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REVIEW

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

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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

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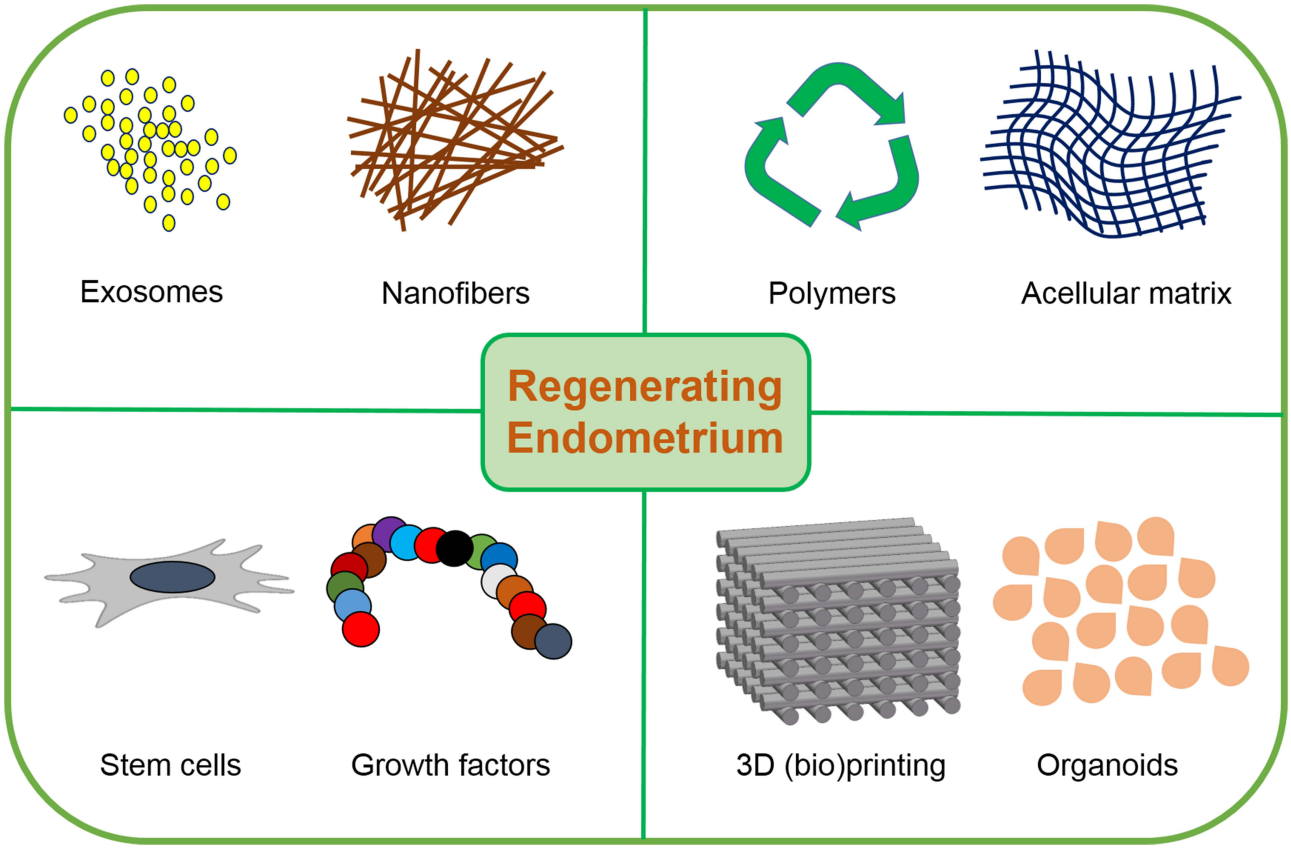
Graphical Abstract



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

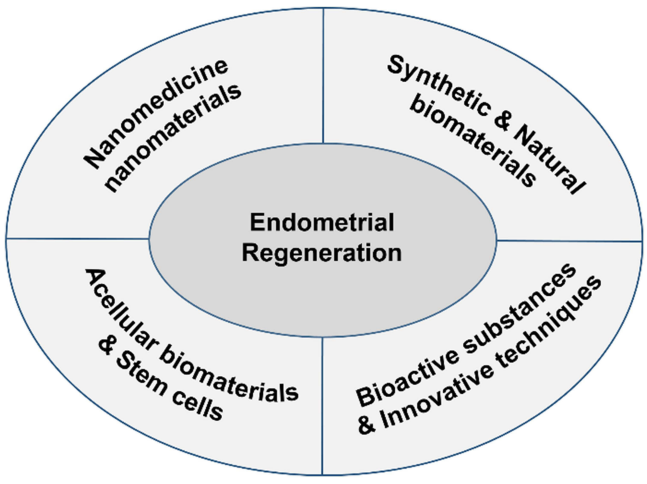


Figure 1 Summary of nanomedicine and biomaterials for endometrial regeneration.

