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# Revolutionizing Reproductive Medicine: A Comprehensive Literature Review on Mesenchymal Stem Cells and Their Potential in Enhancing Endometrial Receptivity for Improved Fertility Outcomes

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## Abstract

**Importance:** Female infertility is influenced by genetic, lifestyle, and medical factors. Concerns about Assisted Reproductive Technologies (ART), particularly Intracytoplasmic Sperm Injection (ICSI), include risks of perinatal defects. This review examines mesenchymal stem cell (MSC) therapy as a potential solution, focusing on its role in enhancing endometrial receptivity, crucial for reproductive success.

**Objective:** The study explores how MSCs improve endometrial receptivity and fertility outcomes, aiming to address gaps in the literature, particularly during the implantation window.

**Evidence review:** A systematic review of PubMed, Embase, and Web of Science databases from the last decade identified 59 relevant articles. Selection criteria included study design, participant characteristics, MSC types, therapeutic routes, and key outcomes.

**Findings:** MSCs enhance endometrial receptivity through regenerative, immune-modulatory, and trophic effects. Molecular evidence links MSCs to critical gene expression and signaling pathways essential for implantation. Ethical considerations and the need for further research to ensure MSC therapy's safety are emphasized.

**Conclusion:** This review offers insights into MSCs' potential in reproductive medicine, highlighting the importance of ethical considerations and further research to support clinical applications.

**Keywords:** Female infertility, Assisted Reproductive Technologies (ART), Mesenchymal Stem Cells (MSCs), Endometrial Receptivity, Intracytoplasmic sperm injection (ICSI).

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**Systematic review (without meta-analysis)**

## Introduction

Worldwide, nature of reproductive health and infertility challenges arises as a complex mechanism, which is influenced by a variety of factors, including genetic predispositions to the effects of unfavorable lifestyle choices (46). Female infertility is mainly influenced by various factors, like surgeries in the pelvic or inguinal region, egg development physiology, ovulation problems, dysfunction of the ovaries, and d blockage in the fallopian tubes (1).

The worldwide prevalence of female subfertility is around 8 to 12% (14). While Assisted Reproductive Technologies (ART) give hope in improving pregnancy rates, they overcome with challenges germane to gametic production and modify the immune system (56). many reports suggest the risks relevant to the use of assisted reproductive technology (ART) in the treatment of subfertility, shows elevated perinatal risks and a greater occurrence of birth (19, 51).

Mainly after the ICSI cycles, there's a concerning of two-fold of major birth defect risks such as cardiovascular, genitourinary, and musculoskeletal systems. especially, ICSI comprises 70% of worldwide IVF treatment cycles, increasing the need to specify this major concern urgently (16, 20).

Despite of development in reproductive medicine, challenges remain for ideal fertility results worldwide. Very innovative solutions arising via stem cells techniques (Figure 1), known for their potential proliferative capacity (46), replicative character, and its capacity to differentiate into variety of tissue-specific cells, are grouped into adult stem cells, early embryonic stem cells, and induced pluripotent stem cells (iPSCs) based on their molecular origins. While adult stem cells, especially MSCs (5, 17), have demonstrated widespread usage in clinical managements, their application is in ethical and safety concerns.

A major development arises with umbilical cord stem cells (UCSTCs), showing success in Phase I clinical trials for treating subfertility due to intrauterine adhesions (IUA). These trials show no serious adverse effects, with some participants producing healthy births. A hopeful avenue in this pursuit opens within the span of regenerative medicine, specifically via the usage of MSCs (18, 40).
Subfertility managements fuel interest in non-traditional ART, mainly MSCs. These complex natures and challenges for couples who are trying for conception, showing growing interest in non-traditional ART, especially MSCs. Adult stem cells especially MSCs could upgrade the fertility medicine. They help tissue repair and immune modulation, hopeful solutions for subfertility.

Many recent studies claim their role in producing growth factors and cytokines, significantly improving ovarian function and therefore endometrial receptivity for embryo implantation. Regenerative medicine mainly coordinates with reproductive health, giving hope on innovative solutions for fertility success. Our review discusses the development in MSC therapy for subfertility managements, especially its efficacy and its unique approach. This study gives attention on its role in improving endometrial receptivity and analysis of the study.

