

Advances in Nanomedicine and Biomaterials for Endometrial Regeneration: A Comprehensive Review

Yanhong Liu, Dongyun Jia , Lin Li , Meiyan Wang

Center for Prenatal Diagnosis, Center for Reproductive Medicine, First Hospital of Jilin University, Changchun, Jilin, People's Republic of China

Correspondence: Meiyan Wang, Email wangmeiyan0426@jlu.edu.cn

Abstract: The endometrium is an extremely important component of the uterus and is crucial for individual health and human reproduction. However, traditional methods still struggle to ideally repair the structure and function of damaged endometrium and restore fertility. Therefore, seeking and developing innovative technologies and materials has the potential to repair and regenerate damaged or diseased endometrium. The emergence and functionalization of various nanomedicine and biomaterials, as well as the proposal and development of regenerative medicine and tissue engineering techniques, have brought great hope for solving these problems. In this review, we will summarize various nanomedicine, biomaterials, and innovative technologies that contribute to endometrial regeneration, including nanoscale exosomes, nanomaterials, stem cell-based materials, naturally sourced biomaterials, chemically synthesized biomaterials, approaches and methods for functionalizing biomaterials, as well as the application of revolutionary new technologies such as organoids, organ-on-chips, artificial intelligence, etc. The diverse design and modification of new biomaterials endow them with new functionalities, such as microstructure or nanostructure, mechanical properties, biological functions, and cellular microenvironment regulation. It will provide new options for the regeneration of endometrium, bring new hope for the reconstruction and recovery of patients' reproductive abilities.

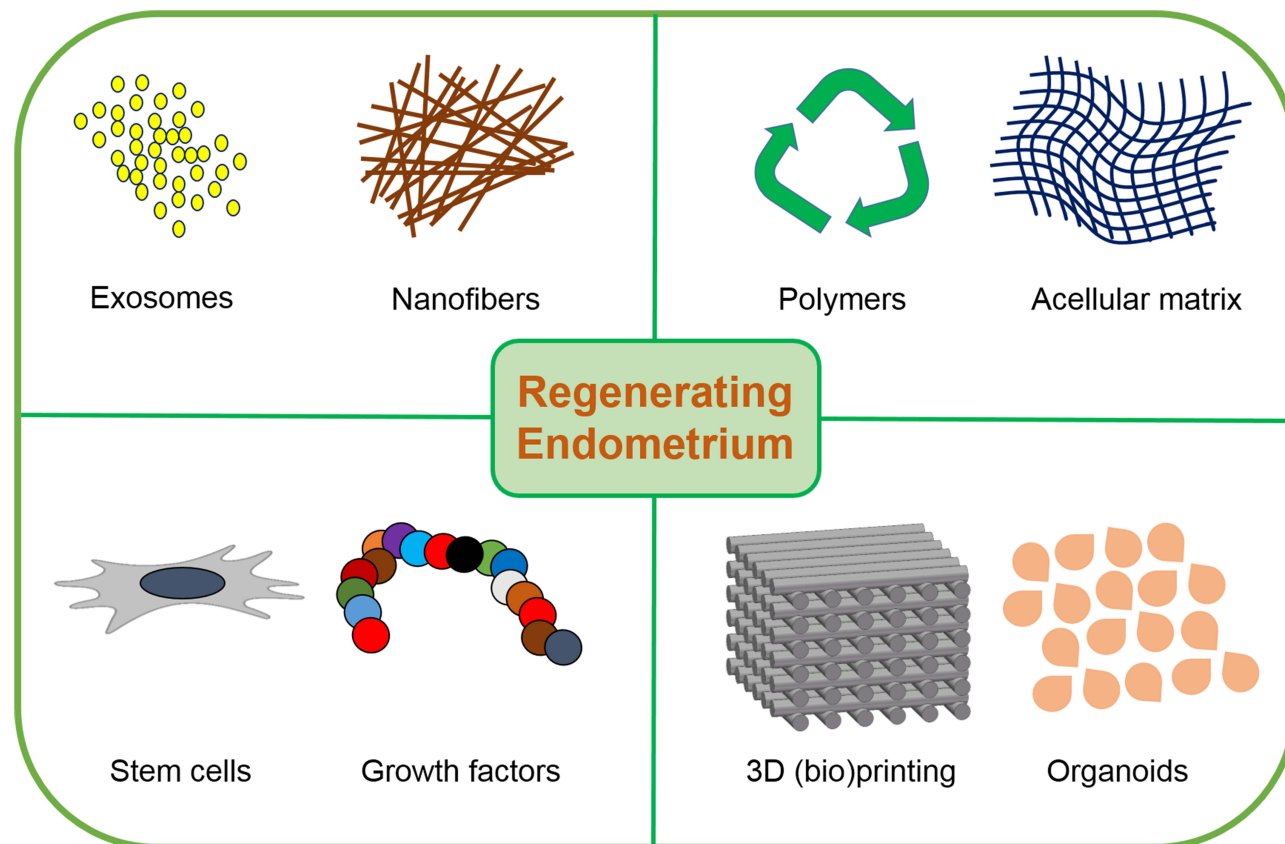
Keywords: nanomedicine, biomaterials, endometrium, regeneration, stem cells

Introduction

The uterus is an important organ for maintaining menstrual physiology and reproductive function in women. The endometrium is one of the important components of the uterus and is the innermost mucosal layer of the uterine body, providing necessary “soil” for embryo implantation and pregnancy maintenance.¹ The endometrium is composed of a functional layer and a basal layer, and it is a dynamic tissue whose thickness and structure are highly influenced by many factors such as hormonal fluctuation.² The functional layer adjacent to the uterine cavity includes a dense layer and a spongy layer, which undergo periodic changes and shedding under the influence of ovarian sex hormones and account for two-thirds of the endometrium thickness. The embryo implantation is located here and it has a high degree of self-healing ability. The basal layer occupies approximately one-third of the thickness of the endometrium and is not affected by ovarian sex hormones and does not undergo periodic changes.³ However, uterine cavity manipulation, infection, and inflammation can easily cause serious damage to the endometrium, making it difficult to regenerate and repair, directly leading to amenorrhea, infertility, miscarriage, or other serious symptoms.⁴

At present, clinically applicable methods for promoting endometrial repair include biomimetic electrical stimulation, compound short-term oral contraceptives, estrogen and progesterone drugs, traditional Chinese medicine, and so on.⁵ More importantly, severe damage to the endometrium is usually irreversible. For example, some intrauterine surgical procedures, infections, and inflammation are risk factors for severe endometrial damage and intrauterine adhesions, which can directly cause infertility, amenorrhea, miscarriage, or other serious symptoms. This can cause apoptosis of endometrial stromal cells, leading to endometrial atrophy and disruption of endometrial homeostasis, inhibiting

Graphical Abstract



endometrial angiogenesis and hindering endometrial regeneration. The damaged basal layer is usually irreversible and often fibrotic, which can be seen in Asherman Syndrome (AS). In addition, poor vascularization, endometrial scarring, and severe uterine adhesions can lead to the inability of fertilized eggs to implant and develop, just like the land turns into cement, where no plants can grow.⁶ Therefore, the key to solving infertility in these patients is how to achieve functional repair and remodeling of the endometrium, including successful epithelialization and revascularization. What's more, anti-infection and inflammation control are important environmental guarantees for optimizing endometrial neogenesis.⁷ However, there is currently no ideal clinical treatment method that simultaneously meets the above requirements, and both surgery and medication treatment have some side effects or minimal efficacy.

In recent years, regenerative medicine and tissue engineering have made significant progress and provided new solutions to the above mentioned clinical problems. Among them, the use of patients' stem cells, combined with the assistance of biomaterials, can create organ substitutes or regenerate damaged tissues such as the uterus and endometrium, minimizing the risk of immune rejection and disease transmission.^{8,9} The necessity of using biomaterials lies in the relatively complex environment of the uterus, using stem cells alone can easily lead to rapid loss of vitality due to a lack of appropriate carriers for the cells, making it difficult to achieve perfect repair effects. Correspondingly, biomaterials can serve as "scaffolds" for carrying stem cells, supplemented with some biomolecules, essential nutrients or drugs to simulate a natural microenvironment, enabling stem cells to play a greater role in reconstruction and repair.¹⁰ Furthermore, extrusion three-dimensional (3D) bioprinting technology has also been widely used to construct biomimetic multi-layer tissue engineering scaffolds containing multiple cell components for endometrial repair. Therefore, some basic requirements for biomaterials should be fulfilled to promote endometrial regeneration.¹¹ Firstly, it is best to be

injectable or soft for surgical operation, which can be easily delivered into the endometrial cavity. Secondly, it should have sufficient biological functions to accelerate the regeneration of the endometrium. Thirdly, it should be able to adhere to the injured uterine wall, preventing the adhesion of wound and tissues, and resisting the impact and flushing of menstruation. Finally, it is better to release or secrete a series of growth factors to stimulate the uterine microenvironment and promote endometrium repair.

The historical context of nanomedicine and biomaterials used for endometrial regeneration can be briefly reviewed as follows. Since 2011, there have been reports of using biomaterials and stem cells for endometrial regeneration, such as growth factor-modified collagen scaffolds, mesenchymal stem cells, etc.^{12,13} Subsequently, from 2013 to 2018, some small molecule compounds such as lipoic acid, alpha-tocopherol, phylloquinone and resveratrol showed therapeutic effects on wound healing of full-thickness rat uterine defects.^{14–16} At almost the same time, acellular matrix, platelet-rich plasma (PRP), polymer hydrogels and scaffolds were then prepared, synthesized and functionalized to meet the needs of endometrial regeneration.^{17–19} After entering 2019, exosomes, organ-on-chips, and 3D (bio)printing technology have experienced rapid development.^{20,21} They have also been used to combine with biomaterials, stem cells, and biomolecules, providing new development opportunities for endometrial regeneration, obtaining diverse functionalities, and achieving exciting experimental results.^{22–24} So this review summarizes the recent advances in developing nanomedicine, nanomaterials, stem cell-based materials, and natural or synthetic biomaterials that promote endometrial regeneration, including design and preparation strategies, structural and functional features using bioactive substances, small molecule drugs, inorganic materials, innovative strategies, and so on (Figure 1).