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-1β (IL-1β)-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-β1 (TGF-β1), 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 microenvironment 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 ($CaCuSi_4O_{10}$) 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.

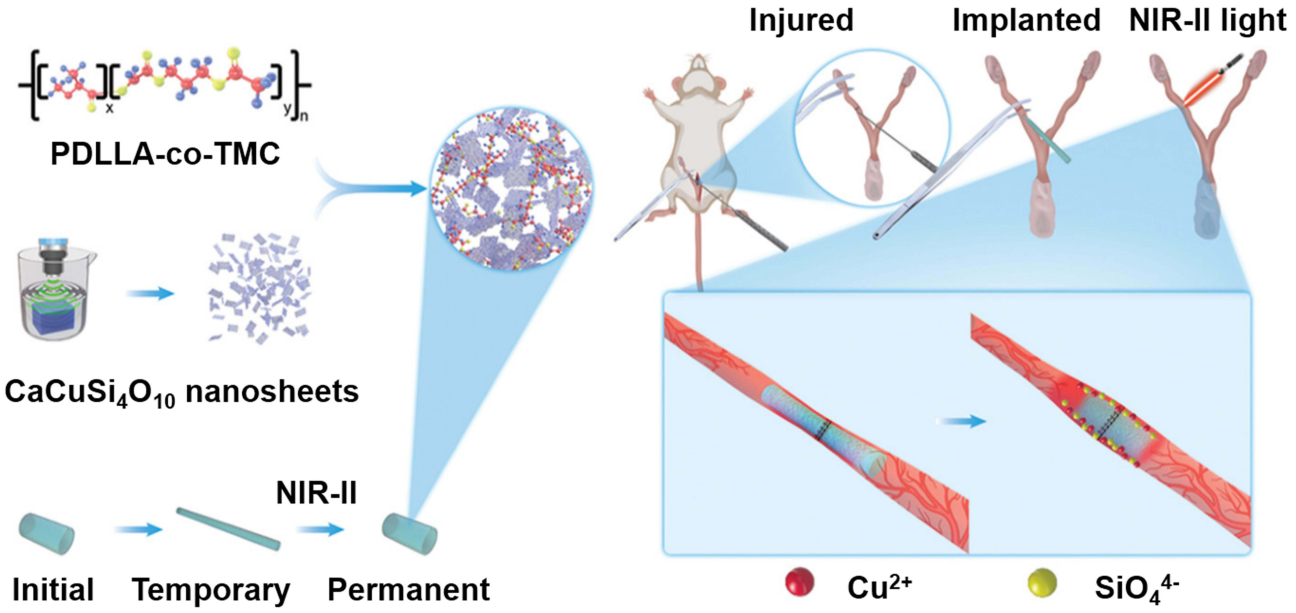


Figure 2 Schematic illustration of NIR-II light-responsive CUP/PT composites for preventing intrauterine adhesion (IUA) and endometrial regeneration. Reprinted from Chenle Dong, Chen Yang, Muhammad Rizwan Younis et al. Bioactive NIR-II Light-Responsive Shape Memory Composite Based on Cuprorivaite Nanosheets 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 (Ca^{2+}) 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, Rezaeipour 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-β1, 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

