

# Stem Cells and Treatment of Infertility: A Literature Review

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## Abstract

Infertility by the inability to achieve a clinical pregnancy after 12 months of consistent, unprotected sexual intercourse or due to an individual's diminished capacity to reproduce independently or with a partner is characterized. This paper aims to comprehensively explore infertility treatments, emphasizing the potential role of stem cells in offering effective and safe solutions. Additionally, it delves into the legal and regulatory challenges associated with stem cell research, focusing on the legislative frameworks in six major European countries. For individuals who do not benefit from traditional assisted reproductive technologies (ART), stem cell-based treatments present a promising alternative. However, ethical dilemmas and unresolved immunological concerns continue to pose significant barriers, necessitating further robust research to facilitate widespread adoption of these therapies. The ethical controversy surrounding the use of human embryonic stem cells (ESCs) arises from the requirement to destroy human embryonic tissue during their extraction. Despite these challenges, stem cell research has paved the way for significant advancements in infertility treatment. Addressing the intricate ethical and legal questions linked to these therapies will require the development of standardized, evidence-based guidelines and best practices, ensuring that patients' reproductive rights while adhering to the foundational principles of medical ethics are upheld.

**Keywords:** Infertility, Assisted Reproductive Technologies (ART), Spermatogonial Stem Cells, Ethics, Treatment

## Introduction

Infertility is defined as the inability to achieve a clinical pregnancy after 12 months of regular, unprotected sexual activity. Multiple factors are associated with this condition, including a woman's age, lifestyle choices (such as drug use, smoking, or alcohol consumption), sexually transmitted infections, pelvic inflammatory disease, obesity, polycystic ovary syndrome (PCOS), and diabetes. Additionally, structural issues like tubal, ovarian, or uterine abnormalities (e.g., endometriosis) can also contribute to infertility in women. Endocrinological disorders or genetic anomalies such as Turner syndrome or Klinefelter syndrome may also play a role. The causes of infertility are attributed to female factors in 40% of cases and male factors in another 40%, with 10–20% resulting from combined factors and 10% remaining unexplained (Figure. 1) (1).

For male infertility, conventional treatments include improving sperm quality, surgical correction of varicocele, and the use of gonadotropins or antioxidants. Female infertility treatments are diverse and may involve gonadotropins, GnRH, FSH, and LH therapies, as well as ovulation-inducing agents like clomiphene citrate or letrozole in cases of PCOS. Hyperprolactinemia may be managed with drugs like bromocriptine or cabergoline. After treatment initiation, regular monitoring of follicular development via ultrasonography is essential (2).

The most common assisted reproductive technologies (ART) include intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection

(ICSI). However, in cases where gamete deficiencies are caused by genetic abnormalities, ART alone may not suffice. In such scenarios, stem cell-based therapies present a novel and promising alternative. This review aims to investigate the potential of stem cells in infertility treatment, focusing on their efficacy and safety (3).

Aim is to explore infertility treatments, emphasizing the potential role of stem cells in offering effective and safe solutions.

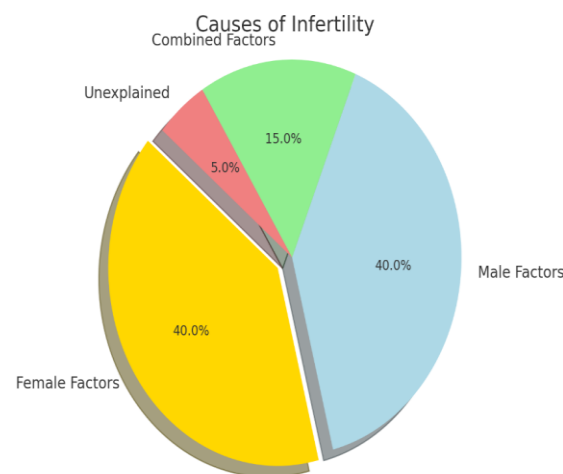


Figure 1. Causes of infertility

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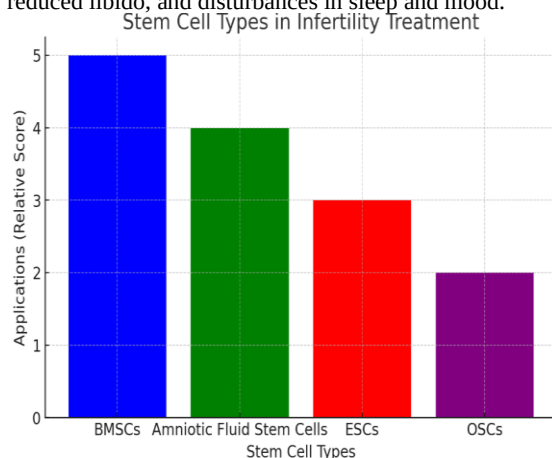
## Methods and Materials

An extensive literature search was conducted using PubMed/MedLine, Web of Science (WoS), and the Cochrane Database to identify studies examining the use of stem cells as a therapeutic option for infertility. The search strategy for clinical applications of stem cells in infertility treatments utilized a combination of keywords such as “stem cells” and “infertility—IVF.” For the ethical, legal, and regulatory aspects of stem cell research, search terms included “stem cell research ethics,” and “stem cell research guidelines and best practices.” All retrieved studies were thoroughly analyzed and selected based on their relevance and the quality of data they provided. A total of 20 sources, covering the time period from 2000 to 2023, were ultimately included in this review.