Nanomedicine and Nanomaterials

Exosomes

Exosomes are nanoscale extracellular vesicles that can be secreted by various cells, containing abundant proteins, messenger ribonucleic acid (mRNA), micro RNA (miRNA), and other molecules.²⁰ Due to their extreme similarity to the molecules of the source cell, they have become promising nanomedicine for many diseases as biologically derived drug delivery systems or innovative therapeutic strategies.^{23,25} Different from stem cells, exosomes possess more prominent biological safety, lower risk of immune response and rejection.^{26,27} The exosomes of stem cells have played an important role in promoting endometrial regeneration, such as significantly promoting angiogenesis, increasing glandular density, inhibiting local tissue fibrosis, and ultimately restoring partial or complete fertility.²⁸ However, the instability and short half-life of exosomes make them easily cleared by host cells after in vivo administration.²⁹

Although cell therapy based on umbilical cord-derived mesenchymal stem cells (UCMSCs) has made some progress, it still has some limitations, such as low infusion, low retention, potential tumorigenicity, and so on.³⁰ To address these issues, a therapeutic technique that did not use cells has been established by combining with nanoscale UCMSC-derived

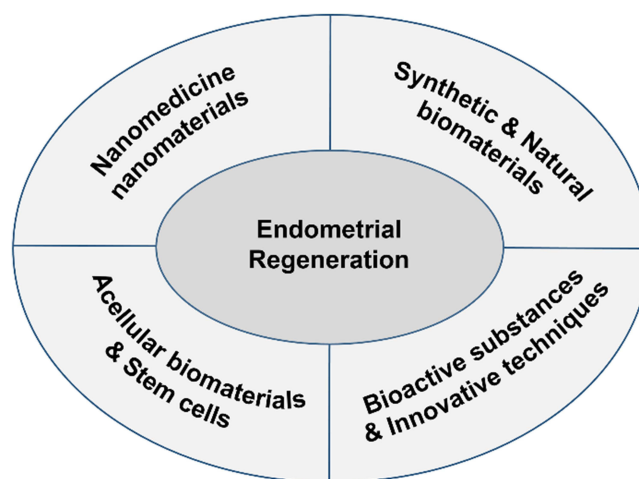


Figure 1 Summary of nanomedicine and biomaterials for endometrial regeneration.

exosomes into collagen scaffold (CS/Exos) through a freeze-drying method.³¹ The CS/Exos construct could mimic a natural extracellular matrix (ECM), deliver exosomes to the damaged sites, increase retention rates, and provide a separation barrier to prevent adhesion. The transplantation of CS/Exos in rat endometrium injury effectively reduced the formation of fibrosis, promoted collagen remodeling and neovascularization, improved endometrium regeneration and glandular structure reconstruction, and facilitated the recovery of fertility, demonstrating the highest pregnancy rate and implantation efficiency. In terms of mechanism, it was found that CS/Exos could promote the infiltration of M1 macrophages during the initial stage of endometrial healing. While in the later stage, it induced macrophage phenotype transformation into M2 type. Findings from this study indicated that the UCMSC-derived exosomes had a strong immune regulatory effect on macrophages by inhibiting inflammatory responses and inducing macrophage transformation into an anti-inflammatory M2 phenotype.^{32,33} As is well known, stem cells can be obtained from many tissue sources, so exosomes are the same. Reports have found that exosomes derived from stem cells of other tissue sources also exhibited strong promoting effects on the regeneration of endometrial damage. In another study, adipose-derived stem cell-derived exosomes (ADSC-exo) were incorporated in decellularized ECM of porcine dermis to promote rat endometrium regeneration.³⁴ The obtained composite materials had excellent cytocompatibility and promoted cell proliferation, migration, and vascularization. Its implantation strengthened local angiogenesis in the damaged rat uterine cavity, promoted myometrial repair, improved endometrial regeneration, and perfectly restored fertility, suggesting that ADSC-exos are also a new option for efficient endometrial regeneration.

In addition, exosomes from other cell sources have also been gradually developed for endometrial regeneration. For example, cytokine interleukin-1 β (IL-1 β)-activated bone mesenchymal stem cell (BMSC)-derived exosomes were loaded into injectable polypeptide hydrogel scaffolds. Its slow release exhibited stronger anti-inflammatory capability. While promoting the production of anti-inflammatory cytokines, it also inhibited the production of inflammatory cytokines and enhanced cell migration, invasion, and angiogenesis *in vitro*. Ultimately, this excellent anti-inflammatory effect promoted endometrial regeneration in a rat endometritis model.³⁵ Likewise, exosomes derived from decidual stromal cells (DSCs) were encapsulated in alginate hydrogel scaffolds for the repair of mouse endometrium damage and the recovery of fertility.³⁶ DSC-derived exosomes in the hydrogel scaffolds effectively induced uterine angiogenesis, rapidly stimulated the transformation ability of mesenchymal cells to epithelial cells, promoted the reconstruction of collagen fibers and endometrial regeneration, mitigated the deposition of aberrant matrix component and excessive fibrogenesis, thereby enhancing the receptivity of endometrium and helping to restore fertility. The authors also elucidated the potential mechanism of promoting collagen remodeling to achieve effective endometrial regeneration and fertility recovery. Overall, miRNAs carried by exosomes may be the main biomolecules playing a major role in repairing uterine damage. In addition, other proteins and various bioactive components may also play important roles.³⁷ Further in-depth and detailed work is still needed to elucidate these patterns to accurately guide the clinical translation and application of exosomes.

Nanomaterials

There are many forms of nanomaterials, including nanofibers, nanosheets, nanotubes, etc.³⁸ Nanofibers have a large specific surface area, 3D microstructure that is extremely similar to the ECM *in vivo*, and an appropriate porosity.³⁹ Most nanofibers are made from polymers or other materials through physical or chemical methods, including electrospinning, phase separation, etc.⁴⁰ Nanofibers have become indispensable and important materials in fields such as targeted gene or drug delivery, tissue repair and regeneration, and water or air filtration.^{41–43}

For instance, Nune et al prepared polycaprolactone (PCL) electrospun nanofiber scaffolds, which were then subjected to the aminolysis-assisted introduction of amine groups and maltose conjugation on the scaffolds.⁴⁴ The functionalized PCL scaffolds significantly enhanced the proliferation and cellular morphology of uterine fibroblasts. This will be a functional patch that can improve myometrial activity and build a bioengineered endometrium in the uterus. Electrospinning technology is also suitable for the manufacturing of various synthetic polymer nanofibers, providing a scaffold with excellent micro/nano structure and function for endometrial regeneration. In another study, Song et al used electrospinning technology to prepare nanofiber materials by combining fibrinogen (fibrin) and poly(L-lactide caprolactone) (P(LLA-CL)), and implanted them into damaged endometrium of rats.⁴⁵ The nanofibers not only increased the thickness and quantity of endometrial glands, but also reduced the area of endometrial fibrosis, promoted

neovascularization, and reduced the deposition of type I collagen. In addition, the nanofibers also downregulated the pro-fibrotic cytokine transforming growth factor- β 1 (TGF- β 1), ultimately restoring fertility and increasing the pregnancy rate in rats with endometrial injury. The gestation period of rats was about 15–19 days. During this period, there were no significant differences in the morphology of the heart, liver, spleen, lungs, and kidneys among the nanofiber group, control group, and sham surgery group, and no malignant tumors occurred. Moreover, there was no significant difference in liver and kidney function indicators among the three groups of animals. This indicated that the nanomaterial had no adverse effects on the main organs and biochemical indicators of animals, proving the biological safety of the materials. Nanofibers have also been used as delivery vehicles for stem cells to exert their immunomodulatory effects on endometrial regeneration, with a prominent example being silk fibroin/poly (caprolactone) (SF/PCL) electrospun nanofibers loaded with ADSCs.⁴⁶ It was found that in rat model of endometrial injury, the construction of stem cells and nanofiber systems could effectively restore glandular morphology, promote glandular regeneration, upregulate CD31 expression for vascularization, and reverse the degree of endometrial fibrosis. Most importantly, the immune micro-environment was correspondingly reshaped, resulting in more lasting therapeutic effects than estrogen therapy.

A new type of nanofibers developed in recent years was derived from human chorionic villi (CV), which fully simulated the ECM microenvironment of MSCs that generated CV and maintained its long-term stemness.⁴⁷ In this study, researchers used this type of CV nanofibers to cultivate MSCs on a large scale, achieving efficient harvesting of exosomes. They further encapsulated the obtained exosomes in CV nanofibers, promoting endometrium regeneration and live birth in rat model of severe uterine injury. This study provides a new cell-free nanomaterial therapy platform for efficient production of exosomes and endometrial remodeling, demonstrating broad clinical application prospects. Another type of nanofibers was derived from decellularized pig skin ECM, which had a nanometer scale diameter and micrometer scale length, good injectability, and magical “homing-like” biological activity.⁴⁸ It was found that these micro/nanofibers could effectively bind to endometrial cells through electrostatic dipole interactions, release bioactive growth factors in situ, effectively recruit endogenous cells for homing, and reduce fibrosis in rat endometrial injury model. Therefore, this easily prepared and suitable for large-scale production of micro/nanofibers significantly accelerated endometrial repair, promoted angiogenesis, and achieved fertility recovery, suggesting its advantages in non-invasive intrauterine injection therapy in clinical practice.

In recent years, nanofibers have also been used to carry inorganic nanomaterials for endometrial regeneration. For instance, shape memory polymer (SMP) poly(D, L-lactide-co-trimethylene carbonate) (PT) nanofibers were used in combination with cuprorivaite ($\text{CaCuSi}_4\text{O}_{10}$) nanosheets (CUPNSs) to develop a second near-infrared (NIR-II) photo-responsive shape memory composite. The PT nanofibers could memorize temporary shapes in a predefined way and restore them to their original shape under appropriate stimulation, opening up possibilities for regenerative medicine applications (Figure 2).^{49–51} In this study, CUPNSs were used as photothermal conversion agents, and PT polymer was used as shape memory building blocks. Due to the photothermal effect of CUPNSs in the NIR-II region, the composite materials exhibited excellent shape memory properties. The slowly released silicon (SiO_4^{4-}) and copper ions (Cu^{2+}) effectively supported angiogenesis, thereby promoting endometrial regeneration in damaged rat endometrium. This composite materials ultimately becomes an intelligent anti-adhesion barrier for uterine adhesions. Except for these, inorganic carbon nanotubes (CNTs) were carried by using thermal responsive poly(polyethylene glycol citrate-co-N-isopropylacrylamide) gel (PPCNg) and polyethersulfone (PES) nanofiber scaffolds for regeneration of rat endometrium and functional recovery, both of the two nanocomposites provided clinicians with promising treatment options.^{52,53} More interestingly, a new antioxidant cerium oxide (CeO_2) nanoenzyme and stem cells were loaded together in the methacrylate gelatin (GelMA) hydrogel microneedles for in situ repair of rat endometrium.⁵⁴ Nanoenzyme and stem cells were located in the backing layer and the tip area respectively, endowing the hydrogel microneedles antioxidant activity and high cellular activity. The damaged endometrium quickly regenerated smooth muscle layers and new blood vessels, and the embryos implanted in the regeneration site lived healthily until late pregnancy.