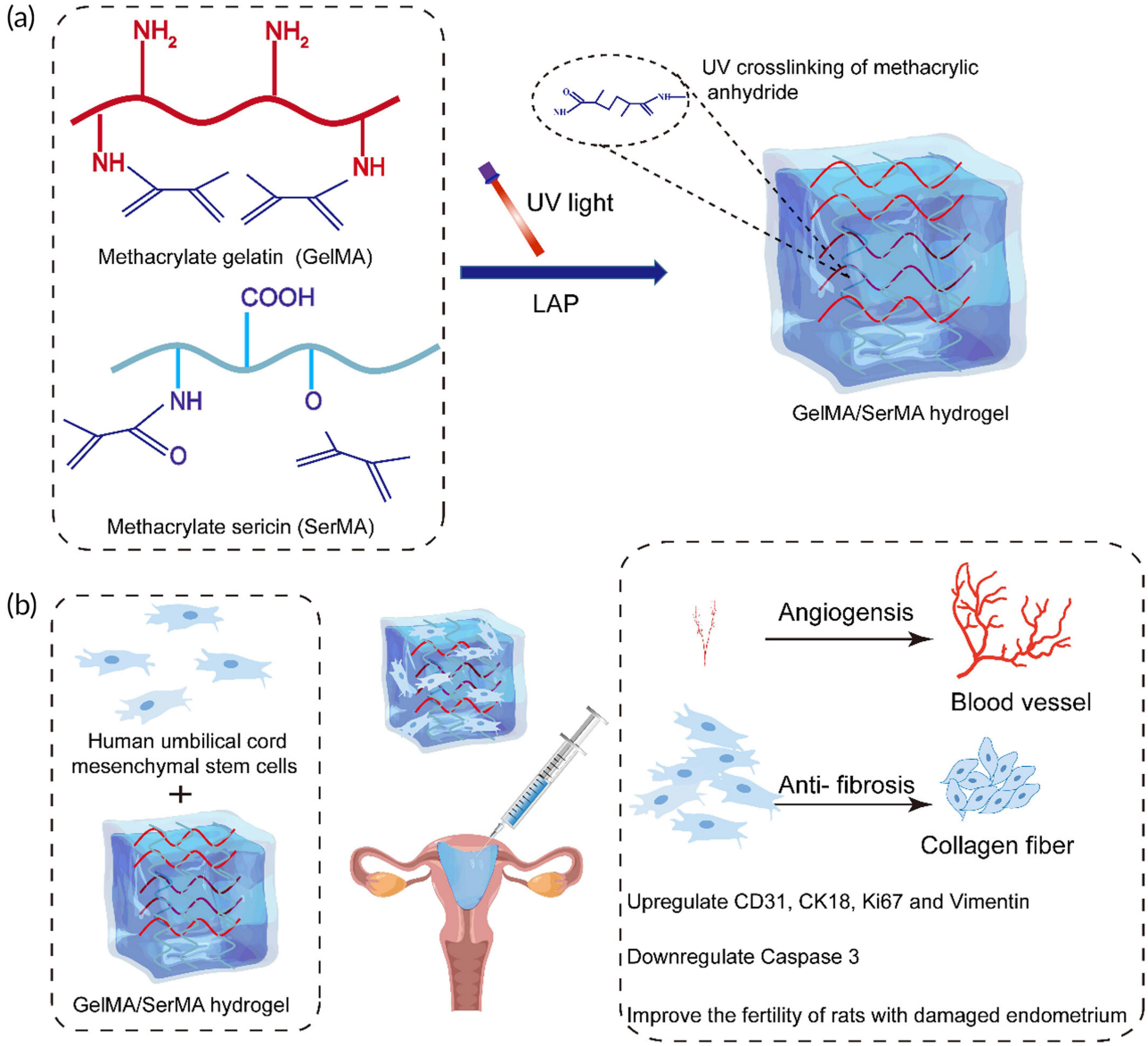


Figure 3 GelMA/SerMA injectable hydrogel encapsulated with HUMSCs for the treatment of uterine injury. (**a**) Preparation of GelMA/SerMA hydrogel. (**b**) GelMA/SerMA hydrogel delivering HUMSCs to treat uterine injury by intrauterine injection. Reprinted from Lixuan Chen, Ling Li, Qinglin Mo et al. 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.

