JOURNAL OF FERTILITY AND REPRODUCTIVE HEALTH
Apr-Jun 2025, VOL. 3, ISSUE 2, pp. 29-32
https://doi.org/10.61577/jfrh.2025.100006

RESEAPRO JOURNALS

MINI REVIEW

OPEN ACCESS

Stem cell applications in reproductive tissue engineering

Amisha Biswal and Priyanka Prusty
Department of Biotechnology, MITS School of Biotechnology, Odisha, India

ABSTRACT

Reproductive tissue damage caused by congenital disorders, aging, disease, or medical treatments poses significant challenges to fertility and reproductive health. Recent advancements in regenerative medicine, particularly the integration of stem cell biology and tissue engineering, offer new therapeutic possibilities for restoring reproductive function. This review highlights current developments in the application of stem cells, such as embryonic stem cells, mesenchymal stem cells, induced pluripotent stem cells, and germline stem cells, in reproductive tissue engineering. These cells, in combination with biocompatible and biodegradable scaffolds, have been explored for regenerating ovarian, uterine, testicular, and endometrial tissues. The design of biomaterial scaffolds that support stem cell differentiation, vascularization, and host integration is a critical focus. Additionally, the emergence of 3D bioprinting, organoid culture, and gene editing technologies has expanded the potential for creating functional reproductive tissues. While early-stage research and preclinical models show promise, clinical translation remains limited due to concerns about immune rejection, tumorigenicity, and long-term efficacy. Ongoing research aimed at overcoming these barriers may soon enable the development of personalized, stem cell-based therapies for treating reproductive disorders and infertility.

KEYWORDS

Tissue engineering; Regenerative medicine; Biocompatible materials; Bioprinting; Gene editing

ARTICLE HISTORY

Received 07 February 2025;
Revised 28 February 2025;
Accepted 07 March 2025

Introduction

Infertility and reproductive tissue damage affect millions of individuals worldwide, with causes ranging from congenital abnormalities and hormonal imbalances to cancer treatments and age-related degeneration. Conventional treatments, such as hormone therapy, assisted reproductive technologies (ART), or surgical reconstruction, have improved reproductive outcomes for many patients but are often limited in restoring full tissue function or offering long-term solutions. In recent years, regenerative medicine has emerged as a transformative field aiming to repair, replace, or regenerate damaged tissues using biological components [1]. Within this domain, reproductive tissue engineering has gained attention as a promising approach to treat infertility and organ dysfunction through the integration of stem cells, biomaterials, and advanced fabrication technologies.

Stem cells have the distinctive ability to renew themselves and develop into multiple cell types, which makes them promising tools for regenerating damaged tissues. Advances in stem cell biology have enabled the isolation, expansion, and directed differentiation of various stem cell types, such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and germline-derived stem cells for potential use in reproductive applications [2,3]. When combined with biocompatible scaffolds, these cells can be guided to form functional reproductive tissues such as ovarian follicles, testicular tubules, endometrial linings, and even complete organoids.

Tissue engineering technologies, including 3D bioprinting, hydrogel-based scaffolds, and microfluidic platforms, have further enhanced the precision and functionality of engineered tissues. These innovations aim not only to restore biological function but also to create disease models for drug screening and reproductive toxicity studies. Despite rapid progress in preclinical research, challenges such as immune compatibility, scaffold degradation, ethical considerations, and clinical translation remain significant.

Types of Stem Cells Used in Reproductive Tissue Engineering

In the field of reproductive tissue engineering, different categories of stem cells are utilized based on their ability to regenerate and differentiate into specialized reproductive cells [4]. Each type offers distinct advantages for therapeutic applications aimed at restoring or replacing damaged reproductive tissues.

Embryonic stem cells (ESCs)

Derived from early-stage embryos, ESCs are pluripotent, meaning they can become nearly any cell type. They have been studied for their potential to generate reproductive tissues such as ovarian follicles and uterine lining [5]. However, ethical concerns and the possibility of forming tumors limit their clinical use.

Induced pluripotent stem cells (iPSCs)

These are adult cells reprogrammed to a pluripotent state, giving them similar properties to ESCs without the associated ethical issues. iPSCs, derived from a patient's somatic cells, offer a lower

***Correspondence:** Ms. Amisha Biswal, Department of Biotechnology, MITS School of Biotechnology, Odisha, India, e-mail: biswalamisha316@gmail.com

risk of immune response and demonstrate potential in generating reproductive cell types and aiding tissue repair. [6].

Mesenchymal stem cells (MSCs)

MSCs are found in tissues like bone marrow, fat, and the umbilical cord. They can differentiate into connective tissue types and are known for their anti-inflammatory and healing abilities [7]. In reproductive medicine, MSCs have been explored for repairing damaged endometrium, ovaries, and uterine tissues.