## Objective and Rationale

This review discusses the MSCs) potential in improving fertility outcomes by enhance the endometrial receptivity. Through systematic review of existing research, we assess MSCs' science and their impact on subfertility factors such as oocyte quality, sperm function, and overall endometrial receptivity. Review the research and preclinical trials develops a scientific rationale for further discussion on MSC-based therapies in subfertility management.

## Significance of the Study

Understanding the mechanism between MSCs and endometrial receptivity is important for development of reproductive medicine. This review discusses an important gap in the literatures by detailing the comprehensive of current knowledge, discussing the potential of MSCs as a therapeutic agent. knowledge gained from this review definitely enlighten future research directions, clinical usages, and

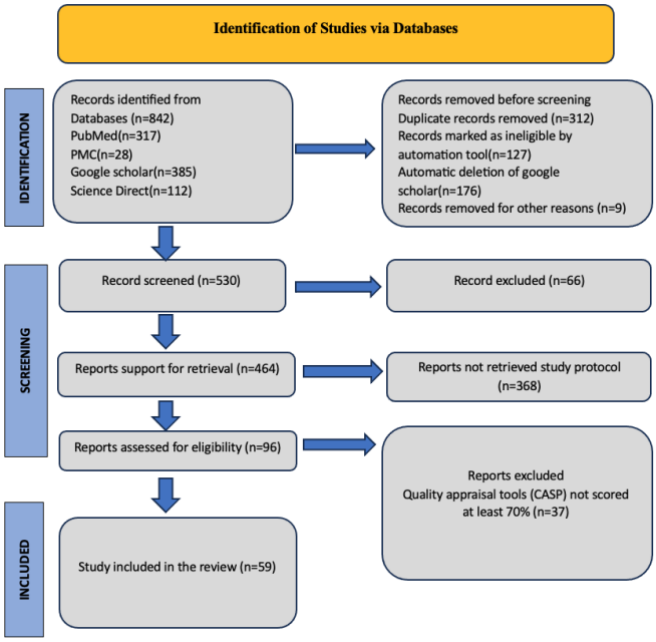
contribute to the development of specific and innovative fertility management.

## Materials and Methods

This review examined studies from the past decade on the influence of mesenchymal stem cells (MSCs) on endometrial receptivity and fertility outcomes, using databases such as PubMed, Embase, and Web of Science. Both experimental and clinical research were included. The search strategy utilized key terms related to stem cells and fertility. The study selection process began with 842 articles

(Flow chart), which were screened through a two-stage process after removing duplicates. Based on relevance and quality, 59 articles were ultimately chosen for review. Inclusion criteria focused on studies published in the last 12 years, peer-reviewed articles with accessible content, and relevant clinical and experimental studies on MSCs and endometrial receptivity.

Exclusion criteria eliminated studies with irrelevant outcomes, animal studies without implications for human fertility, and low-evidence studies. Data extraction involved collecting information on study type, participant characteristics, MSC types, administration routes, and key outcomes related to endometrial receptivity and fertility. The quality of the selected studies was assessed based on their design, sample size, and methodology. Data synthesis was performed by analyzing the key results and interventions. Finally, a critical appraisal highlighted the importance of these findings for future research and clinical practice.




**Flow Chart. Identification of Studies**

## Data Collection, Data Organization and Data Analysis:

### Endometrial Receptivity

Endometrial receptivity refers to the endometrium's ability to receive and support the implantation of a fertilized egg. The endometrium undergoes changes throughout the menstrual cycle due to hormonal influences, creating an optimal microenvironment for embryo implantation (2, 21). Critical during the implantation window (days 19 to 21 of a 28-day cycle), endometrial receptivity is assessed using ultrasound and biomarkers. A uterine lining thickness below 7 mm indicates suboptimal conditions for embryo transfer (42).

Factors contributing to a thin endometrium include inflammation, iatrogenic factors from surgeries, and structural uterine patterns (21, 42). Disruptions in endometrial physiology can hinder pregnancy, making receptivity vital for fertility (57).

Recurrent Implantation Failure (RIF) presents a significant challenge, often stemming from endometrial receptivity issues, underscoring the interaction between the embryo and its uterine environment (23, 55). Factors such as thin endometrium, hormonal imbalances, and uterine abnormalities negatively affect receptivity, contributing to unexplained infertility and impacting fertility treatments (3, 44).