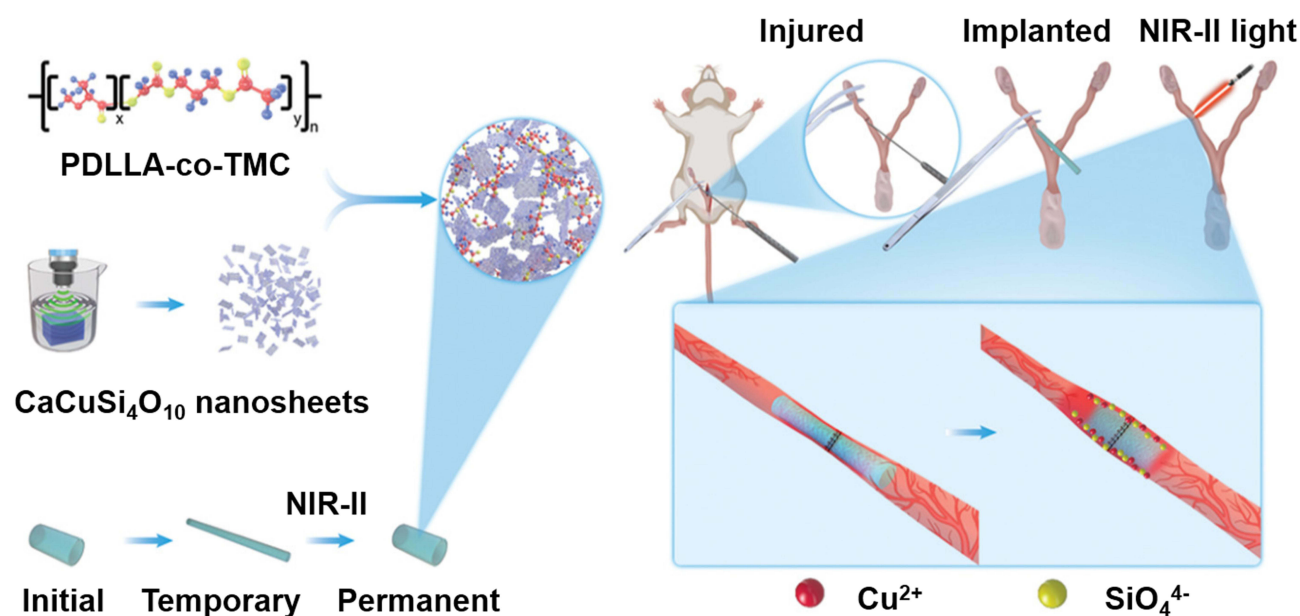


Figure 2 Schematic illustration of NIR-II light-responsive CUP/PT composites for preventing intrauterine adhesion (IUA) and endometrial regeneration. Reprinted from Chenle Dong, Chen Yang, Muhammad Rizwan Younis et al. Bioactive NIR-II Light-Responsive Shape Memory Composite Based on Cuprorivaite Nanosheets for Endometrial Regeneration. *Advanced Science*. 2022;9(12): e2102220. Creative Commons.⁵¹

Natural Biomaterials

Natural Polymers

Due to their advantages of economic availability, low cost, good biocompatibility and biological activity, naturally sourced polymers such as collagen, gelatin, alginate, hyaluronic acid (HA), sericin, etc. have been widely used as biomaterial scaffolds for implanting and repairing injured endometrium.⁵⁵ Collagen is a primary structural supporting protein of natural ECM, with biocompatibility and biodegradability. It can not only regulate the cell viability of endometrial stromal cells (ESCs) in chronic endometritis (CE), promote their proliferation and migration, achieve endometrial epithelial tissue regeneration, restore normal endometrial environment, but also alleviate inflammation by inducing macrophage polarization to M2 type, and promote the recovery of CE endometrial immune microenvironment.⁵⁶

Zheng et al prepared a dual-crosslinked hydrogel by using recombinant type III collagen (RC) and oxidized sodium alginate (OSA), which could be self-assembled and injected into the damaged endometrium of female mouse uterine injury model in a controlled manner.⁵⁷ The Schiff base reaction between RC and OSA underwent regular dynamic covalent crosslinking, and the interaction of calcium ion (Ca²⁺) further generated ionic bonds, forming a reversible and degradable double network structure. This hydrogel facilitated controllable and non-invasive injection and retention in the uterine cavity for therapeutic purposes. The degradation process of the RC/OSA hydrogel was suitable, and its ingredients would disappear completely, promoting the viability and proliferation of endometrial stromal cells. This double-crosslinked hydrogel could also accelerate the regeneration and structural reconstruction of endometrial matrix after severe injury in vivo by maintaining the homeostasis of endometrial hormones. This study achieved satisfactory therapeutic effects without using exogenous cells or growth factors, which has important clinical value for endometrial regeneration. A similar study used the conjugation between RC and HA to form hydrogel, which also played a key role in reconstructing the integrity of endometrium, promoting its repair and restoring the fertility of mice. The possible mechanism may be that it increased cell adhesion and growth, and exerted anti-fibrosis effects.⁵⁸ In another study, Rezaei-pour et al impregnated borosilicate bioactive glass (BG) onto collagen scaffolds as an enhancing material for endometrial healing.⁵⁹ The uniformly distributed BG increased the elastic modulus of the porous collagen scaffold, and the composite scaffold promoted angiogenesis and collagen deposition both in vitro and in vivo. In addition, in a rat AS model with mechanical injury established using a dissecting knife, this scaffold significantly promoted endometrial regeneration by reducing inflammation and calcification.

Dai's team from the Chinese Academy of Sciences loaded bone marrow-derived mesenchymal stem cells (BMSCs) onto degradable collagen membranes, and then transplanted the collagen/BMSCs constructs into the rats with partial full-thickness hysterectomy.⁶⁰ The porous structure of collagen membrane scaffold allowed the loaded BMSCs to adhere and migrate. After transplantation into the damaged uterus, the stem cells carried by the collagen scaffold increased the local concentration of stem cells at the site of injury, secreted higher levels of basic fibroblast growth factor (bFGF), TGF- β 1, insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF), increased the proliferation of endometrial and muscle cells, promoted microvascular regeneration, and restored the ability of endometrium to accept embryos and support their development.

Gelatin is a derivative of collagen, which has good gelling properties, biocompatibility, and biodegradability. Gelatin-based hydrogels have the limitations of poor mechanical properties and thermal stability, while serine, the main component of natural silk, has good water solubility and biocompatibility, which can promote cell adhesion and proliferation, resist oxidation, and inhibit tyrosinase activity. Using methacrylate sericin (SerMA) to improve the properties of GelMA (Figure 3), the obtained UV-crosslinked composite hydrogel loaded stem cells significantly

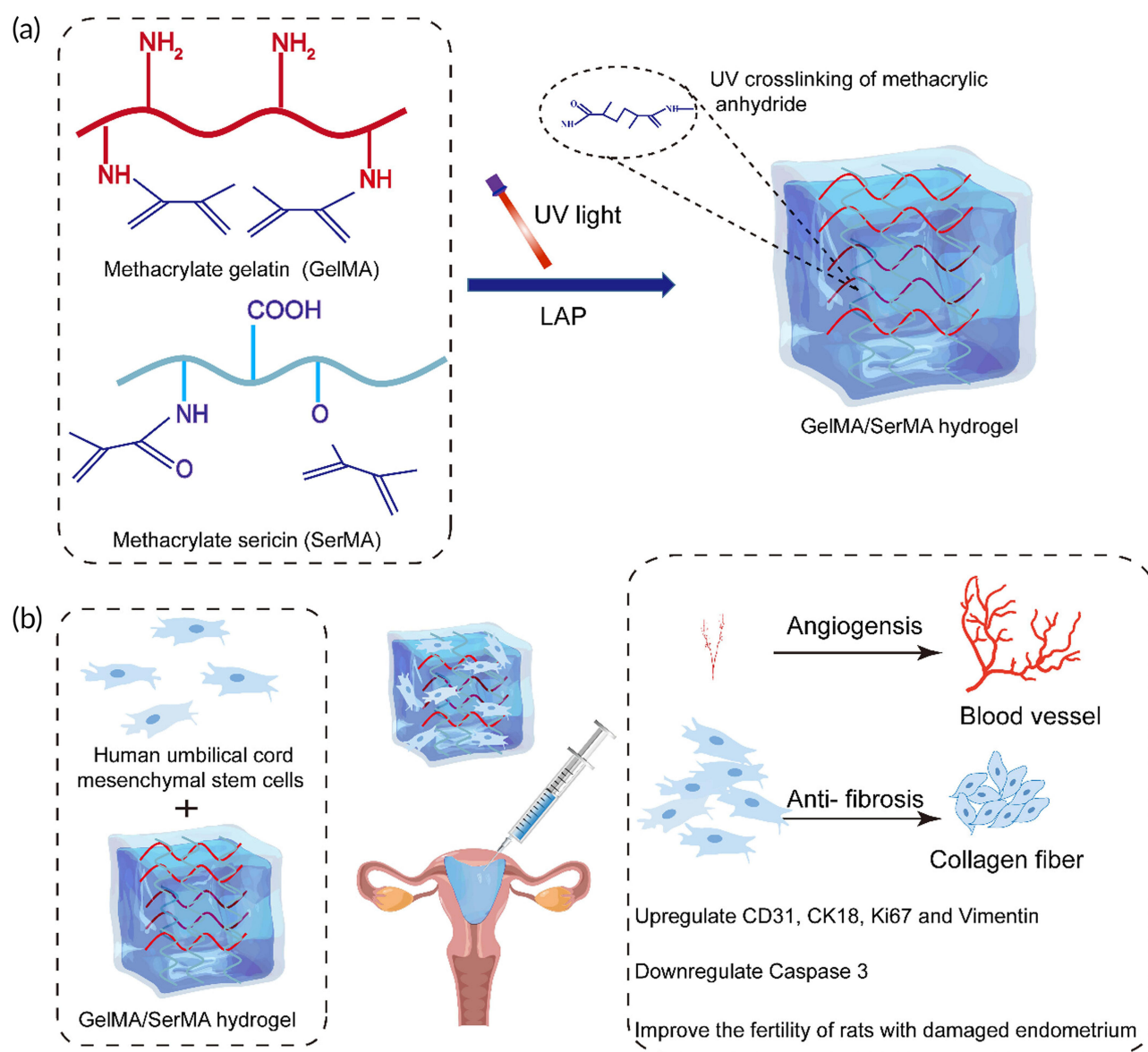


Figure 3 GelMA/SerMA injectable hydrogel encapsulated with HUMSCs for the treatment of uterine injury. (a) Preparation of GelMA/SerMA hydrogel. (b) GelMA/SerMA hydrogel delivering HUMSCs to treat uterine injury by intrauterine injection. Reprinted from Lixuan Chen, Ling Li, Qinglin Mo et al. An injectable gelatin/sericin hydrogel loaded with human umbilical cord mesenchymal stem cells for the treatment of uterine injury. *Bioengineering & Translational Medicine*. 2022;8(1): e10328. Creative Commons.⁶¹

increased the thickness of endometrium, alleviated endometrial stromal fibrosis, and the regenerated endometrium was easier to meet the survival and fertility of transplanted embryos in mouse model of endometrial injury.⁶¹