Germline stem cells

These include spermatogonial stem cells (SSCs) (in males) and oogonial stem cells (in females), which naturally give rise to sperm and eggs. Research is ongoing to determine how these cells can be used to restore fertility in individuals affected by genetic conditions or treatments like chemotherapy [8].

Perinatal stem cells

Stem cells obtained from amniotic fluid and umbilical cord tissues are ethically non-controversial and abundant. They possess regenerative properties and have shown encouraging results in preclinical models for repairing reproductive organs.

Biomaterials and Scaffold Technologies

Biomaterials and scaffold technologies play a vital role in reproductive tissue engineering by providing structural and biochemical support for stem cell growth, differentiation, and tissue formation. Scaffolds are designed to mimic the natural extracellular matrix (ECM), creating a conducive environment for cell attachment, nutrient diffusion, and tissue integration. Both natural materials-such as collagen, gelatin, alginate, and fibrin, and synthetic polymers like PLGA, PCL, and PEG are commonly used. Natural materials offer excellent biocompatibility and biological signaling, while synthetic options provide greater control over degradation rates and mechanical strength [9]. Hydrogels, due to their high-water content and cell-friendly structure, are particularly effective in supporting follicle development and endometrial regeneration. Advanced approaches such as decellularized reproductive tissues preserve native architecture and bioactive cues, making them ideal for whole-organ scaffolds. Additionally, 3D bioprinting allows for precise, customizable scaffold fabrication, often combining cells and biomaterials to recreate complex tissue structures (Table 1). The integration of smart biomaterials with bioactive molecules further enhances regenerative outcomes, positioning scaffold technologies as a cornerstone in the development of effective, stem cell-based reproductive therapies [10].

Table 1. Common biomaterials and scaffold types in reproductive tissue engineering.

Type	Material examples	Features	Applications
Natural Polymers	Collagen, Gelatin, Fibrin, Alginate	Biocompatible, bioactive, mimic ECM	Ovarian follicles, endometrial lining
Synthetic Polymers	PLGA, PCL, PEG, PLLA	Controlled degradation, customizable properties	Uterine, testicular scaffold models
Hydrogels	Hyaluronic acid, Matrigel, PEG-based gels	High water content, cell-friendly environment	Oocyte culture, 3D follicle growth
Decellularized Tissues	Uterus, ovary, or testis-derived ECM	Natural architecture, contains native signals	Whole-organ scaffolding
3D Bioprinted Scaffolds	Custom bioinks using cells + biomaterials	High precision, patient-specific designs	Organ-on-chip, artificial ovaries/testes

Applications in Female Reproductive Tissue Engineering

Reproductive tissue engineering offers transformative approaches to restore or replace damaged female reproductive organs using stem cells and biomaterials. Three major focus areas are the ovary, uterus (including the endometrium), and the vaginal–cervical complex.

Ovarian tissue engineering

Ovarian damage caused by chemotherapy, aging, or genetic disorders can lead to infertility and hormonal imbalance. Engineering functional ovarian tissue using stem cells, especially MSCs and iPSCs, has shown promise in restoring endocrine function and supporting follicle development [11]. 3D scaffolds like alginate and collagen hydrogels are often used to mimic the ovarian microenvironment and promote tissue maturation.

Uterine and endometrial regeneration

The uterus, especially its inner lining (endometrium), is vital for implantation and pregnancy. Endometrial damage can impair fertility, but regenerative strategies using bone marrow-derived or endometrial stem cells have shown potential in restoring endometrial structure and function [12]. Scaffold-based therapies, including decellularized uterine matrices and biopolymer hydrogels, promote cell growth, angiogenesis, and tissue integration, offering hope for patients with uterine factor infertility.

Vaginal and cervical reconstruction

Conditions like congenital absence (e.g., MRKH syndrome) or trauma may require vaginal or cervical reconstruction. Bioengineered tissues created using stem cells and biodegradable scaffolds can restore anatomical structure and mucosal function. These constructs support epithelial regeneration, vascularization, and mechanical integrity, and some have already been tested in early clinical settings with promising results.

Applications in Male Reproductive Tissue Engineering

Male reproductive tissue engineering aims to restore fertility

https://doi.org/10.61577/jfrh.2025.100006

and sexual function by regenerating or replacing damaged reproductive structures using stem cells, biomaterials, and bioengineering techniques. Key areas of focus include the testes, seminiferous tubules, and erectile tissue.

Testicular tissue regeneration

Damage to testicular tissue due to trauma, cancer treatments, or genetic disorders can impair testosterone production and spermatogenesis. Regenerative strategies using stem cells, such as spermatogonial stem cells and MSCs, have shown promise in restoring hormonal function and supporting the development of germ cells. Biomaterial scaffolds help recreate the testicular microenvironment and support cell survival and differentiation [13].