### Endometrial Receptivity Assessment

Endometrial receptivity testing determines the optimal implantation window for embryo transfer by analyzing gene expression from endometrial biopsies. The endometrial state is classified as receptive, pre-receptive, or post-receptive (52). Personalized embryo transfer aims to enhance implantation and pregnancy success rates (11). However, concerns exist regarding the test's accuracy and consistency across treatment cycles. The Endometrial Receptivity Array (ERA) is one such test, but current evidence does not support its routine use (13). Kochar et al. reported that even with endometrial interventions, RIF persists; their study showed improved outcomes using Mesenchymal Stem Cells mixed with Platelet Rich Plasma (22).

### Mesenchymal Stem Cells (MSCs)

MSCs are multipotent stromal cells capable of differentiating into various cell types (25, 28). Found in tissues like bone marrow and adipose tissue, they can self-regenerate and play a significant role in regenerative medicine. Their immunomodulatory properties allow them to treat immune-related disorders through anti-inflammatory effects. MSCs also secrete growth factors and cytokines, enhancing tissue repair. Their low immunogenicity facilitates allogeneic transplantation, and they can be isolated from diverse sources for therapeutic applications.

MSCs have significant therapeutic potential, with harvesting from various tissues being crucial for regenerative medicine. Bone marrow is a primary

source, obtained through minimally invasive aspiration techniques. Adipose tissue, accessible via liposuction, is another common source for MSCs (8, 38).

Additionally, umbilical cord tissue (9), particularly Wharton's jelly, and placenta-derived MSCs are important for research and clinical use. Other sources include peripheral blood, dental pulp, synovial fluid, and amniotic fluid. The choice of source depends on access, therapeutic goals, and patient-specific needs, highlighting MSCs' versatility (25, 31).

### MSCs and Reproductive Health

MSCs show promise in enhancing endometrial receptivity and overall reproductive health (37). Their regenerative abilities allow differentiation into endometrial cells, promoting tissue repair. MSCs also possess anti-inflammatory effects (30,33, 47), reducing chronic inflammation that can impair receptivity.

Additionally, they improve immune tolerance in the endometrium, stimulate angiogenesis, and remodel the extracellular matrix, facilitating embryo attachment. Current research focuses on these mechanisms to improve fertility outcomes, highlighting MSCs as important therapeutic agents in subfertility.

## Molecular Evidence of MSCs and Improving Endometrial Receptivity

The endometrium, comprising basal and functional layers, is crucial for embryo implantation and menstruation (Table 1). Successful pregnancy relies on the interaction between a high-quality embryo and the endometrium. Recurrent Implantation Failure (RIF) occurs when good-quality embryos fail to implant despite multiple transfers, with underlying causes linked to embryo quality, maternal factors, or both. Recent studies have strongly associated RIF with endometrial function alterations (20, 39,48, 58).

Tabeeva et al illustrate the role of Mesenchymal Stem Cells (MSCs) in angiogenesis and mesenchymal-epithelial transition (40, 54), emphasizing the potential of MSCs to enhance endometrial receptivity through molecular techniques. MicroRNAs (miRNAs) (Fig 5) have been identified for their roles in post-transcriptional gene regulation, particularly concerning implantation and embryo receptivity.

Zhang et al explored the in vivo tracing of Human Umbilical Mesenchymal Stem Cells (HUMSCs) and HUMSC-exosome hydrogels in a rat model, demonstrating retention in thin endometrial tissue post intrauterine injection. Their findings highlighted the importance of dynamic protein production in the endometrium across menstrual phases, revealing receptivity signaling pathways and potential biomarkers (52).

Transcriptomic and proteomic studies have uncovered significant genes and pathways, with epigenetic modifications influencing gene expression. Investigating the immune microenvironment has revealed specific cell populations and cytokines essential for embryo tolerance. Additionally, extracellular vesicles, such as exosomes, carry critical molecular signals for endometrial health (32).

The endometrial function's temporal and spatial variations, primarily driven by hormonal regulation and paracrine factors, can lead to dysfunctions such as thin endometrium and adhesions. Asherman's syndrome often results from intrauterine adhesions post-surgery, reducing viable endometrial surface area and impairing fertility.