HA is a glycosaminoglycan widely present in various tissues, with good biocompatibility, biodegradability, anti-inflammatory, and antioxidant activities, which is very beneficial for embryonic development.⁶² Therefore, it plays an important role in endometrial proliferation and is suitable as a drug sustained-release material for endometrial regeneration.⁶³ The excellent properties and functional groups of HA make it relatively easy to conjugate or crosslink with other materials, serving as a scaffold to support mouse endometrial regeneration or as a carrier for delivering bioactive substances for rat endometrial regeneration, such as collagen, polyvinyl alcohol, fibrin, etc.^{58,64,65} For example, an injectable HA and fibrin composite hydrogel synergistically regenerated murine uterine infertility through encapsulating decidualized endometrial stromal cells (dEMSCs).⁶⁵ In this study, thrombin was used to accelerate the crosslinking of HA/fibrin hydrogel, facilitate sufficient stiffness, and achieve efficient cell delivery to integrate and engraft onto the damaged site of endometrium. Using hydrogel to load cells could prevent the loss of cells when injected into the uterine horns, leave as many as cells in the uterus, and repair the damaged endometrium. The secretion of leukemia inhibitory factor (LIF) by the dEMSCs might play a crucial role in their therapeutic effect, reduction of fibrous tissue, increase in endometrium thickness, and functional recovery. So after 7 days of embryo transfer, successful pregnancy was achieved as early as 2 weeks, indicating that in the regenerated model, *in vivo* embryo implantation and development could be confirmed. In another study, Hu et al modified HA with adipate dihydrazide, and then combined it with aldehyde functionalized Pluronic F127 (F127-CHO) to prepare injectable hydrogel with thermal response property. Subsequently, poly(lactide-co-glycolide) (PLGA) microspheres loaded with asiaticoside were prepared and used together with human UCMSCs for repairing rat uterine scars.⁶⁶ Asiaticoside could be slowly released from the composite hydrogel, effectively promoted the adhesion and proliferation of stem cells, enhanced vascularization, and promoted the repair of rat uterine scar by reducing endometrial fibrosis and restoring uterine cavity morphology.

Acellular Matrix

Decellularized uterine ECM can provide tissue-specific biological matrix and 3D structural microenvironment for cell adhesion and growth, and regulate cell differentiation, angiogenesis, immune response, and tissue repair through functional microvasculature and biochemical stimulation.^{67,68} ECM-based matrix or hydrogels have been applied to reconstruct and strengthen the endometrium for pregnancy.^{69,70}

In one study, Gu et al performed a recellularization process on decellularized uterine matrix patches by reinoculating BMSCs to construct functional rat endometrium.⁷¹ The transplantation of recellularized uterine graft successfully regenerated the functional endometrium, resulting in pregnancy rates and fetal numbers comparable to the control group with intact uterus. Especially due to the regulatory effect of BMSCs, the recellularized uterine graft significantly enhanced the regeneration of the injured endometrium *in vivo*. This also fully demonstrates that the unique natural structure and biological functional components of uterine tissue have attracted the attention of researchers. Therefore, the differences in decellularization treatment of partial or whole uterus in endometrial regeneration have also been of concern to researchers. For example, Ahn et al developed two different types of uterus-derived decellularized extracellular matrix (UdECM) from the endometrium-specific layer (Endo-UdECM) or the whole uterus (Whole-UdECM) of pig to evaluate the regenerative effect of different tissue sources on mouse endometrial damage.⁷² The Endo- and Whole-UdECMs both showed no cytotoxicity, and their cell viability was 90% higher than that of the control collagen gel. The incubated human ESCs exhibited better physiological functions and more supportive embryo growth, indicating similarities between UdECM and the *in vivo* microenvironment. Due to better proliferation of epithelial cells and formation of new blood vessels, the thickness of the thin endometrium in mice was significantly restored. Therefore, although UdECMs from different sources have shown different efficacy on endometrial hyperplasia, adhesion, and implantation failure, the transplantation of both the Endo- and Whole-UdECMs effectively improved the fertility of thin endometrium and provided personalized therapeutic potential for regenerative medicine.

To further enhance the therapeutic effects of dECMs on endometrial regeneration, López-Martínez et al supplemented growth factors into decellularized endometrial hydrogels. They used platelet-derived growth factor (PDGF), bFGF, and IGF-1 to bioengineer functional hydrogels for mouse endometrium repair.⁶⁹ The combination of these growth factors and

dECMs was effectively injected through the uterine horn in a minimally invasive manner, promoting wound healing and neovascularization of uterine injuries. ECM scaffolds prepared by decellularizing uterine tissue typically contain the structural and functional molecular composition of natural tissue ECM, such as growth factors, collagen, fibronectin, glycoprotein, laminin, etc. These components have a certain positive effect on the loaded stem cells or endogenous cells damaged in situ, which is beneficial for improving the regeneration efficiency of the endometrium. For example, uterine decellularized scaffolds were also utilized as a natural vehicle to support the growth and differentiation of menstrual blood stem cells (MenSCs) for promoting endometrial regeneration.⁷³ That was because female menstrual blood was a potential effective source of adult stem cells and was expected to become an excellent choice for endometrial regeneration.⁷⁴ The cultured MenSCs effectively infiltrated into the uterine acellular scaffold, successfully differentiating into epithelial cells and smooth muscles, providing a new direction for the repair of the human endometrium.

Besides uterine tissue, decellularized matrix derived from other tissues has also received attention from scholars in the field of endometrial regeneration. Among them, Bai et al decellularized and lyophilized the amniotic membrane, and reinoculated autologous oral mucosal epithelial cells (OMECs) to regenerate rat endometrial epithelium and repair IUA.⁷⁵ The decellularization process removed epithelial cells, eliminated immune rejection, and promoted the adhesion, proliferation, and differentiation of seeded cells. In addition, the lyophilization procedure made the amniotic membrane easier to store, avoiding the risk of pathogen transmission. The transplantation of OMEC-seeded amniotic membrane significantly suppressed the fibrosis rate of IUA, increased the proportion of collagen deposition, improved the secretion of growth factors conducive to angiogenesis, and promoted uterine cavity recovery and endometrial epithelium regeneration.

Stem Cell-Based Biomaterials

Stem cells have differentiation potential and can produce almost all other specialized cells, such as bone cells, muscle cells, or brain cells.⁷⁶ Stem cells obtained from healthy donors or patients themselves have the potential to repair or regenerate damaged tissue or organs through self-renewal and multilineage differentiation, and are expected to be used to treat some critical diseases, such as diabetes, Parkinson's disease, osteoarthritis, etc.⁷⁷ Many types of stem cells have been studied for the treatment of uterine tissue damage, including embryonic stem cells (EmSCs), BMSCs, UCMSCs, ADSCs, endometrial stem cells (EnSCs), amniotic membrane stem cells (AMSCs), among others.^{5,78} New strategies such as direct use of stem cells or stem cell-based genetic modification, as well as other innovative technologies, have also made some progress in repairing endometrial damage.^{79–81}

For example, to effectively repair endometrial basal damage and increase the pregnancy rate in women with severe AS, BMSCs were injected into the tail vein of rats, significantly improving reproductive outcomes.⁸² While reducing fibrosis of damaged endometrium and reconstructing functional endometrium, the pregnancy rate increased to 70%. Interestingly, compared to the sham surgery group, the rats in the treatment group achieved a comparable conception rate. However, all AS rats in the group that did not receive any BMSC treatment did not become pregnant, indicating the extraordinary effect of BMSCs in restoring damaged endometrium. On the other hand, stem cells can also regulate the secretion of various growth factors through paracrine effects, thereby exerting immune regulation and angiogenesis, stimulating endometrium regeneration. For example, Wang et al used adenovirus to transduce the IGF-1 gene into BMSCs and developed engineered BMSCs overexpressing IGF-1 to enhance their therapeutic effect on endometrial damage.^{83,84} The overexpression of IGF-1 activated the nuclear factor kappa-B pathway, inducing increased expression of anti-inflammatory IL-10, ultimately helping to eliminate inflammation and promote endometrial regeneration in rats. This study suggests that genetically engineered BMSCs have broad prospects in treating uterine injury. Unlike using genetic engineering technology to modify stem cells, the culture medium of stem cells also plays an important role in endometrial regeneration. One study has applied BMSC-conditioned medium (BMSC-CM) to rat uterine defects.⁸⁵ The use of BMSC-CM significantly accelerated the endometrial repair of uterine defects, indicating that the abundant chemokines and cytokines produced by the paracrine effect of BMSCs, especially interleukin-6 (IL-6), were of great significance for the regeneration and repair of endometrium in rats.

According to reports, in a rabbit model, BMSCs combined with estrogen had a typical synergistic effect in restoring structural morphology of endometrium and improving endometrial regeneration.⁸⁶ The combination of BMSCs with

estrogen not only strongly promoted the differentiation of stem cells into endometrial epithelial cells, but also enhanced the regenerative outcome of transplanted cells on endometrium injury. Ma et al used 560 μm -sized uniform Matrigel microspheres to deliver MSCs to the damaged endometrium of rats, thus developing a minimally invasive injection strategy for endometrium regeneration in rats (Figure 4).⁸⁷ After 21 days of injecting MSCs, the thickness of the endometrium significantly increased by more than double, and the fertility rate increased from 25% to 75%. This indicates that the transplantation of MSCs provides a minimally invasive solution for the repair of endometrium and is expected to be widely used in clinical practice. Even so, Matrigel's delivery of MSCs also has serious drawbacks, such as high cost, slow gelation, and differences between batches. Besides, it has been reported that a clinical trial of directly injecting twice the clinical-grade human UCMSCs to treat uterine injury has been proven to be safe and effective.⁸⁸ The researchers have found improvements in endometrial thickness, uterine volume, and cesarean scar diverticulum all improved, although there were no significant differences. Finally, the researchers also noted that the number of administered cells, the retention time of cells, and postoperative examination methods are key factors affecting the success or failure of treatment. Studies have already taken note of these aspects and improved the efficiency of stem cell therapy for endometrial injury using appropriate biomaterials. Human AMSCs, originating from the placenta, have been proven to have enormous potential in cell therapy and tissue regeneration due to its safety, availability, and non-ethical considerations.⁸⁹ The transplantation of human AMSCs has been sequentially used to promote endometrial repair and regeneration in morphology and function.^{90–93} More than that, the thermoresponsive biomaterial PPCNg has also been used as a delivery vehicle of human AMSCs for promoting endometrial regeneration in rat model.⁵² The combination treatment group showed a significant increase in endometrial thickness and the number of endometrial glands, while the fibrosis area was significantly reduced, accompanied by a higher pregnancy rate.