Seminiferous tubule and sperm cell restoration

The seminiferous tubules are the functional units of the testes responsible for sperm production. Reconstructing these structures using bioengineered scaffolds and SSCs is a major challenge but holds potential for restoring fertility in men with non-obstructive azoospermia [14]. Researchers have developed 3D culture systems and scaffold matrices that support SSC proliferation and early stages of spermatogenesis.

Erectile tissue repair

Erectile dysfunction resulting from vascular damage or penile injury may be addressed using tissue engineering. Stem cells and hydrogels have been explored to regenerate corpora cavernosa tissue, improve blood flow, and restore erectile function. Preclinical studies show promising results, with improved vascularization and tissue elasticity in engineered constructs [15].

Mechanisms of Stem Cell Differentiation and Tissue Integration

Stem cell-based reproductive tissue engineering relies on precise control of differentiation and successful integration into host tissues. Key molecular signalling pathways, such as Wnt, Notch, BMP, and TGF-β, play crucial roles in guiding stem cells toward specific reproductive lineages. These pathways regulate gene expression, cell fate decisions, and tissue patterning during development and regeneration.

In addition to signaling, epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNAs are essential in regulating stem cell plasticity and commitment [16]. These epigenetic factors ensure the stable expression of lineage-specific genes while suppressing unwanted differentiation, helping maintain functional tissue identity during regeneration.

For successful tissue engineering, host integration and vascularization are equally important. After implantation, stem cell-derived constructs must interact with the surrounding native tissue to support survival, functional maturation, and long-term performance. Biomaterials and scaffolds often incorporate angiogenic factors or support endothelial cell recruitment to promote vascular integration [17,18].

Together, these molecular and epigenetic mechanisms, along with a favorable microenvironment, ensure that stem cells differentiate appropriately, integrate with host tissue, and contribute to the restoration of reproductive function.

Preclinical and Clinical Studies

The development of stem cell-based reproductive tissue engineering relies heavily on both preclinical and clinical studies to evaluate safety, efficacy, and translational potential. These investigations are essential in moving laboratory findings toward real-world therapeutic applications [19].

In vivo animal models

In vivo animal models provide a controlled environment to study tissue regeneration, immune response, and functional integration of engineered reproductive tissues. Rodents, rabbits, and non-human primates are commonly used to evaluate outcomes such as follicle development, endometrial repair, testicular regeneration, and erectile tissue restoration. These models help replicate pathological conditions and offer insights into cell behavior and scaffold performance before human application.

Translational challenges

Despite success in animal studies, translating these findings to human applications presents several challenges [20]. Differences in anatomy, physiology, and immune response between animals and humans can affect reproducibility. Standardizing cell types, scaffold materials, and delivery methods remains complex. Additional concerns include the risk of tumor formation, immune rejection, and ethical considerations surrounding stem cell use.

Ongoing clinical trials and case reports

Several early-phase clinical trials and case reports are currently exploring regenerative therapies for conditions like Asherman's syndrome, premature ovarian failure, and erectile dysfunction. Techniques involving mesenchymal stem cells, platelet-rich plasma, and tissue scaffolds have shown promising initial outcomes in restoring function and structure. However, long-term data are still needed to confirm safety and efficacy for broader clinical adoption.

Conclusion

The integration of stem cell biology with reproductive tissue engineering holds transformative potential for addressing infertility and restoring reproductive function in both men and women. Considerable advancements have been achieved in isolating stem cells, creating functional biomaterials, and establishing preclinical models that closely replicate human physiology. These advancements have laid the groundwork for generating functional reproductive tissues such as ovarian follicles, endometrial linings, testicular structures, and erectile tissue constructs. While early clinical trials and case reports show promise, widespread clinical application is still limited by challenges including immune rejection, ethical concerns, standardization of protocols, and long-term safety. The continued refinement of scaffold technologies, genetic and epigenetic modulation, and patient-specific cell therapies will be essential in overcoming these hurdles. Moreover, interdisciplinary collaboration between cell biologists, material scientists, clinicians, and bioengineers is vital to accelerate the translation of laboratory innovations into real-world therapies. With ongoing research, stem cell-driven reproductive tissue engineering is expected to transform fertility preservation and

https://doi.org/10.61577/jfrh.2025.100006

therapeutic approaches, providing new possibilities for individuals facing reproductive health challenges.

Disclosure statement

The authors declare that they have no competing interests.