Cen et al suggest that MSCs can regenerate endometrial tissue in cases of intrauterine adhesions (4). They found that transplanting menstrual stem cells (MenSCs) from patients with Asherman’s syndrome resulted in restored endometrial morphology and thickness, with several patients achieving pregnancies post-transplantation (4, 26).

Sudoma et al. (38) identified a unique population of MSCs and epithelial progenitor cells in the human endometrium, pointing to low endometrial receptivity as a significant barrier to embryo implantation in reproductive-aged women. Zhao et al noted that menstrual blood-derived MSCs can modulate the EGF/Ras p21 pathway to address thin endometrium (24, 57).

**Table 1:** **Mechanisms of MSC on Improve the Endometrial Receptivity**

| Molecular Mechanism | Study/Source | Findings/Implications |
|---|---|---|
| **Angiogenesis** | Tabeeva et al., 2023 | MSCs contribute to angiogenesis in the endometrium, facilitating tissue regeneration. |
| **Mesenchymal-Epithelial Transition** | Tabeeva et al., 2023 | MSCs promote mesenchymal-epithelial transition, a critical process for tissue repair. |
| **MicroRNA Regulation** | Jin-Xiang Wu et al., 2022; Zhao et al., 2021; Marinaro et al., 2019 | Studies scrutinize microRNAs for their regulatory roles in post-transcriptional gene regulation during implantation and receptivity. |
| **Proteomic Profiling** | Sapozhak et al., 2020; Various studies | Advanced proteomic profiling unveils dynamic protein landscapes in the endometrium, shedding light on critical signaling pathways. |
| **Extracellular Vesicles** | Marinaro et al., 2019; Sapozhak et al., 2020 | Exploration of exosomes as carriers of molecular signals, including interferon-γ-inducible protein 10, interleukin-1 receptor antagonist, vascular endothelial growth factor, and more. |
| **Immunomodulation** | Gao et al., 2022; | MSCs demonstrate immunomodulatory effects crucial for embryo tolerance and tissue regeneration. |
| **Growth Factor Regulation** | Zhao et al., 2021; Sapozhak et al., 2020 | MSCs regulate growth factors, including the EGF/Ras p21 pathway, presenting a promising therapeutic target for thin endometrium. |
| **Inflammatory Priming** | Marinaro et al., 2019 | Inflammatory priming of extracellular vesicles from endMSCs, indicating potential immunomodulatory effects in endometrial healing. |
| **TGF-b Receptor Inhibition** | Gurung et al., 2018 | Inhibition of TGF-b receptor enhances anti-inflammatory, angiogenic, and proliferative processes in MSCs. |
| **Paracrine Signaling** | Sapozhak et al., 2020; Marinaro et al., 2019; Gao et al., 2022 | Paracrine interactions between stem cells and endometrial cells contribute to improved receptivity. |
| **Gene Expression Changes** | Lu et al., 2019; Esmaeilzadeh et al., 2020 | Changes in gene expression related to receptivity markers, impacting the establishment of pregnancy. Elevated expression of LIFR, ER, and PR in endometrium. |
| **Epigenetic Modulation** | Szukiewicz et al., 2021 | Epigenetic modulation in MSCs influenced by estrogen and progesterone holds potential for preventing endometriosis. |
| **Anti-Inflammatory Effects** | Perrini et al., 2016; Zhu et al., 2022 | MSC-derived microvesicles exhibit anti-inflammatory effects, alleviating endometrial inflammation. |
| **SDF-1/CXCR4 Axis** | Xia et al., 2019 | Electroacupuncture enhances BMSC migration through the SDF-1/CXCR4 axis, promoting endometrial repair. |

Although definitive markers for MSC identification are still under study, the International Society for Cellular Therapy outlines essential criteria for MSC characterization, including specific surface markers and differentiation potential (6, 34). Recent research indicates that MenSCs derived from women with thin endometrium enhance epithelial endometrial cells' proliferation and invasion without affecting apoptosis (57). Guo et al noted higher expression levels of receptivity markers in older women, although other key markers showed no significant differences between age groups (14).