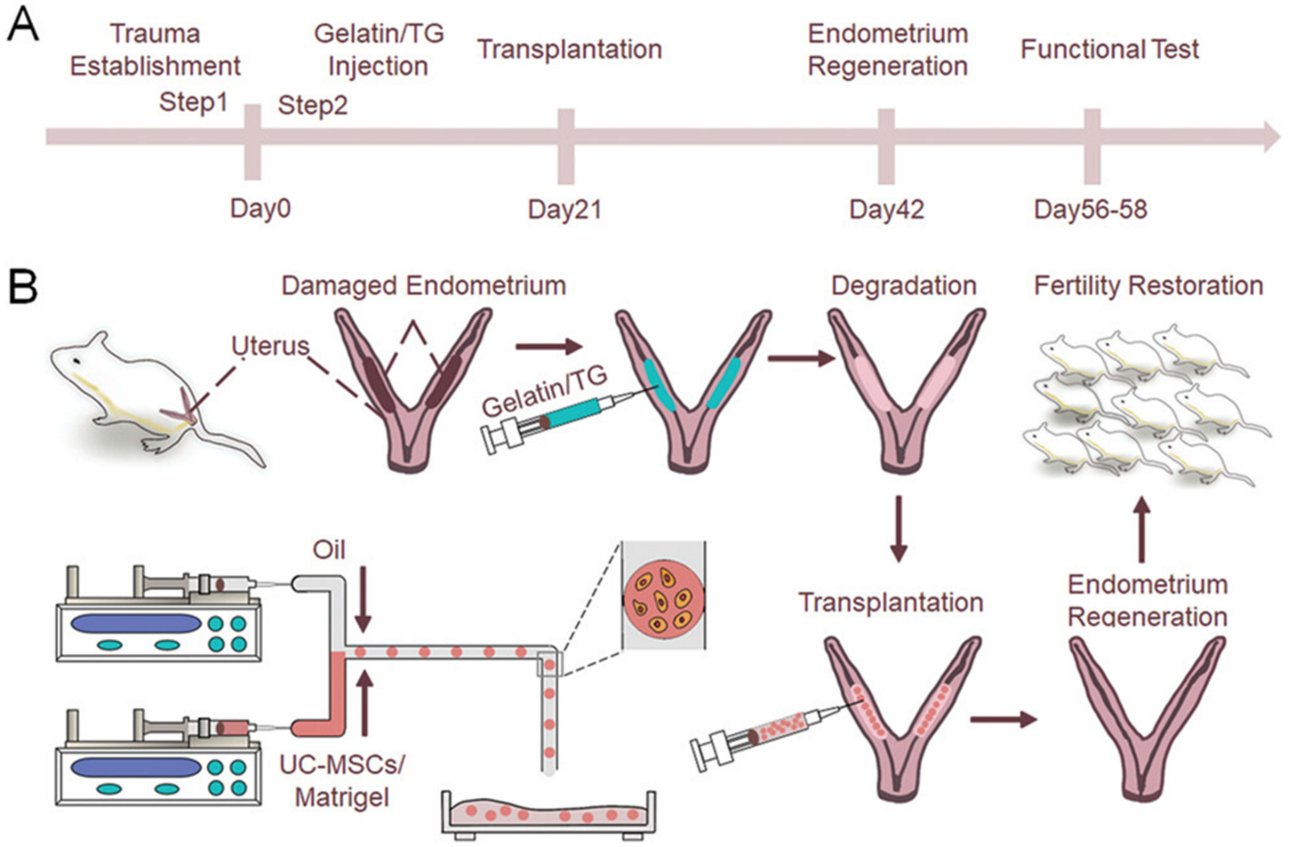


Figure 4 Schematic diagram of using matrix gel microspheres to deliver (UCMSCs) to regenerate injured endometrium. (**A**) Animal model production, therapeutic cell delivery, and postoperative examination. (**B**) Preparation and injection of matrix gel loaded with UCMSCs in damaged uterus and regenerated 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-1β 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-1α) 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-1α and E7 peptides (Figure 5), achieving almost