## Results

Stem cells have shown potential for application in a wide range of infertility-related conditions. One significant example is primary ovarian insufficiency (POI), a condition characterized by an irreversible decline in ovarian function. Beyond fertility issues, prolonged low estrogen levels associated with POI can lead to vasomotor symptoms, urogenital complications, osteoporosis, type II diabetes, and cardiovascular and cerebrovascular risks (4,5,6). Clinically, identifying the underlying causes of POI is critical, as it can result from factors such as follicular depletion, accelerated follicular atresia, or dysfunctional eggs. Among the promising therapeutic strategies for POI, tissue engineering approaches using mesenchymal stem cells (MSCs) have shown great potential. Studies confirm the viability of stem cell-based therapies combined with biomaterials in treating POI.

Premature ovarian failure (POF) is another prevalent reproductive disorder characterized by premature menopause, elevated gonadotropin levels, and low estrogen levels occurring before the age of 40 (7). While its exact causes and mechanisms remain incompletely understood, POF is often accompanied by a variety of perimenopausal symptoms, including hot flashes, night sweats, hair thinning, dry skin and mucous membranes, reduced libido, and disturbances in sleep and mood.



**Figure 2. The applications of different stem cell types in infertility treatments highlighting their diverse potential roles.**

Hormone replacement therapy (HRT) is the primary treatment for POF; however, the use of bone marrow mesenchymal stem cells (BMSCs) has demonstrated a positive impact on ovarian reserve function (8).

The therapeutic benefits of BMSCs are attributed to mechanisms such as homing, paracrine signaling, modulation of ovarian angiogenesis, anti-inflammatory and anti-apoptotic effects, anti-fibrosis properties, and immune regulation. Conditioned medium derived from BMSCs is rich in cytokines such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF-1). These cytokines inhibit apoptosis and promote granulosa cell proliferation both in vitro and in vivo, playing a significant role in enhancing ovarian function through BMSC-based interventions (9, 10). Stem cells are undifferentiated cells capable of self-renewal and differentiation, making them valuable for tissue repair and regeneration. As described by Saha et al. (11) there are various types of stem cells, each with potential applications in infertility treatments. Stem cell-based therapies for infertility involve either the direct transplantation of stem cells or their paracrine factors into reproductive tissues, or the in vitro differentiation of stem cells into germ cells or gametes (11).

The latter approach is particularly significant due to the multiple mechanisms through which it can operate. Paracrine factors released by stem cells can promote the differentiation of surrounding cells into mature cell lines, modulate inflammatory or reparative processes within nearby tissues, and influence the behavior of stem cells themselves, particularly mesenchymal stem cells (MSCs), which secrete these factors. These paracrine interactions also facilitate communication between stem cells and more differentiated cells, enabling reparative processes and improved tissue function. Animal studies have demonstrated the potential of these stem cell-based approaches to enhance reproductive outcomes, indicating their ability to restore or improve fertility. However, while these findings are promising, there is currently insufficient evidence to confirm their efficacy and safety in human clinical applications. Further research and clinical trials are needed to translate these experimental findings into viable human therapies (12, 13, 14,15, 16).

## Discussion

A fundamental concept in reproductive biology has been that women possess a finite ovarian reserve established at birth. However, this notion has been challenged by the discovery of ovarian stem cells (OSCs), which are believed to have the capacity to generate new oocytes under specific conditions postnatally. Nearly a decade after their identification, OSCs have been successfully isolated in both mice and humans, though their functional role remains a topic of active debate. OSCs present a promising opportunity for fertility preservation, particularly by enabling life-saving treatments without the risk of reintroducing malignant cells during transplantation (Fig.2). Recent studies have demonstrated encouraging results with ovarian tissue cryopreservation (OTC), especially for patients with oncological or autoimmune disorders predisposed to premature ovarian insufficiency or infertility. These findings suggest that OTC, combined with subsequent

transplantation, could serve as a viable alternative to hormone replacement therapy (HRT) (17). Similarly, amniotic fluid stem cells have been found to differentiate into granulosa cells, helping to prevent follicular atresia and maintain follicular health. Wang et al. demonstrated that endometrial repair and functional recovery can be achieved using human embryonic stem cell (hESC)-derived endometrial cells. These hESCs were derived from cloned blastocysts created through somatic cell nuclear transfer (SCNT), with the resulting embryonic stem cells (ntESCs) offering further therapeutic possibilities (18). In another study, highlighted the antioxidant effects of extracellular vesicles (EVs) derived from endometrial mesenchymal stem cells (EnMSCs), which were isolated from human menstrual blood. These EVs, characterized by their multipotentiality and surface marker expression, were shown to improve embryo developmental competence, likely due to their reactive oxygen species (ROS) scavenging activity. The endometrial side population (ESP), primarily composed of endothelial cell precursors, plays a critical role in uterine vascularity and implantation. Deficiencies in endometrial angiogenesis and immune regulation are major contributors to recurrent implantation failure (RIF) and recurrent miscarriage (19). Studies by Dominici et al. documented significant increases in endometrial thickness following EnMSC transfer in women with thin endometria or hypo-responsiveness to estrogen, further underscoring the regenerative potential of this approach (20).