Tersoglio et al demonstrated sustained increases in endometrial thickness post-MSC intervention (42), while Xin et al. reported that MSC apoptotic bodies can improve macrophage modulation and endometrial regeneration through enhanced mitochondrial bioenergetics (49). BMSCs show promise in treating conditions like intrauterine adhesions and thin endometrium due to their ability to differentiate and exhibit immunomodulatory properties (12). Studies have also indicated that adipose-derived MSCs can significantly improve uterine conditions and reduce fibrosis (50).

Zhuang et al highlighted the role of hUCMSCs (52) in recovering severe endometrial damage, suggesting that paracrine signaling mechanisms are crucial for endometrial repair (59). Sapozhak et al noted that endometrial MSCs improve receptivity in cases of thin endometrium syndrome, enhancing assisted reproductive technology outcomes (36).

Marinaro et al found that endometrial-derived MSCs enhance embryo quality and development through their extracellular vesicles, indicating potential benefits for assisted reproduction (27). Notably, endometrial MSCs show differential receptivity marker expression in RIF and non-RIF cases, with implications for understanding receptivity and pregnancy establishment (10).

Additionally, the use of innovative approaches, such as A83-01 to enhance MSC properties (15), and novel biomaterials for MSC transplantation (18), showcases the potential for integrating MSC therapy in clinical practices for improving endometrial receptivity. Overall, ongoing research into the molecular mechanisms of MSCs highlights their potential therapeutic applications for enhancing endometrial receptivity and improving fertility outcomes.

**Delivery of MSCs for Improving Endometrial Receptivity**

As described in the various studies above, improving endometrial receptivity via MSC delivery is an actively promising area, with evolving protocols and variety of strategies (Table 2).

**Evaluating Mesenchymal Stem Cell Therapy for Endometrial Receptivity**

Studying MSC therapy for uterine endothelial injury employs a systematic approach, incorporating various monitoring and assessment parameters to confirm improvements through both traditional and molecular studies (2). Imaging studies, including regular ultrasound examinations, provide vital information on uterine morphology, blood flow, and the thickness of the endometrial lining (2). Doppler ultrasound specifically assesses blood flow in uterine arteries, aiding in evaluating vascular function improvements (6).

Endometrial biopsy and histological analysis offer insights into tissue structure, vascularization, and cellular composition changes. Immunohistochemistry assesses endothelial cell marker expression, such as CD31 or vWF, which are critical for evaluating vasculogenic regeneration (4). Biomarkers related to endothelial function and regeneration, such as VEGF and angiopoietin-1, are measured to understand molecular changes within the uterine cavity. Furthermore, the assessment of inflammatory markers provides an overview of the inflammatory response.

Functional tests, such as the Endometrial Receptivity Analysis (ERA) or molecular marker analysis, enhance the success of MSC therapy by preparing the uterine environment for implantation. Patient outcomes, including pregnancy rates and menstrual cycle regularity, serve as crucial clinical markers. Tracking successful pregnancies and live births, alongside improvements in cycle regularity and symptom relief—particularly for issues related to endothelial injury—contributes to evaluating patient well-being during MSC therapy. Standardized assessments of quality of life further enhance this evaluation.

**Table 2:** Delivery Methods of MSCs in Various Modalities

| Delivery Method | Description |
|---|---|
| Intrauterine Infusion | Direct injection into the uterine cavity via catheter or hysteroscopic guidance. - Provides a localized delivery of MSCs to the target area. |
| **Systemic Administration** | Involves intravenous infusion or intra-arterial delivery into the uterine artery. - Allows for widespread distribution of MSCs throughout the body or targeted delivery to the uterus. |
| **Combination Approaches** | Inducing controlled endometrial injury before MSC delivery. - Co-administering cytokines/growth factors to enhance therapeutic effects. - Aims to create a more conducive environment for MSC action. |
| **Use of Biocompatible Scaffolds** | Incorporates three-dimensional structures for MSC delivery. - Aids in cell retention and optimization of the local microenvironment. - Offers a supportive framework for MSCs to exert their regenerative effects. |
| **Monitoring and Imaging Techniques** | Utilizes ultrasound or magnetic resonance imaging for tracking MSC location and distribution. - Essential for proper targeting and ensuring the effectiveness of the delivered MSCs. |
| **Preclinical Studies and Trials** | Thorough evaluation of safety and efficacy through preclinical studies and clinical trials. - Considers individual patient factors and specific causes of infertility to tailor the delivery method. |
| **Consultation with Professionals** | Paramount for personalized advice and treatment planning. - Involves consultation with medical professionals or reproductive specialists to guide patients in navigating the dynamic and evolving field of MSC therapy. |

Follow-up assessments, including long-term evaluations and periodic check-ins, ensure sustainable improvements and allow for adjustments to treatment plans. Molecular studies are integral in advancing our understanding of MSC therapy's effects (7). For instance, RNA sequencing provides detailed insights into transcriptome changes post-MSC therapy, while protein expression studies using techniques like western blotting assess alterations in proteins linked to endothelial function (9).