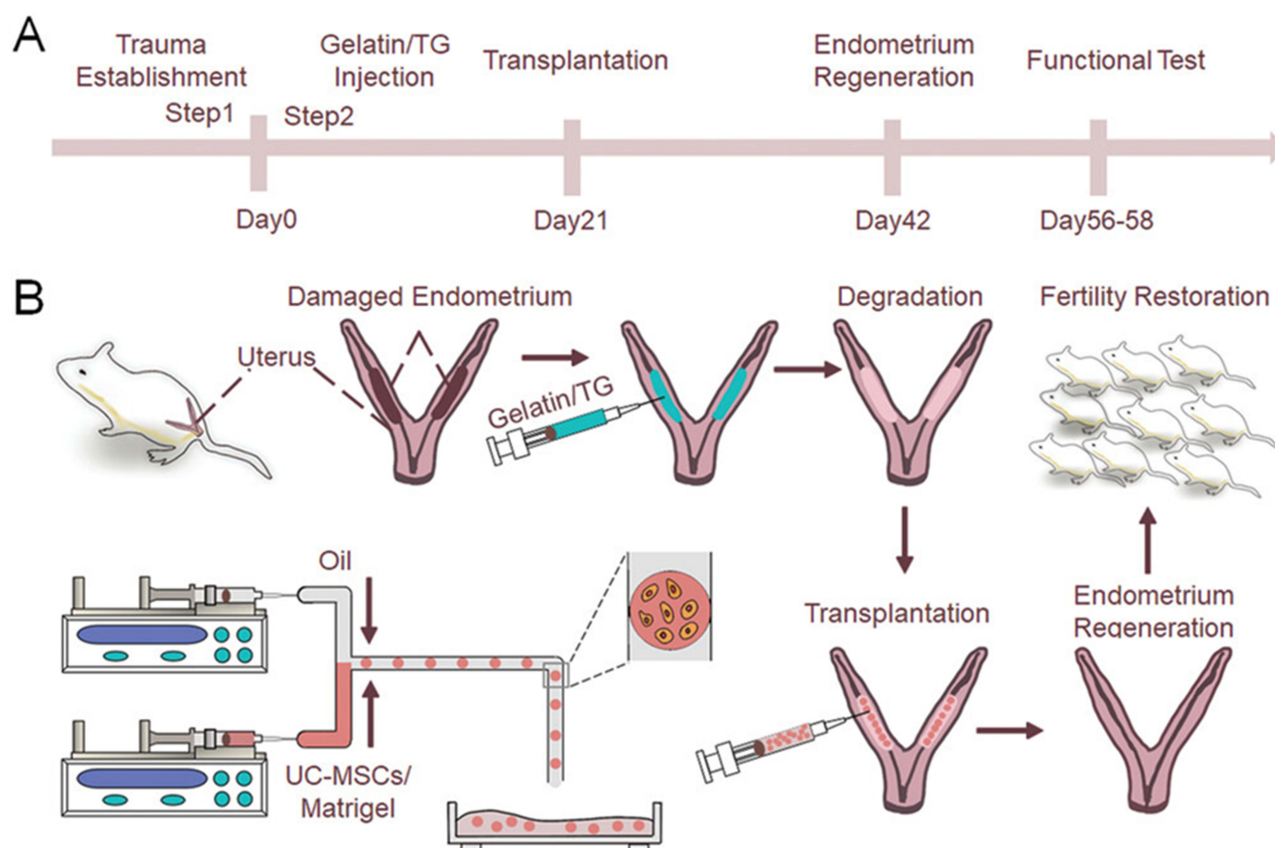


Figure 4 Schematic diagram of using matrix gel microspheres to deliver (UCMSCs) to regenerate injured endometrium. **(A)** Animal model production, therapeutic cell delivery, and postoperative examination. **(B)** Preparation and injection of matrix gel loaded with UCMSCs in damaged uterus and regenerated endometrium of rats. Reprinted from Bing Xu, Yuanxiong Cao, Zheng Zheng et al. Injectable Mesenchymal Stem Cell-Laden Matrigel Microspheres for Endometrium Repair and Regeneration. *Advanced Biology*. 2021;2000202. Copyright 2021 Wiley-VCH GmbH.⁸⁷

Although various stem cell-based biomaterials have made good progress, there are still some obstacles in clinical application, including stem cell survival rate, stability, tumorigenicity, immunogenicity, and therapeutic efficacy.⁹⁴ Especially, the impact of freeze-thaw processes during cell cryopreservation on cell activity, function, and paracrine ability needs to be studied more systematically.⁹⁵ However, it is foreseeable that in the near future, stem cells and their derived biomaterials from various sources will undoubtedly become the “living medicine” for clinical treatment beneficial to human life.

Synthetic Biomaterials

Biomaterials synthesized through chemical methods have been widely used for endometrial regeneration, thanks to their ability to design material structures and functions according to actual needs.⁹⁶ One of the major advantages of these materials is their biocompatibility and biodegradability.⁹⁷ For example, Pluronic F-127 (PF-127) is a therapeutic compound approved by the US Food and Drug Administration (FDA). PF-127 aqueous solution of medium concentration (15–30%, w/w) can be transformed from liquid at room temperature to hydrogel at physiological temperature for drug delivery and tissue engineering.⁹⁸ For example, Yang et al combined PF-127 hydrogel with Vitamin C (Vc) and BMSCs to enhance endometrial regeneration in rats.⁹⁹ They established a rat IUA model through mechanical injury and treated it with BMSCs and Vc embedded in the PF-127 hydrogel. The results showed that Vc could promote the survival of BMSCs encapsulated in PF-127 hydrogel, and their combination use repaired the damaged endometrium, making it have thicker endometrium, more glands, fewer fibrosis areas, and lower levels of proinflammatory IL-1 β expression. The PF-127 hydrogel presents a meaningful platform for cell therapy and endometrial repair of IUA. In addition, PF-127 has also been utilized to fabricate thermo-responsive injectable hydrogel, and simultaneously encapsulated with human UCMSCs and AMs to repair rat uterine scar.⁶⁶ The composite hydrogel promoted the proliferation of rat endometrial cells and the regeneration of rat uterine glands, inhibited endometrial fibrosis, and ameliorated uterine cavity restoration. Some other hydrogels similar to the above that loaded and released drugs have also made outstanding contributions to the regeneration of rat endometrium, such as aloe/poloxamer hydrogel delivering β -estradiol,¹⁰⁰ thermosensitive ϵ -polylysine-heparin-poloxamer hydrogel releasing keratinocyte growth factor (KGF),¹⁷ etc.

In addition to hydrogels, other forms of synthetic biomaterials have also been used for endometrial regeneration. For instance, the PCL nanofiber scaffolds mentioned in the “Nanofiber section” prepared by Nune et al, were subjected to aminolysis-assisted introduction of amine groups and maltose conjugation on the scaffolds.⁴⁴ The functionalized PCL scaffolds significantly enhanced the proliferation and cellular morphology of uterine fibroblasts. In another study, to overcome the limitations of low concentrations of β -estradiol at the site of endometrial injury by oral medication, a silicone rubber uterine stent for continuous drug release was designed and implanted into the uterine cavity of rats.¹⁰¹ The slow release of β -estradiol in the uterus could last for more than 60 days, and its concentrations both in the uterus and serum significantly increased. The drug sustained-release stent provided an extremely large amount of drugs for local uterine cavity injury, which will greatly benefit the repair of endometrial injury and alleviate uterine adhesions. Other synthetic biomaterials mentioned earlier included SMPs of PT loading CUPNSs, which slowly released silicon and copper ions to support angiogenesis and promote endometrial regeneration in rats.^{49–51} And PPCNg and PES nanofiber scaffolds, delivering stem cells and CNTs, also promoted the regeneration and function of the damaged endometrium.^{52,53}

Functional Biomaterials Based on Bioactive Substances, Small Molecule Drugs and Inorganic Materials

Growth Factors

As is well known, VEGF is involved in the pathological and physiological processes of angiogenesis, including vascular reconstruction, permeability, and tumorigenesis.¹⁰² It has a specific stimulating effect on endothelial cell proliferation. In one study, to induce efficient angiogenesis in thin endometrium treatment, Yang et al used microfluidic electrospray technique to fabricate hydrogel microspheres based on methacrylated hyaluronic acid (HAMA), and loaded VEGF.¹⁰³ The HAMA microspheres contributed to achieving satisfactory VEGF loading capacity and controlled release behavior, promoting the formation of blood vessels *in vitro* and *in vivo*, thereby enhancing endometrial regeneration of thin mouse

endometrium. This makes HAMA microspheres containing VEGF a potential drug delivery platform for treating thin endometrium and other biomedical fields. Different from it, another cytokine, granulocyte-macrophage colony-stimulating factors (GM-CSFs), is widely expressed in the female reproductive system and closely related to epithelial cells and reproductive function, including human embryo development, cell cluster survival rate, pregnancy rate and birth rate.¹⁰⁴ To further evaluate its impact on endometrial receptivity and repair, Liu et al intraperitoneally injected GM-CSFs, which significantly promoted proliferation of primary endometrial glandular cells and migration of stromal cells, and increased endometrial thickness, Ki67 expression levels, and the number of endometrial glandular cells in a thin endometrial mouse model.¹⁰⁵ The possible mechanism was the activation of phosphorylated Akt (p-Akt) and an increase in ribosomal protein S6 kinase β -1 (p70S6K) and c-Jun N-terminal kinase (c-Jun) expression levels. In addition, GM-CSF directly injected or loaded into polymer microspheres also exhibited the ability to recruit macrophages and regulate their phenotype from M1 to M2, inhibit endometrial tissue fibrosis, improve endometrial cell proliferation and vascular reconstruction, thereby improving the repair of endometrial damage and restoring mouse fertility.^{104,106} Chemokines are a class of small cytokines or signaling proteins secreted by cells that have the ability to induce directed chemotaxis of nearby cells.^{107,108} As one of the most famous chemotactic agents, stromal-derived factor-1 alpha (SDF-1 α) can specifically regulate the recruitment, migration, and proliferation of MSCs, thereby significantly promoting the repair of various tissues including the endometrium.¹⁰⁹ Moreover, the E7 peptide with EPLQLKM sequence helps collagen matrix selectively capture MSCs in vitro, and this specific affinity can promote wound healing and angiogenesis.¹¹⁰ Therefore, Xin et al functionalized collagen scaffolds with SDF-1 α and E7 peptides (Figure 5), achieving almost