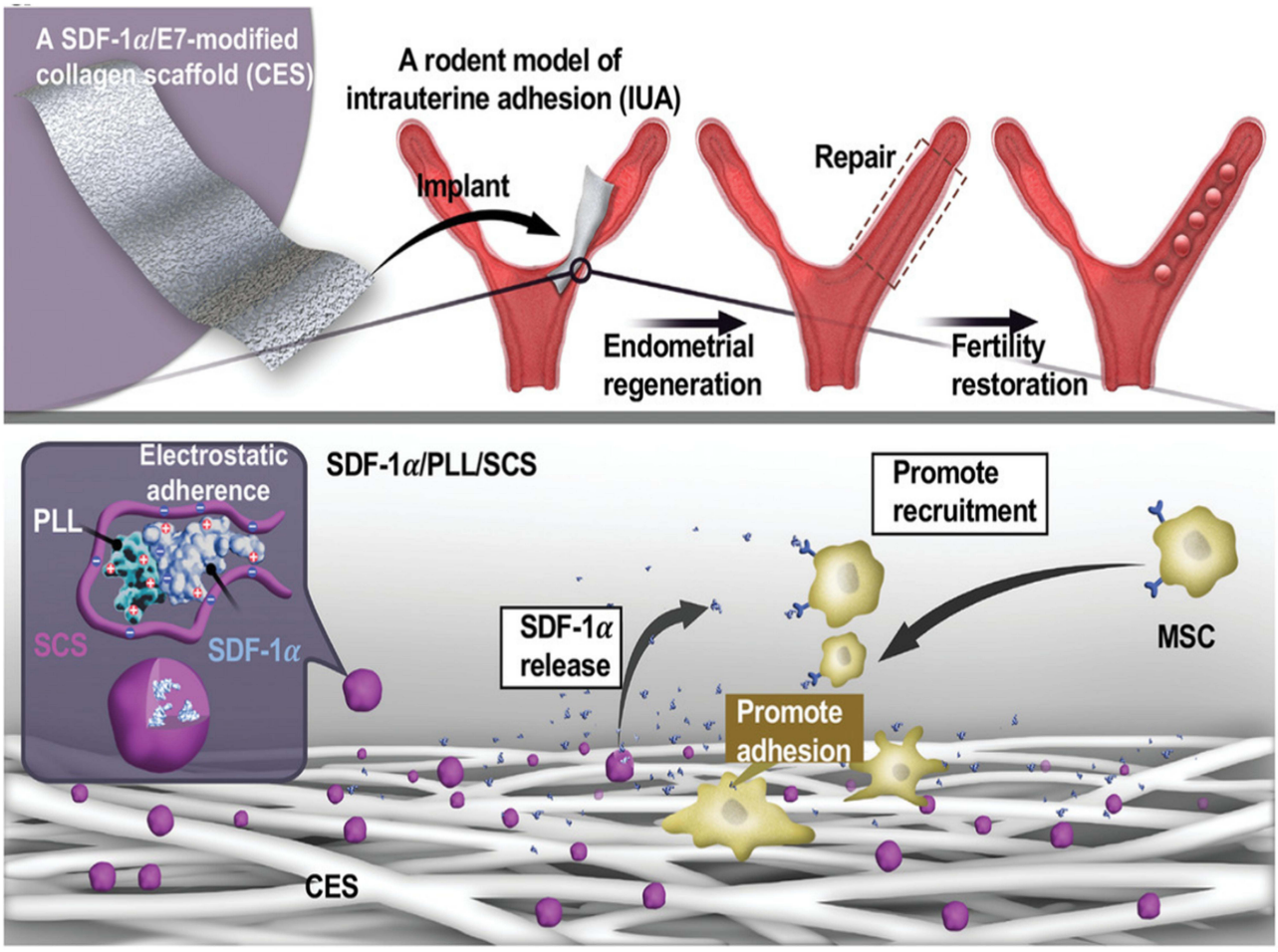


Figure 5 Schematic illustration of collagen scaffolds (CES) modified with SDF-1α/E7 peptide for endometrial repair through recruitment and capturing MSCs. Reprinted from Liaobing Xin, Xiaowen Zheng, Jianmin Chen et al. An Acellular Scaffold Facilitates Endometrial Regeneration and Fertility Restoration 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] Bafor 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.