Immunohistochemistry and immunofluorescence facilitate the identification and quantification of specific proteins in tissue samples, elucidating cellular and tissue changes (45). Cytokine and growth factor analyses, conducted via enzyme-linked immunosorbent assay (ELISA), yield valuable information on the inflammatory and regenerative responses of the uterine microenvironment (41).

Molecular studies, such as DNA methylation analysis and microRNA profiling, further contribute to understanding gene expression and cellular processes (4). Next-generation sequencing techniques, including whole genome sequencing (WGS) and single-cell RNA sequencing (scRNA-Seq), provide comprehensive insights into genetic variations and cellular diversity (53). The choice of specific molecular studies depends on research objectives and advancements in the field. Continuous updates from recent literature and

consultations with experts ensure the effective application of the latest methodologies (57).

### Ethics on Using MSCs

Stem cell therapy, particularly using MSCs, has gained prominence in regenerative medicine due to their unique advantages, such as accessibility, differentiation potential, and immunoregulatory properties (51). However, challenges include population heterogeneity and safety concerns regarding tumorigenicity and embolization risks (3, 55). Despite no documented tumor cases in treated individuals, ongoing research and long-term monitoring are crucial to assess risks (29). Ethical and regulatory compliance, along with patient suitability and safety evaluations, are vital in MSC collection and therapy (6).

## Result

This literature review explores the complex molecular mechanisms of MSCs and their role in enhancing endometrial receptivity (41). Advanced techniques, including microRNA analysis, proteomic profiling, and transcriptomics, identify consistent diagnostic biomarkers in receptive endometria (3). MSCs from various sources, such as menstrual blood-derived stromal cells, bone marrow, and umbilical cord, show therapeutic potential through modulation of signaling pathways and improved endometrial regeneration, adhering to International Association of Cell Therapy criteria (2).

Investigations demonstrate post-MSC transplantation improvements in endometrial thickness and receptivity, with paracrine interactions exhibiting anti-inflammatory effects (9). Synergistic methods, like combining MSC transplantation with electroacupuncture, enhance therapeutic outcomes (43).

The review highlights the promise of MSC therapy for resolving infertility linked to uterine endothelial injury (7). It emphasizes multifaceted evaluation approaches, including imaging, biopsy, biomarker analysis, and functional tests, alongside ethical considerations regarding tumorigenicity and embolization risks. Ultimately, the review provides a comprehensive exploration of MSC therapy, advocating for continued research and clinical expertise to optimize outcomes in reproductive medicine.

## Discussion

Endometrial receptivity is crucial for fertility, referring to the uterine lining's ability to support embryo implantation (2). This temporal event occurs during the implantation window in the latter part of the menstrual cycle and necessitates precise hormonal fluctuations and structural modifications within the endometrium (35). Issues such as a thin endometrium or inflammation can hinder implantation, making endometrial receptivity vital in assisted reproductive technologies (ART). Mesenchymal stem cells (MSCs), with their regenerative and immunomodulatory properties, show significant promise in enhancing receptivity (3). Sourced from bone marrow, adipose tissue, and menstrual blood, MSCs can modulate inflammation, stimulate angiogenesis, and optimize the endometrial microenvironment.

Advanced molecular studies, including miRNA and proteomic analyses, provide diagnostic insights into receptivity dynamics. Current research emphasizes the therapeutic potential of MSCs, particularly those derived from menstrual blood, in addressing conditions like a thin endometrium. While MSCs offer significant benefits, ethical considerations must address challenges related to population heterogeneity and tumorigenicity. Optimal MSC collection methods must consider patient suitability, ethical standards, tissue source availability, and safety assessments. Clinical expertise is essential in guiding decisions within regenerative medicine.