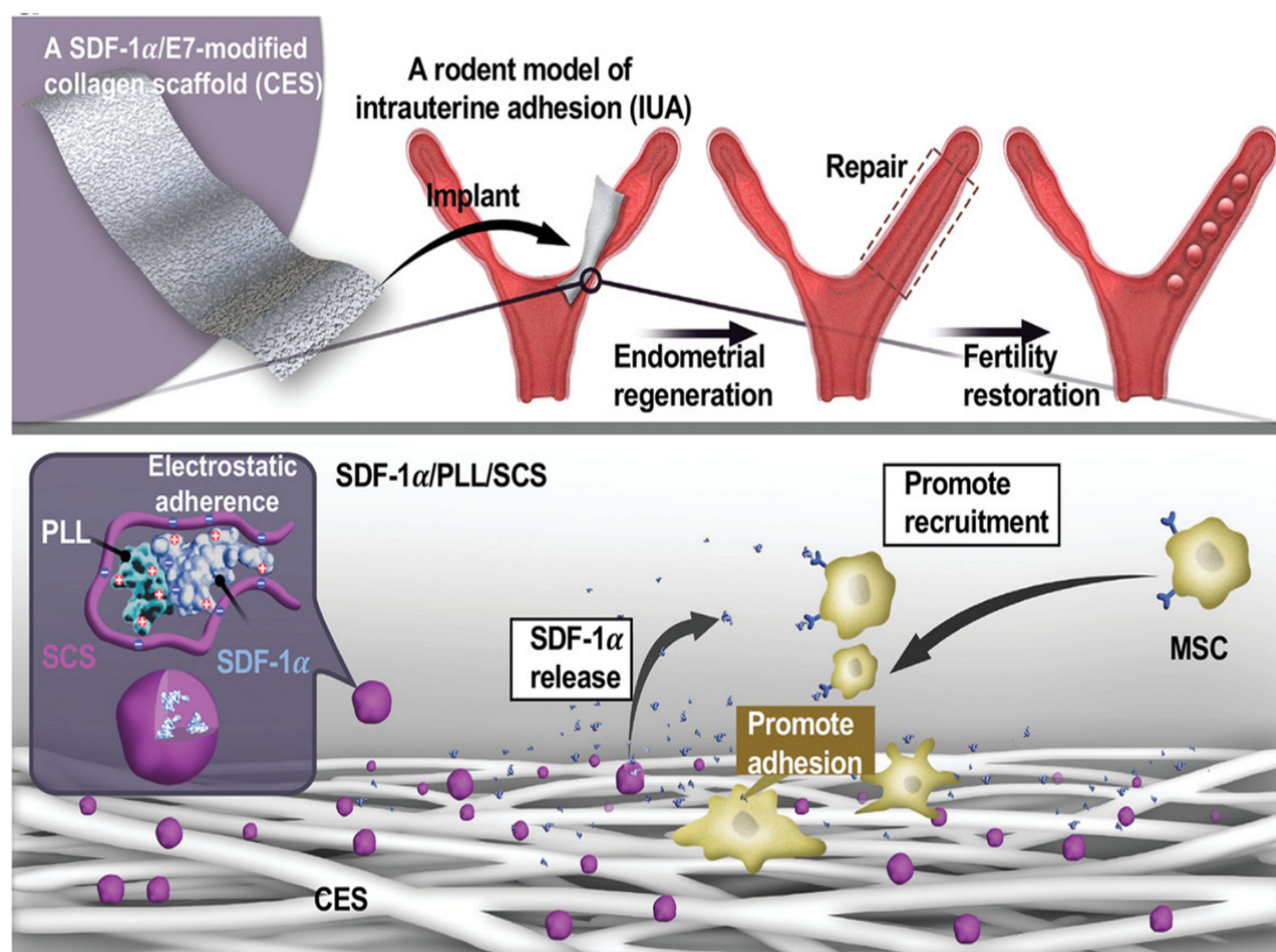


Figure 5 Schematic illustration of collagen scaffolds (CES) modified with SDF-1 α /E7 peptide for endometrial repair through recruitment and capturing MSCs. Reprinted from Liaobing Xin, Xiaowen Zheng, Jianmin Chen et al. An Acellular Scaffold Facilitates Endometrial Regeneration and Fertility Restoration via Recruiting Endogenous Mesenchymal Stem Cells. *Advanced Healthcare Materials*, 2022, 11, 2201680. Copyright 2022 Wiley-VCH GmbH.¹¹¹

complete repair of the endometrium and restoration of fertility in a rat IUA model. Mechanistically, the implantation of functional scaffolds might promote the synergistic recruitment of endogenous MSCs by macrophages.¹¹¹

Dai et al designed a recombinant bFGF that was fused with the collagen-binding domain (CBD) at the N-terminal and could target the collagen membrane to repair scar endometrium caused by trauma, enabling infertile mothers to conceive.^{12,112} Their research has made significant breakthroughs in both animal experiments and clinical studies. This bFGF delivery system (CBD-bFGF) with special targeted binding ability to collagen membrane can effectively overcome the problems of rapid diffusion, side effects, and short half-life of exogenous delivery of native bFGF, and reduce repeated doses.¹² The collagen membrane gradually degraded as the tissue was reconstructed, and the release rate of CBD-bFGF was adjusted correspondingly to maintain an effective concentration at the target site and promote tissue regeneration. The collagen membrane modified with CBD-bFGF effectively integrated into adjacent tissues, accompanied by collagen degradation, significant cellularization, and a large number of newly formed blood vessels, successfully achieving regeneration and remodeling of rat endometrium and uterine horn. In addition, this research team also used ultrasound-guided hysteroscopy to locally inject CBD-bFGF (100 µg, 2–4 times) around the scarred endometrium through the cervix in a clinical study.¹¹² The sustained release of bFGF promoted scar remodeling, improved endometrial angiogenesis, increased endometrial thickness, and resulted in successful pregnancies in three patients. This fully demonstrates that the bFGF therapy for human scar endometrium is safe and effective.

There are studies reporting that macrophages play a crucial role in the healing process, including clearing dead or damaged cells, recruiting and supporting stem cells to regenerate tissue and promote the formation of new blood vessels, replenishing new tissue in the area, and so on.¹¹³ This is seen as a turning point, bringing regenerative immunology from an idea into a serious research field, and finding new strategies for significantly improving tissue regeneration. LIF is an extremely important growth factor in the IL6 cytokine family and a major nutritional factor involved in many biological processes such as development, inflammation, and regeneration after injury.¹¹⁴ In female reproduction, LIF is crucial for uterine receptivity and initiation of blastocyst implantation. Research has shown that LIF is typically upregulated in trauma response and promotes tissue regeneration of many cell types, suggesting that LIF may play a critical role in endometrial repair. Xue et al incubated collagen scaffolds in LIF solution (0.25, 0.5, or 1.0 µg) and then sutured them into the resected uterine horns to evaluate the effect of LIF on the regeneration of fully damaged rat endometrium and uterine horn.¹¹⁵ The LIF/collagen scaffolds significantly increased the number of endometrial cells, improved vascularization and the percentage of alpha smooth muscle actin (α -SMA) positive areas, and increased pregnancy rates and fetus numbers. On the contrary, the infiltration of inflammatory cells was inhibited, while the pro-inflammatory cytokine IL-12 was downregulated and the anti-inflammatory cytokine IL-10 was upregulated, which might be attributed to the strong immunoregulatory function of LIF.

Unlike various growth factors, PRP is a concentrated component of blood, rich in high concentrations of growth factors and cytokines, which can significantly promote cell proliferation, differentiation, and angiogenesis, thereby enhancing endometrial regeneration.¹¹⁶ In animal experiments of ethanol-induced endometrium disorders, thrombin-activated PRP therapy promoted epithelial lining proliferation, matrix reconstruction, fibrosis reduction, epithelial thickening, increased expression of α -SMA, stimulated endometrium regeneration in mouse, and achieved healthy birth of live offspring.¹¹⁷ As another treatment platform to maintain patient safety, previous reports have shown that miRNA could regulate inflammation by stimulating M2 polarization in macrophages, demonstrating its potential as an inflammatory therapeutic agent.^{118,119} However, the limitation of naked miRNA is that it can be rapidly degraded or inactivated by nucleases in the blood.¹²⁰ Park et al encapsulated miRNA into liposomes, which could specifically target macrophages, promote M2 polarization, and reduce inflammation.¹²¹ When administered in vivo, the angiogenesis of damaged endometrium in the mouse AS model was improved, and uterine fibrosis was relieved, resulting in good uterine recovery.

Small Molecule Drugs and Inorganic Materials

As mentioned earlier, lower doses of asiaticoside can stimulate collagen synthesis, promote the production of glycosaminoglycans, accelerate the cell cycle, and increase local tissue tension.¹²² In one study, asiaticoside has been incorporated into polymeric microspheres and thermo-responsive injectable hydrogel to enhance cell proliferation and

angiogenesis, reduce endometrial fibrosis, and facilitated the repair of rat uterine scars through slow release.⁶⁶ Similarly, alpha-tocopherol (α -tocopherol) and phylloquinone are fat-soluble vitamins, α -tocopherol was first identified as an important dietary factor for maintaining normal reproduction in rats over 90 years ago, and it is highly correlated with the reproductive process.¹²³ And the deficiency of phylloquinone can lead to serious complications and risks during pregnancy, making it prone to bleeding and ultimately death.¹²⁴ Bafar et al found that phylloquinone could reduce uterine contractility in mouse, while α -tocopherol could increase contractility. But both could directly regulate uterine contraction force and modulate reproductive function in uterine disorders.¹⁵

Kang et al reported that treating thin mouse endometrium with botulinum toxin A (BoTA) could increase endometrial receptivity and angiogenesis, thereby improving the endometrial environment. The therapeutic mechanism might be that insulin-like growth factor binding protein-3 (IGFBP3) could regulate the hydrolysis and cleavage osteopontin (OPN) protein.¹²⁵ This indicates that BoTA is an effective treatment strategy for treating patients with thin endometrium. Additionally, β -estradiol is an essential steroid hormone in the human body that can effectively promote endometrial regeneration and angiogenesis after menstruation.^{101,126} It is commonly used as an adjuvant therapy and to prevent adhesions after gynecological surgery. Recently, β -estradiol has also been incorporated into different forms of biomaterials to enhance the regeneration of rat endometrium, including injectable aloe/poloxamer hydrogel, heparin-poloxamer thermosensitive hydrogel, and silicone rubber stent.^{100,101,127} As a powerful antioxidant, alpha lipoic acid (ALA) has been found to effectively increase scar tissue thickness, upregulate the expression levels of α -SMA and VEGF, and accordingly promote wound healing in rat with full-thickness uterine injury.¹⁴ When the optimized concentration of thrombin was used to construct and strengthen the cross-linking of HA/fibrin composite hydrogel, efficient cell delivery was achieved.⁶⁵ That was because different concentrations of thrombin affected the hardness of the hydrogel, and sufficient hardness promoted the integration of the transplanted cells and made it easier to enter the surface of the damaged mouse endometrium.