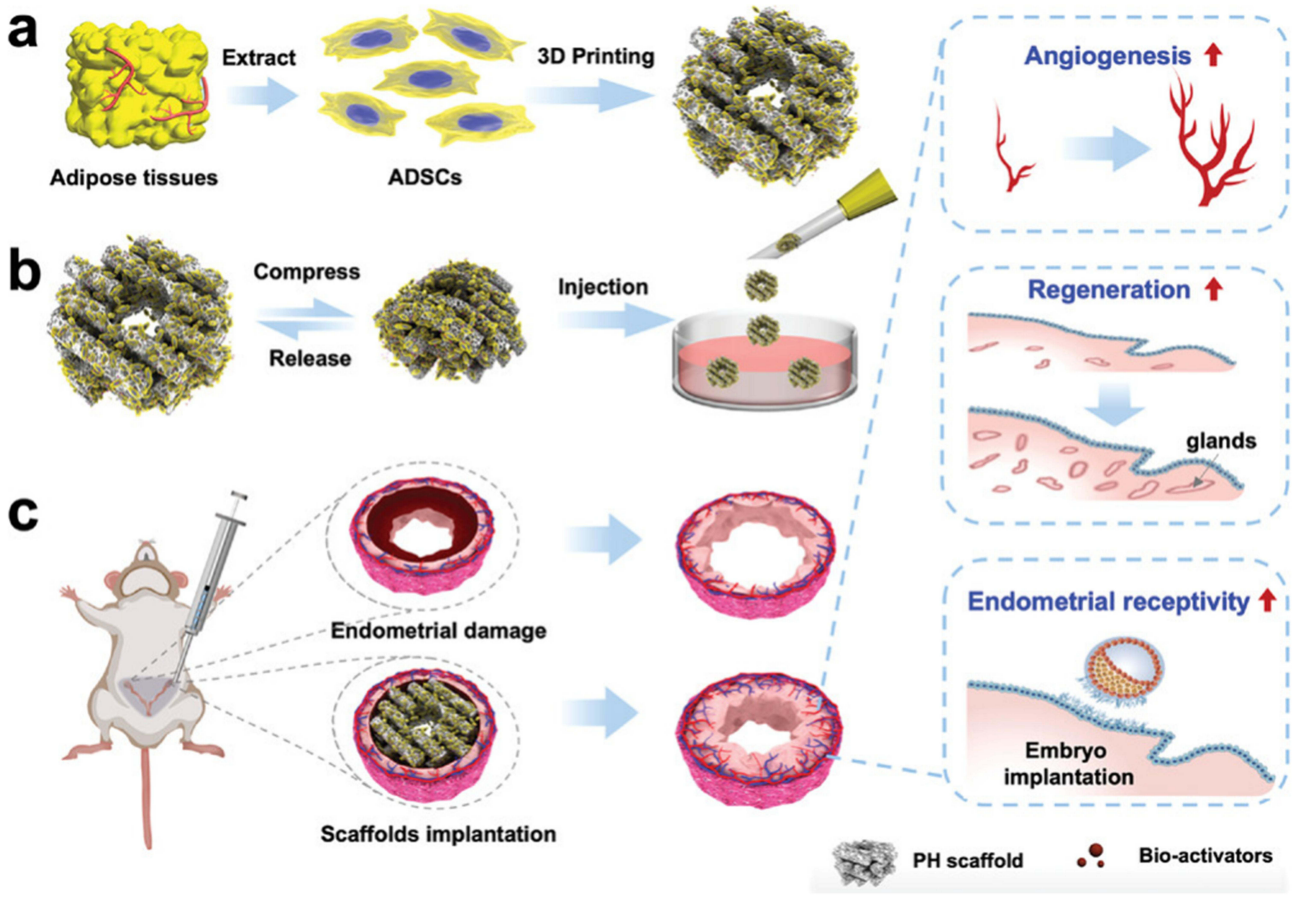


Figure 6 Schematic diagram of injectable 3D printed porous hydrogel (PH) scaffolds delivering ASCs to promote endometrial regeneration. (**a**) ASCs were encapsulated in injectable PH scaffolds. (**b**) The shape of PH scaffolds could be customized, displaying deformation recovery and injection ability. (**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, 2303368. 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 1 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-1, SDF-1α, 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 ($CaCuSi_4O_{10}$) 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-gycolide); PT, poly(D, L-lactide-co-trimethylene carbonate); PES, polyethersulfone; SMPs, shape memory polymers; KGF, keratinocyte growth factor; IGF-1, insulin-like growth factor 1; SDF-1α, 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; Cu^{2+}, copper ion; Ag^{+}, silver ion.

