** human Embryonic Stem Cells, **ICM:** Inner Cell Mass, **IVF:** In Vitro Fertilisation, **PGCs:** Primordial Germ Cells, **FMSCs:** Foetal Mesenchymal Stem Cells, **VEGF:** Vascular Endothelial Growth Factor, **HGF:** Hepatocyte Growth Factor, **LIF:** Leukaemia Inhibitory Factor, **TGF:** Transforming Growth Factor, **Bcl-2:** B-cell lymphoma 2, **MMP:** Matrix Metalloproteinase, **Thy-1:** Thymocyte Antigen 1, **SSEA4:** Stage-Specific Embryonic Antigen-4, **KITLG:** Membrane-Bound Kit Ligand, **AZF:** Azoospermia Factor, **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats, **GSCs:** Germ Stem Cells, **FACS:** Fluorescence-Activated Cell Sorting, **-COOH:** Carboxyl, **PGC-LC:** Primordial Germ Cell-Like Cells, **POF:** Premature Ovarian Failure, **PCOS:** Polycystic Ovary Syndrome, **AS:** Asherman's syndrome, **RIF:** Recurrent Implantation Failure, **IACUC:** Institutional Animal Care and Use Committee, **ESHRE:** European Society of Human Reproduction and Embryology, **FSH:** Follicle Stimulating Hormone, **HIV:** Human Immunodeficiency Virus, **hUC-MSCs:** human Umbilical Cord Mesenchymal Stem Cells, **hAM-MSCs:** human Amniotic Membrane-Derived Mesenchymal SCs, **Ad-MSCs:** Adipose Tissue-Derived MSCs, **hMensSCs:** human Menstrual Stem Cells, **hBM-MSC:** human Bone Marrow MSCs, **IUAs:** Intrauterine Adhesions, **OS:** Oxidative Stress, **PBMCs:** Peripheral Blood Mononuclear Cells, **PRP:** Platelet-Rich Plasma, **em-MSCs:** endometrial MSCs, **ICSI:** Intra-Cytoplasmic Sperm Injection, **KS:** Klinefelter's Syndrome, **ED:** Erectile Dysfunction, **PDE5:** Phosphodiesterase Type-5 inhibitors

Conclusion and Recommendations

Infertility is a global health issue that imposes substantial psychological, social, and economic burdens on affected couples, arising from a wide range of male and female reproductive disorders. Conventional therapies, including hormonal treatments, surgical interventions, and assisted reproductive technologies, offer favorable outcomes but do not address all infertility types, underscoring the need for alternative approaches. Stem cells have considerable potential due to their capacity for self-renewal, differentiation, and secretion of paracrine factors that support tissue repair.

While human clinical trials are increasing and early results are encouraging, no stem cell therapy has yet been approved for routine clinical use. Large, well-designed

randomized trials are essential to establish the efficacy and safety of specific stem cell types, particularly MSCs, which have shown the most encouraging outcomes. Additionally, MSC-derived extracellular vesicles represent a potential cell-free therapeutic strategy, warranting further investigation to fully explore their clinical applications in infertility treatment.

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