In addition to the above-mentioned drugs, many other small bioactive molecules have also been reported to regulate hormone imbalance, inflammation, oxidative stress, and apoptosis, and play a crucial role in rat endometrial regeneration, including resveratrol,¹⁶ zingerone,¹²⁸ metformin,¹²⁹ etc. On the other hand, inorganic materials, such as BG, copper ion (Cu^{2+}), silver ion (Ag^+), etc., were also loaded into various hydrogels and continuously released to promote the proliferation of endometrial epithelial cells, showed antibacterial activity, and enhanced the repair of mouse and rat endometrium.^{130,131}

Innovative Technologies

As one of the innovative strategies, 3D bioprinting technology was utilized by Nie et al to engineer a biomimetic endometrial construct with a two-layer structure using a hydrogel composed of sodium alginate and HA for rat endometrial tissue regeneration.¹³² The upper and lower layers of the 3D bioprinted grid-like graft were composed of endometrial epithelial cell layer and ESC cell layer, respectively. In the rat model of partial hysterectomy, the bioprinted graft fulfilled the morphological and structural repair of the endometrial wall and significantly promoted the reproductive effect of the regeneration area, with a success rate of 75%. Similarly, 3D bioprinting has also been used to construct hydrogel scaffold containing mesenchymal stem cells derived from human induced pluripotent stem cells (hiMSCs), providing suitable microenvironment and higher viability for cells.²¹ The transplantation of the hiMSC-embedded 3D printing hydrogel scaffold improved the regeneration of rat endometrium, including endothelial cells and stromal cells, and also restored the embryonic pregnancy function of the injured endometrium. In another study, a composite hydrogel was 3D-printed with GelMA and methacrylate collagen (ColMA), and the successful encapsulation of AMSCs in the hydrogel significantly prevented the adhesion of uterus cavity in rat IUA model.¹³³ Despite this, 3D printing still needs to overcome some technical issues and may effectively combine interdisciplinary complementarity to achieve better outcomes.¹³⁴

In addition, hiMSCs from patient tissues can also be loaded into 3D-printed hydrogel scaffolds to effectively treat endometrial injury and restore reproductive function of women of childbearing age.¹³⁵ Lu et al utilized microfluidic 3D printing technique to prepare injectable porous hydrogel (PH) scaffolds using GelMA and PEO solutions to deliver ADSCs and enhanced rat endometrial regeneration. After injection into the body, the PH scaffolds recovered their

original shapes, exhibiting high cell viability and cell migration of ADSCs, improving angiogenesis, regeneration and endometrial receptivity in injured rat endometrium (Figure 6).¹³⁶ It is very interesting that as one of the innovative technologies, surgical robots have been designed for endometrial regeneration surgery to restore female fertility. The surgical robot system consists of a flexible hysteroscope, support arms, and additional new instruments, which can easily perform surgeries and reduce damage to the uterus.¹³⁷

With the rapid development of the latest technologies, sophisticated patient-derived endometrial organoids have also been designed and developed using synthetic hydrogels containing peptides and epithelial and stromal cells to stimulate internal tissues, study the physiological and pathological characteristics, and understand the repair patterns of human endometrium.^{138–140} The transplantation of organoids constructed from acellular porcine endometrial hydrogel containing tissue-specific extracellular matrix can also effectively promote the repair of mouse endometrium and improve reproductive prognosis.^{24,141} Correspondingly, organ-on-chips for disease reproduction and female uterine regeneration have also been developed as a new modeling strategy for evaluating endometrial disease or regeneration quality.^{22,142} In the near future, innovative research on organ-on-chips and organoids is expected to address a series of challenges in animal experiments, such as animal use, individual differences, and imbalanced results between groups, to provide standardized evaluation models for endometrial regeneration and repair.¹⁴³ The combination of organ-on-chips, organoids, and reproductive science will explore bright prospects for endometrial repair and regeneration, achieving great success. However, organ-on-chips and organoids technologies for the reproduction system are still in their early and immature stages.^{144,145} To achieve the great goal of studying the basic laws of endometrial tissue and promoting its perfect regeneration, more innovative research and progress are still needed.

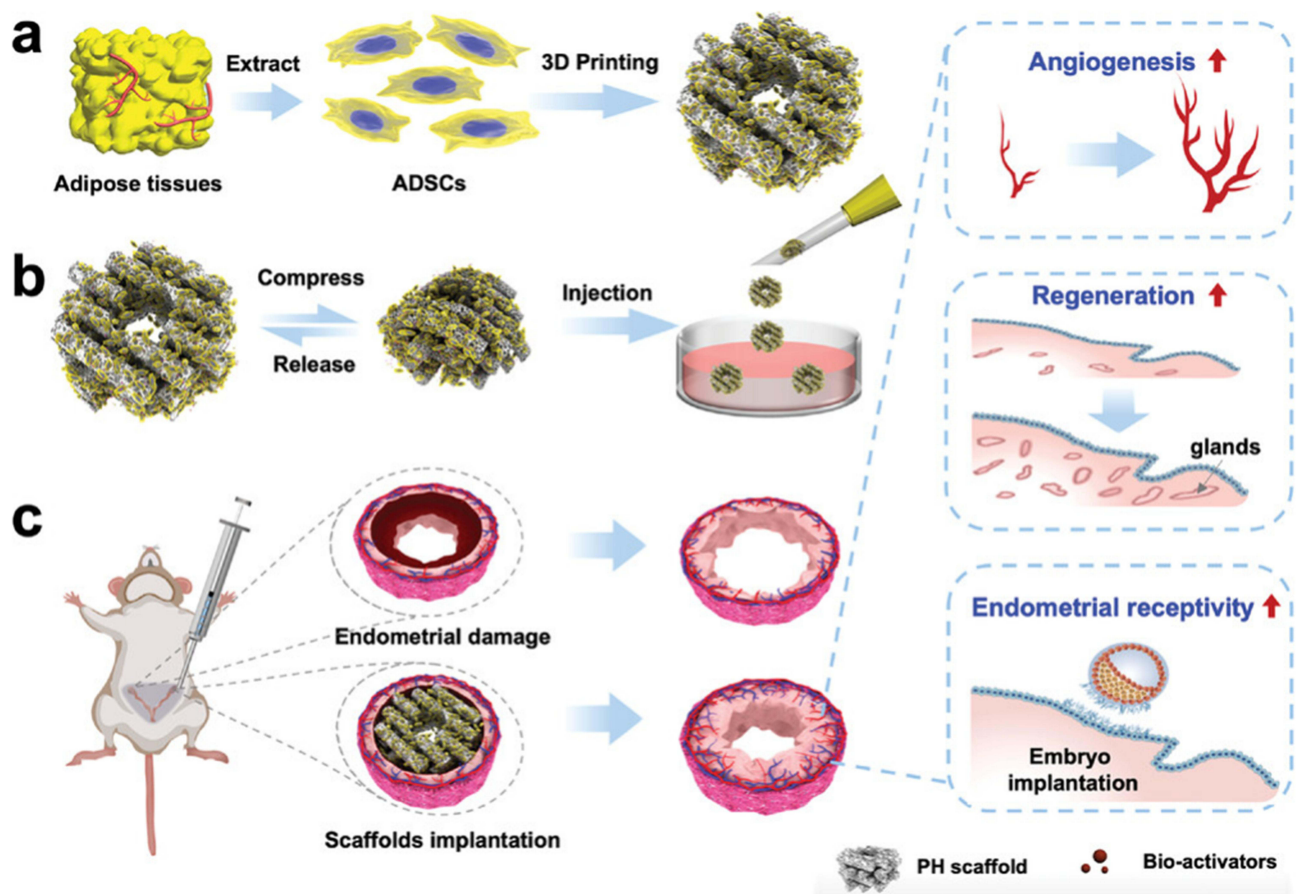


Figure 6 Schematic diagram of injectable 3D printed porous hydrogel (PH) scaffolds delivering ADSCs to promote endometrial regeneration. (a) ADSCs were encapsulated in injectable PH scaffolds. (b) The shape of PH scaffolds could be customized, displaying deformation recovery and injection ability. (c) The cell-scaffold constructs accelerated the regeneration of damaged endometrium in rats. Reprinted from Shun Lu, Xiaocheng Wang, Wenzhao Li et al. Injectable 3D-Printed Porous Scaffolds for Adipose Stem Cell Delivery and Endometrial Regeneration. *Advanced Functional Materials*, 2023, 23033368. Copyright 2023 Wiley-VCH GmbH.¹³⁶

Current Problems and Future Perspective

Above, we have reviewed the design and characteristics of nanomedicine and biomaterials, as well as the application pathways, dosages, and achieved effects of exosomes for endometrial regeneration. All of these contents have been briefly summarized in [Tables 1 and 2](#). In addition, we should pay more attention to some important issues. Firstly, through molecular design and structural modification, the composition of biomaterials can be cleverly regulated to achieve adjustable physical, chemical, and biological properties. In terms of tissue source of natural biomaterials, one of the main limitations of obtaining hydrogels or scaffolds from human endometrial ECM is that it is difficult to obtain enough uterine tissue for large-scale production of acellular biomaterials. Considering the unique properties of the endometrium and the inherent need for regeneration, the designed biomaterial scaffold or patch should have high biodegradability. The regeneration process requires a specific time period, so the degradation of biomaterials should not be too fast or too slow, but it is best to achieve uniform degradation within a certain period of time, which also poses specific challenges to the chemical structure of biomaterials. Moreover, the degradation products should be non-toxic and not cause significant local inflammatory reactions or organ toxicity. Secondly, by adding or loading appropriate bioactive substances, the immune and regeneration signaling pathways can be regulated, achieving good functional repair effects. Although stem cells and growth factors can facilitate therapeutic effects in endometrial regeneration and reproductive medicine, they are often associated with higher risks of tumor development, rejection, and immune reactivity, so their safety needs further verification. Finally, by optimizing animal experimental design, positive and efficient clinical results can be obtained, guiding product conversion and market application. However, there are still some obstacles to the regeneration of intact endometrial tissue, which involves many types of cells, including endometrial cells, progenitor cells, stem cells, etc., requiring an appropriate microenvironment to maximize the support of stem cell functions such as self-renewal, expansion, and induction of differentiation.¹⁴⁶

Excitingly, stem cells and biomaterials have already entered the clinical trial stage of regenerating endometrium. For example, Wu et al investigated the implantation of MenSCs into damaged endometrium of the uterus, which increased endometrial thickness and improved pregnancy rate in IUA patients.¹⁴⁷ Their study isolated autologous stem cells from the menstrual blood of 12 infertile women aged between 22 and 40, and transplanted MenSCs into their respective uterus. The intrauterine transplantation of autologous MenSCs significantly improved endometrial thickness and achieved a high clinical pregnancy rate (41.7%). In another clinical study evaluating PRP treatment for thin endometrium, researchers found that intrauterine infusion of PRP significantly increased endometrial thickness in all 10 patients, and ultimately, 5 out of 10 patients successfully became pregnant, demonstrating the effectiveness of PRP in promoting the growth of thin endometrium.¹⁹ Some other clinical trials have also found that the use of PRP could alleviate local inflammation caused by endometrial damage, reduce scar growth and adhesion formation, and ultimately improve pregnancy efficiency.^{148–150} In addition, some other clinical trials have also shown that SIS scaffolds, collagen scaffolds, and HA hydrogels could effectively repair endometrial fibrosis, prevent adhesion, and improve the pregnancy outcome of IUA infertile patients.^{151–153} The clinical trials of the series of new technologies and biomaterials mentioned above have fully demonstrated their potential clinical application significance.