## Conclusion

For couples unable to benefit from conventional assisted reproductive technologies (ART), stem cell-based therapies offer a promising alternative. However, ethical concerns and immunological challenges continue to pose significant hurdles. Further scientific research and conclusive data are needed before these techniques can be widely adopted for mainstream clinical use. The use of embryonic stem cells (ESCs) is particularly controversial, as their collection involves the destruction of human embryonic tissue, raising ethical dilemmas. While ESCs are genetically unrelated to patients, this aspect further complicates their use in clinical applications. Nonetheless, stem cell research has led to significant advancements in infertility treatment, offering hope for many individuals and couples. Efforts to address the ethical and legal complexities surrounding stem cell therapies must be sustained and expanded. An international consensus is crucial to prevent inequalities, such as individuals traveling to countries where specific techniques are legal while being inaccessible in their home nations due to prohibitive laws or costs. Such disparities would disadvantage those without the means to access treatments abroad.

## References

- Boulet SL, Mehta A, Kissin DM, Warner L, Kawwass JF, Jamieson DJ. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. *Journal of the American Medical Association*. 2015;313:255-63.
- Kroese ACJ, de Lange NM, Collins J, Evers JL. Surgery or embolization for varicoceles in subfertile men. *Cochrane Database of Systematic Reviews*. 2012;(10):CD000479.
- Attia AM, Abou-Setta AM, Al-Inany HG. Gonadotrophins for idiopathic male factor subfertility. *Cochrane Database of Systematic Reviews*. 2013;(8):CD005071.
- Steiner N, Ruiter-Ligeti J, Frank R, Al Shatti M, Badeghiesh A, Rotshenker-Olshinka K, et al. Do oral ovulation induction agents offer benefits in women 38 to 43 years of age undergoing insemination cycles? *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2021;258:273-7.
- Wang AT, Mullan RJ, Lane MA, Hazem A, Prasad C, Gathaiya NW, et al. Treatment of hyperprolactinemia: A systematic review and meta-analysis. *Systematic Reviews*. 2012;1:33.
- Aboulghar M, Mansour R, Serour G, Abdrazek A, Amin Y, Rhodes C. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. *Fertility and Sterility*. 2001;75(1):88-91.
- Ali I, Padhiar AA, Wang T, He L, Chen M, Wu S, et al. Stem cell-based therapeutic strategies for premature ovarian insufficiency and infertility: A focus on aging. *Cells*. 2022;11:3713.
- Ling L, Hou J, Liu D, Tang D, Zhang Y, Zeng Q, et al. Important role of the SDF-1/CXCR4 axis in the homing of systemically transplanted human amnion-derived mesenchymal stem cells (hAD-MSCs) to ovaries in rats with chemotherapy-induced premature ovarian insufficiency (POI). *Stem Cell Research & Therapy*. 2022;13:79.
- Kuchakzadeh F, Ai J, Ebrahimi-Barough S. Tissue engineering and stem cell-based therapeutic strategies for premature ovarian insufficiency. *Regenerative Therapy*. 2024;25:10-23.
- Shi L, Zhang Z, Deng M, Zheng F, Liu W, Ye S. Biological mechanisms and applied prospects of mesenchymal stem cells in premature ovarian failure. *Medicine*. 2022;101:e30013.
- Saha S, Roy P, Corbitt C, Kakar SS. Application of stem cell therapy for infertility. *Cells*. 2021;10:1613.
- Desai N, Rambhia P, Gishto A. Human embryonic stem cell cultivation: Historical perspective and evolution of xeno-free culture systems. *Reproductive Biology and Endocrinology*. 2015;13:9.
- Kehler J, Hübner K, Garrett S, Schöler HR. Generating oocytes and sperm from embryonic stem cells. *Seminars in Reproductive Medicine*. 2005;23:222-33.
- Wang J, Liu C, Fujino M, Tong G, Zhang Q, Li XK, et al. Stem cells as a resource for treatment of infertility-related diseases. *Current Molecular Medicine*. 2019;19:539-46.
- Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126:663-76.
- Murakami K, Hamazaki N, Hamada N, Nagamatsu G, Okamoto I, Ohta H, et al. Generation of functional oocytes from male mice in vitro. *Nature*. 2023;615:900-6.
- Fang F, Li Z, Zhao Q, Li H, Xiong C. Human induced pluripotent stem cells and male infertility: An overview of current progress and perspectives. *Human Reproduction*. 2018;33:188-95.

18. Hou J, Yang S, Yang H, Liu Y, Liu Y, Hai Y, et al. Generation of male differentiated germ cells from various types of stem cells. *Reproduction*. 2014;147:R179-R188.
19. Lee Y, Kang E. Stem cells and reproduction. *BMB Reports*. 2019;52:482-89.
20. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells: The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8:315-7.