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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 μL of exosomes suspension (3×10^{11} mL^{-1})	Immunomodulatory functions	Endometrial regeneration, fertility restoration	[31]
ADSCs	Loading in decellularized ECM and injection	100 μL PBS containing 100 mg ECM@ADSC-Exos	Releasing endogenous growth signals, promoting neovascularization	Angiogenesis, endometrial regeneration, fertility restoration	[34]
IL-1β activated BMSCs	Loading in polypeptide hydrogel and injection	200 μL β-exo@pep (20 μg mL^{-1})	Inhibiting intrauterine inflammation through NF-κB signaling pathway	Angiogenesis, endometrial regeneration, treatment of endometritis	[35]
DSCs	Loading in in alginate hydrogel and injection	50 μL 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.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Garcia-Alonso L, Handfield LF, Roberts K, et al. Mapping the temporal and spatial dynamics of the human endometrium in vivo and in vitro. *Nat Genet*. 2021;53(12):1698–1711. doi:10.1038/s41588-021-00972-2
2. Wang F, Qualls AE, Marques-Fernandez L, Colucci F. Biology and pathology of the uterine microenvironment and its natural killer cells. *Cell Mol Immunol*. 2021;18(9):2101–2113. doi:10.1038/s41423-021-00739-z
3. Hellstrom M, Bandstein S, Brannstrom M. Uterine tissue engineering and the future of uterus transplantation. *Ann Biomed Eng*. 2017;45(7):1718–1730.
4. Zhang L, Yu Z, Qu Q, Li X, Lu X, Zhang H. Exosomal lncRNA HOTAIR promotes the progression and angiogenesis of endometriosis via the miR-761/HDAC1 axis and activation of STAT3-mediated inflammation. *Int J Nanomed*. 2022;17:1155–1170. doi:10.2147/IJN.S354314
5. Liu T, He B, Xu X. Repairing and regenerating injured endometrium methods. *Reprod Sci*. 2023;30(6):1724–1736. doi:10.1007/s43032-022-01108-5
6. Hu X, Wu H, Yong X, et al. Cyclical endometrial repair and regeneration: molecular mechanisms, diseases, and therapeutic interventions. *MedComm*. 2023;4(6):e425. doi:10.1002/mco2.425
7. Yoshimasa Y, Maruyama T. Bioengineering of the Uterus. *Reprod Sci*. 2021;28(6):1596–1611. doi:10.1007/s43032-021-00503-8
8. Feng H, Yue Y, Zhang Y, et al. Plant-derived exosome-like nanoparticles: emerging nanosystems for enhanced tissue engineering. *Int J Nanomed*. 2024;19:1189–1204. doi:10.2147/IJN.S448905
9. Leonel ECR, Dadashzadeh A, Moghassemi S, et al. New solutions for old problems: how reproductive tissue engineering has been revolutionizing reproductive medicine. *Ann Biomed Eng*. 2023;51:2143–2171. doi:10.1007/s10439-023-03321-y
10. Gargus ES, Rogers HB, McKinnon KE, Edmonds ME, Woodruff TK. Engineered reproductive tissues. *Nat Biomed Eng*. 2020;4(4):381–393. doi:10.1038/s41551-020-0525-x
11. Almeida GHD, Iglesia RP, Araujo MS, et al. Uterine tissue engineering: where we stand and the challenges ahead. *Tissue Eng Part B Rev*. 2022;28(4):861–890. doi:10.1089/ten.teb.2021.0062
12. Li X, Sun H, Lin N, et al. Regeneration of uterine horns in rats by collagen scaffolds loaded with collagen-binding human basic fibroblast growth factor. *Biomaterials*. 2011;32(32):8172–8181. doi:10.1016/j.biomaterials.2011.07.050
13. Gargett CE, Ye L. Endometrial reconstruction from stem cells. *Fertil Steril*. 2012;98(1):11–20. doi:10.1016/j.fertnstert.2012.05.004
14. Micili SC, Goker A, Sayin O, Akokay P, Ergur BU. The effect of lipoic acid on wound healing in a full thickness uterine injury model in rats. *J Molecul Histol*. 2013;44(3):339–345. doi:10.1007/s10735-013-9485-8
15. Bafor EE, Ebidame VO, Elvis-Offiah UB, et al. A role of alpha-tocopherol and phylloquinone in the modulation of uterine contractility and reproductive function in mouse models. *Medicina*. 2017;53(3):190–202. doi:10.1016/j.medici.2017.05.002
16. Sayin O, Micili SC, Goker A, et al. The role of resveratrol on full - Thickness uterine wound healing in rats. *Taiwan J Obstet Gynecol*. 2017;56(5):657–663. doi:10.1016/j.tjog.2017.08.015
17. Xu HL, Xu J, Shen BX, et al. Dual regulations of thermosensitive heparin-poloxamer hydrogel using epsilon-polylysine: bioadhesivity and controlled KGF release for enhancing wound healing of endometrial injury. *ACS Appl Mater Interfaces*. 2017;9(35):29580–29594. doi:10.1021/acsami.7b10211
18. Shoae-Hassani A, Mortazavi-Tabatabaei SA, Sharif S, et al. Differentiation of human endometrial stem cells into urothelial cells on a three-dimensional nanofibrous silk-collagen scaffold: an autologous cell resource for reconstruction of the urinary bladder wall. *J Tissue Eng Regen Med*. 2015;9(11):1268–1276. doi:10.1002/term.1632
19. Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: a pilot study. *JBRA Assist Reprod*. 2017;21(1):54–56. doi:10.5935/1518-0557.20170013
20. Pegtel DM, Gould SJ. Exosomes. *Annu Rev Biochem*. 2019;88:487–514. doi:10.1146/annurev-biochem-013118-111902
21. Ji W, Hou B, Lin W, et al. Bioprinting a human iPSC-derived MSC-loaded scaffold for repair of the uterine endometrium. *Acta Biomater*. 2020;116:268–284. doi:10.1016/j.actbio.2020.09.012
22. Mancini V, Pensabene V. Organs-on-chip models of the female reproductive system. *Bioengineering*. 2019;6(4):103. doi:10.3390/bioengineering6040103
23. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. *Cell Biosci*. 2019;9:19. doi:10.1186/s13578-019-0282-2