However, there is still a gap between the research and its clinical application of endometrial repair and regeneration. This is because compared to other tissues in the human body, the biggest uniqueness of endometrium lies in its dynamic microenvironment throughout the menstrual cycle, and biomaterials must be able to match this feature in structure and function. On the other hand, it is also necessary to consider how to maintain the long-term stable endocrine function of transplanted and regenerated endometrial tissue to meet and match the needs of female pregnancy and embryo implantation. Last but not least, the design of restorative biomaterials should also take into account the characteristic changes in tissue structure and function caused by endogenous hormone changes in menopausal women due to osteoporosis or cardiovascular disease. So far, most studies on biomaterials for endometrial repair and regeneration in animal experiments have been conducted using small animals such as mice and rats. However, it is necessary to promote in vivo research on biomaterials with promising applications in large animals, which will have more advantages and persuasiveness for future clinical application trials and human marketing. Especially for studying the in vivo biocompatibility, immunogenicity, biodegradability, integration with body tissues, biological functions, and in vivo safety issues of

Table I Nanomedicine and Biomaterials Used for Endometrial Regeneration

Materials	Sources	Architectures	Advantages	Disadvantages	Safety	Refs.
Nanomedicine	Exosomes	Nanovesicles	Nanoscale size, abundant biomolecules, biodegradability, cargo carrying capacity	Instable, short half-life in vivo, easily be cleared by host cells	Low risk of immune response and rejection	[31, 34–36]
Nanomaterials	Polymers, CUPNSs, CNTs, CeO ₂	Nanofibers, nanosheets, nanotubes, nanoparticles	Large specific surface area, 3D microstructure similar to ECM, appropriate porosity	Low production efficiency, poor mechanical properties	No organ toxicity, no difference in biochemical indicators	[44–48, 51–54]
Natural biomaterials	Collagen, HA, sodium alginate, fibrin, gelatin, sericin, GelMA ColMA, SerMA	Scaffolds, hydrogels, nanofibers	Biocompatibility, biodegradability, biological activity, low cost	Poor mechanical properties	Good biocompatibility	[57–61, 65, 66]
Acellular biomaterials	Decellularized uterine matrix, decellularized amniotic membrane	Scaffolds, patches	Tissue-specific biological composition, 3D structural microenvironment	Risk of pathogen transmission, poor mechanical properties	Good biocompatibility	[69, 71–73, 75]
Stem cell-based biomaterials	BMSCs, ADSCs, dEMSCs, UCMSCs, DSCs, OMECs, EmSCs, ESCs, EnSCs, hiMSCs, EECs, AMSCs, BMSC-CM	Injectable solutions	Multilineage differentiation, paracrine effect, immunoregulation, injectability	Restricted source, ethical concerns, technical limitations	Good biocompatibility, no side effect	[52, 82–88, 90–93]
Synthetic biomaterials	PPCNg, PF-127, PCL, PLGA, PT, PES, ε -polylysine-heparin-poloxamer, aloe/poloxamer	Scaffolds, microspheres, SMPs, hydrogels	Easy to adjust structure and property, high yield, biocompatibility, biodegradability, processability	Lack of biological functionality, using solvents, technical complexity	Good biocompatibility	[17, 44, 49–53, 66, 99–101]
Growth factors	KGF, IGF-I, SDF-1 α , E7, PDGF, GM-CSF, bFGF, CBD-bFGF, PRP, LIF	Solid, injectable solutions	Rich biological activity, injectability, regulating cellular metabolism, widely applicable	Instable, prone to degeneration and inactivation	Good biocompatibility, few cells grow abnormally	[12, 103–105, 111, 112, 115, 117, 121]
Small molecule drugs	Thrombin, asiaticoside, phylloquinone, BoTA, α -tocopherol, ALA, resveratrol, zingerone, metformin, Vc, miRNA, E7	Solid, injectable solutions	Low cost, convenient storage, high purity, and high stability between batches, spatiotemporal regulation	Requiring carriers, Unclear local action dosage and duration	High safety, good biocompatibility	[14–16, 66, 101, 123, 125–129]
Inorganic materials	Borosilicate BG, Cu ²⁺ , Ag ⁺	Nanoparticles, ions	Stable structure and chemical properties, biologically activity, nanoscale	Requiring carriers, poor mechanical properties	Good biocompatibility	[51, 59, 130, 131]

Abbreviations: CUPNSs, cuprorivaite (CaCuSi₄O₁₀) nanosheets; CNTs, carbon nanotubes; Fibrin, fibrinogen; HA, hyaluronic acid; GelMA, methacrylate gelatin; ColMA, methacrylate collagen; SerMA, methacrylate sericin; BMSCs, bone marrow mesenchymal stem cells; ADSCs, adipose derived stem cells; dEMSCs, decidualized endometrial stromal cells; UCMSCs, umbilical cord mesenchymal stem cells; DSCs, decidual stromal cells; OMECs, oral mucosal epithelial cells; EmSCs, embryonic stem cells; ESCs, endometrial stromal cells; EnSCs, endometrial stem cells; hiMSCs, MSCs derived from human induced pluripotent stem cells; EECs, endometrial epithelial cells; AMSCs, amniotic membrane stem cells; BMSC-CM, BMSC-conditioned medium; PPCNg, poly(polyethylene glycol citrate-co-N-isopropylacrylamide) gel; PF-127, Pluronic F-127; PCL, polycaprolactone; PLGA poly (lactide-co-glycolide); PT, poly(D, L-lactide-co-trimethylene carbonate); PES, polyethersulfone; SMPs, shape memory polymers; KGF, keratinocyte growth factor; IGF-I, insulin-like growth factor I; SDF-1 α , stromal derived factor-1 alpha; E7, EPLQLKM peptide; PDGF, platelet-derived growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; bFGF, basic fibroblast growth factor; CBD-bFGF, collagen-binding domain-bFGF; PRP, platelet rich plasma; LIF, leukemia inhibitory factor; miRNA, micro messenger ribonucleic; α -tocopherol, alpha-tocopherol; BoTA, botulinum toxin A; ALA, alpha lipoic acid; Vc, vitamin C; BG, bioactive glass; Cu²⁺, copper ion; Ag⁺, silver ion.

Table 2 Overview of Cell Sources, Application Methods and Amounts, Mechanism, and Treatment Effect of Exosomes for Endometrial Regeneration

Cell Sources	Application Methods	Application Mounts	Mechanism	Treatment Effect	Refs.
UCMSCs	Loading in collagen scaffold and implantation	100 μ L of exosomes suspension (3×10^{11} mL ⁻¹)	Immunomodulatory functions	Endometrial regeneration, fertility restoration	[31]
ADSCs	Loading in decellularized ECM and injection	100 μ L PBS containing 100 mg ECM@ADSC-Exos	Releasing endogenous growth signals, promoting neovascularization	Angiogenesis, endometrial regeneration, fertility restoration	[34]
IL-1 β activated BMSCs	Loading in polypeptide hydrogel and injection	200 μ L β -exo@pep (20 μ g mL ⁻¹)	Inhibiting intrauterine inflammation through NF- κ B signaling pathway	Angiogenesis, endometrial regeneration, treatment of endometritis	[35]
DSCs	Loading in in alginate hydrogel and injection	50 μ L solution of 3×10^{11} mL ⁻¹ exosomes	Mitigating aberrant matrix component deposition and excessive fibrogenesis	Angiogenesis, endometrial regeneration, fertility restoration	[36]

such biomaterials, it is of great significance. This is the most important factor to consider when launching endometrial repair products. Finally, when it comes to the use of allogeneic, xenogeneic, or even embryonic stem cells, ethical, legal, and social factors must also be considered.

In the near future, rapidly developing cutting-edge technologies will make it possible to manufacture personalized tissues and artificial organs, and minimize the incidence of organ rejection, thus fundamentally changing the field of regenerative medicine. In addition, the integration of artificial intelligence is expected to integrate various clinical parameters and biomarkers, and the development of predictive machine learning models will also be able to identify patterns related to subtle changes in the endometrium and specific patient responses to treatment, thereby helping to develop more targeted treatment or regeneration strategies. Overall, with the continuous development and innovation of regenerative medicine, new treatment options will continue to emerge, promoting the perfect regeneration of the endometrium.

Conclusion

In this review, we summarized the use of nanomedicine and biomaterials to repair and regenerate the endometrium, overcoming the shortcomings of traditional drug treatment methods. The ideal biomaterials for regenerating endometrial tissue must first have excellent biocompatibility, appropriate degradability and mechanical properties. On the other hand, the injectability of hydrogel materials also has unique advantages in drug delivery, 3D (bio)printing, and other fields. In addition, the synergistic effect between growth factors and stem cells can help biomaterials reconstruct an ideal biomimetic repair microenvironment for endometrial damage. Future research should focus more on utilizing innovative technology and strategies to enhance the synergistic effect of stem cells and growth factors, to achieve a therapeutic effect of one plus one is greater than two. Some newly developed nanocarrier systems and their sustained and controlled release technologies, as well as local targeted drug delivery technologies, will bring new solutions for endometrium reconstruction. Finally, the most important thing is that when applying any innovative biomaterials and technologies in clinical practice, patient safety should always be the top priority. Therefore, researchers and developers should focus on safety issues in future research and clinical applications.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by the Jilin Provincial Scientific and Technological Development Program (YDZJ202401190ZYTS).

Disclosure

The authors report no conflicts of interest in this work.

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