The implications of endometrial receptivity and MSCs are significant in reproductive medicine. Understanding endometrial receptivity through molecular investigations and advanced diagnostic tools can enhance the assessment of implantation windows, ultimately optimizing ART success rates (53).

The therapeutic potential of MSCs, especially concerning challenges associated with a thin endometrium, provides a novel avenue for improving outcomes in patients experiencing recurrent implantation failure (RIF) (1). The regenerative and immunomodulatory functions of MSCs, as demonstrated in various studies, highlight their potential application in enhancing endometrial receptivity and addressing factors contributing to subfertility (2). Moreover, ethical considerations surrounding MSC use emphasize a judicious approach, ensuring compliance with established criteria and continuous monitoring of safety measures (8). As research progresses, integrating MSC-based interventions into clinical practice could offer targeted and effective therapeutic methods for

individuals facing complex reproductive challenges, contributing to advancements in fertility treatments (35).

Future research on endometrial receptivity and MSCs aims to identify molecular mechanisms using advanced omics and single-cell analyses (4). Studies should focus on optimizing MSC therapeutic potential for challenges such as RIF and thin endometrium, refining isolation, characterization, and transplantation protocols (7). Prospective studies may develop targeted diagnostic tools based on molecular biomarkers for precise timing of embryo implantation, thereby enhancing ART success rates (7).

Applications for MSCs span orthopedics, cardiovascular diseases, autoimmune disorders, and wound healing. Collaborative approaches and initiatives are defining the market landscape, influenced by regulatory frameworks and ethical considerations. MSC therapies are positioned to address specific unmet medical needs, emphasizing the importance of innovation and clinical translation. Future research must prioritize ethical considerations, safety profiles—including tumorigenic risks, standardization of MSC characterization, and long-term patient monitoring. Overall, multidisciplinary research that integrates molecular biology, stem cell biology, and clinical medicine holds the potential to revolutionize fertility treatments.

## Conclusion

In conclusion, research on endometrial receptivity and MSCs in reproductive medicine presents a multifaceted approach for future development. Understanding receptivity, alongside molecular studies and diagnostic advancements, enhances the assessment of implantation timing (Table 3). The therapeutic potential of MSCs, particularly in addressing challenges like Recurrent Implantation Failure (RIF) and thin endometrium, offers hope for reshaping clinical approaches in reproductive health.

Future research will delve into the molecular mechanisms governing endometrial receptivity using advanced technologies. Refining MSC-based interventions and developing diagnostic tools for personalized embryo implantation timing in ARTs are essential. Ethical considerations and safety profiles will remain focal points, addressing important risks and standardizing criteria. The interdisciplinary collaboration of molecular and stem cell biology with clinical reproductive medicine promises targeted therapeutic solutions for fertility challenges.

**Table 3:** **MSCs and Different Phases of Menstrual Cycle**

| Menstrual Cycle Phase | Days | Endometrial Receptivity | Mesenchymal Stem Cells Application |
|---|---|---|---|
| Menstrual (Days 1-5) | 1-5 | Low estrogen and progesterone, shedding of the endometrial lining | - |
| **Proliferative (Days 6-14)** | 6-14 | Rising estrogen levels, thickening of the endometrial lining, increased blood flow | Potential infusion of mesenchymal stem cells to support tissue regeneration and vascularization |
| **Ovulatory (Day 15)** | 15 | Surge in luteinizing hormone (LH), ovulation occurs | Mesenchymal stem cells may play a role in modulating the immune response and promoting tissue repair post-ovulation |
| **Early Luteal (Days 16-18)** | 16-18 | Increased progesterone, glandular and stromal changes, vascularization | Possible application of mesenchymal stem cells to enhance progesterone effects and support tissue remodeling |
| **Mid-Luteal (Days 19-23)** | 19-23 | Sustained high progesterone, increased glandular secretion, spiral artery development | Mesenchymal stem cells may contribute to the maintenance of a supportive microenvironment for potential embryo implantation |
| **Late Luteal (Days 24-28)** | 24-28 | Declining progesterone if no pregnancy, pre-menstrual changes, breakdown of the endometrial tissue | Mesenchymal stem cells might be applied to promote tissue repair and regeneration, potentially preparing the endometrium for the next cycle |

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