References

1. Sadri-Ardekani H, Atala A. Regenerative medicine for the treatment of reproductive system disorders: current and potential options. Adv Drug Deliv Rev. 2015;82:145-152. https://doi.org/10.1016/j.addr.2014.10.019
2. Priester C, MacDonald A, Dhar M, Bow A. Examining the characteristics and applications of mesenchymal, induced pluripotent, and embryonic stem cells for tissue engineering approaches across the germ layers. Pharm. 2020;13(11):344. https://doi.org/10.3390/ph13110344
3. Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. Int J Cell Biol. 2016;2016(1):6940283. https://doi.org/10.1155/2016/6940283
4. Ding X, Wang J, Wu J. In vitro differentiation of germ cells from stem cells. Curr Mol Pharmacol. 2016;9(4):305-310. https://doi.org/10.2174/1874467208666150928154053
5. Yamanaka S. Pluripotent stem cell-based cell therapy—promise and challenges. Cell stem cell. 2020;27(4):523-531. https://doi.org/10.1016/j.stem.2020.09.014
6. Rančić N, Rascanin S, Miljkovic M, Jovanovic M. Induced pluripotent Stem Cells: Where we are currently?. Naučni časopis urgentne medicine-Halo 194. 2020;26(3):153-161. https://doi.org/10.5937/halo26-27861
7. Rungsiwiwut R, Virutamasen P, Pruksananonda K. Mesenchymal stem cells for restoring endometrial function: An infertility perspective. Reprod Med Biol. 2021;20(1):13-19. https://doi.org/10.1002/rmb2.12339
8. Skaletsky NN, Skaletskaya GN, Sevastianov VI. Prospects for the use of spermatogonial stem cells in the treatment of male infertility. Cancer. 2020;2:6. https://doi.org/10.15825/1995-1191-2019-4-134-142
9. Liu X, Wu K, Gao L, Wang L, Shi X. Biomaterial strategies for the application of reproductive tissue engineering. Bioact Mater. 2022;14:86-96. https://doi.org/10.1016/j.bioactmat.2021.11.023
10. Golebiowska AA, Intravaia JT, Sathe VM, Kumbar SG, Nukavarapu SP. Decellularized extracellular matrix biomaterials for regenerative therapies: advances, challenges and clinical prospects. Bioact Mater. 2024;32:98-123. https://doi.org/10.1016/j.bioactmat.2023.09.017
11. Kuchakzadeh F, Ai J, Ebrahimi-Barough S. Tissue engineering and stem cell-based therapeutic strategies for premature ovarian insufficiency. Regen Ther. 2024;25:10-23. https://doi.org/10.1016/j.reth.2023.11.007
12. Ahn J, Sen T, Lee D, Kim H, Lee JY, Koo HS, et al. Uterus-derived decellularized extracellular matrix-mediated endometrial regeneration and fertility enhancement. Adv Funct Mater. 2023;33(34):2214291. https://doi.org/10.1002/adfm.202214291
13. Shams A, Eslahi N, Movahedin M, Izadyar F, Asgari H, Koruji M. Future of spermatogonial stem cell culture: application of nanofiber scaffolds. Curr Stem Cell Res Ther. 2017;12(7):544-553. https://doi.org/10.2174/1574888X12666170623095457
14. Salem M, Khadivi F, Javanbakht P, Mojaverrostami S, Abbasi M, Feizollahi N, et al. Advances of three-dimensional (3D) culture systems for in vitro spermatogenesis. Stem cell res ther. 2023;14(1):262. https://doi.org/10.1186/s13287-023-03466-6
15. Andrew TW, Kanapathy M, Murugesan L, Muneer A, Kalaskar D, Atala A. Towards clinical application of tissue engineering for erectile penile regeneration. Nat Rev Urol. 2019;16(12):734-744. https://doi.org/10.1038/s41585-019-0246-7
16. Seale NM, Varghese S. Biomaterials for pluripotent stem cell engineering: from fate determination to vascularization. J Mater Chem B. 2016;4(20):3454-3463. https://doi.org/10.1039/C5TB02658J
17. Crowder SW, Leonardo V, Whittaker T, Papathanasiou P, Stevens MM. Material cues as potent regulators of epigenetics and stem cell function. Cell stem cell. 2016;18(1):39-52. https://doi.org/10.1016/j.stem.2015.12.012
18. Wang Y, Keshavarz M, Barhouse P, Smith Q. Strategies for regenerative vascular tissue engineering. Adv Biol. 2023;7(5): 2200050. https://doi.org/10.1002/adbi.202200050
19. Tang SW, Tong WY, Pang SW, Voelcker NH, Lam YW. Deconstructing, replicating, and engineering tissue microenvironment for stem cell differentiation. Tissue Eng Part B Rev. 2020;26(6):540-554. https://doi.org/10.1089/ten.TEB.2020.0044
20. Rady D, Abbass MM, El-Rashidy AA, El Moshy S, Radwan IA, Dörfer CE, et al. Mesenchymal stem/progenitor cells: the prospect of human clinical translation. Stem Cells Int. 2020;2020(1): 8837654. https://doi.org/10.1155/2020/8837654

https://doi.org/10.61577/jfrh.2025.100006