24. Zhang H, Xu D, Li Y, et al. Organoid transplantation can improve reproductive prognosis by promoting endometrial repair in mice. *Internat J Biolog Sci*. 2022;18(6):2627–2638. doi:10.7150/ijbs.69410
25. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478):aau6977. doi:10.1126/science.aau6977
26. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. *Signal Transduct Target Ther*. 2024;9(1):17. doi:10.1038/s41392-023-01704-0
27. Zhang K, Cheng K. Stem cell-derived exosome versus stem cell therapy. *Nat Rev Bioeng*. 2023;2023:1–2.
28. Muthu S, Bapat A, Jain R, Jeyaraman N, Jeyaraman M. Exosomal therapy-a new frontier in regenerative medicine. *Stem Cell Investig*. 2021;8:7. doi:10.21037/sci-2020-037
29. Wang X, Xia J, Yang L, Dai J, He L. Recent progress in exosome research: isolation, characterization and clinical applications. *Cancer Gene Ther*. 2023;30(8):1051–1065. doi:10.1038/s41417-023-00617-y
30. Cai X, Li Y, Gao F, Muhammad B, Yang H. Therapeutic effect and study of human umbilical cord blood mononuclear cells in patients with ischaemic bowel disease. *Sci Rep*. 2024;14(1):6121. doi:10.1038/s41598-024-56720-z
31. Xin L, Lin X, Zhou F, et al. A scaffold laden with mesenchymal stem cell-derived exosomes for promoting endometrium regeneration and fertility restoration through macrophage immunomodulation. *Acta Biomater*. 2020;113:252–266. doi:10.1016/j.actbio.2020.06.029
32. Abebayehu D, Spence AJ, McClure MJ, Haque TT, Rivera KO, Ryan JJ. Polymer scaffold architecture is a key determinant in mast cell inflammatory and angiogenic responses. *J Biomed Mater Res A*. 2019;107(4):884–892. doi:10.1002/jbm.a.36605
33. Gnecchi M, Danieli P, Malpasso G, Ciuffreda MC. Paracrine mechanisms of mesenchymal stem cells in tissue repair. *Methods Mol Biol*. 2016;1416:123–146.
34. Jin X, Dai Y, Xin L, et al. ADSC-derived exosomes-coupled decellularized matrix for endometrial regeneration and fertility restoration. *Mater Today Bio*. 2023;23:100857. doi:10.1016/j.mtbio.2023.100857
35. Zhao C, Li J, Cai H, et al. An injectable hydrogel scaffold with IL-1beta-activated MSC-derived exosomes for the treatment of endometritis. *Biomater Sci*. 2023;11(4):1422–1436. doi:10.1039/D2BM01586B
36. Liang Y, Shuai Q, Zhang X, et al. Incorporation of decidual stromal cells derived exosomes in sodium alginate hydrogel as an innovative therapeutic strategy for advancing endometrial regeneration and reinstating fertility. *Adv Healthc Mater*;2024. e2303674. doi:10.1002/adhm.202303674
37. Chen TQ, Wei XJ, Liu HY, Zhan SH, Yang XJ. Telocyte-derived exosomes provide an important source of wnts that inhibits fibrosis and supports regeneration and repair of endometrium. *Cell Transplant*. 2023;32:9636897231212746. doi:10.1177/09636897231212746
38. Lai H, Huang R, Weng X, Huang B, Yao J, Pian Y. Classification and applications of nanomaterials in vitro diagnosis. *Heliyon*. 2024;10(11):e32314. doi:10.1016/j.heliyon.2024.e32314
39. Hiwrale A, Bharati S, Pingale P, Rajput A. Nanofibers: a current era in drug delivery system. *Heliyon*. 2023;9(9):e18917. doi:10.1016/j.heliyon.2023.e18917
40. Naidu KCB, Kumar NS, Banerjee P, Reddy BVS. A review on the origin of nanofibers/nanorods structures and applications. *J Mater Sci Mater Med*. 2021;32(6):68. doi:10.1007/s10856-021-06541-7
41. Ogueri KS, Laurencin CT. Nanofiber technology for regenerative engineering. *ACS Nano*. 2020;14(8):9347–9363. doi:10.1021/acsnano.0c03981
42. Abadi B, Goshtasbi N, Bolourian S, Tahsili J, Adeli-Sardou M, Forootanfar H. Electrospun hybrid nanofibers: fabrication, characterization, and biomedical applications. *Front Bioeng Biotechnol*. 2022;10:986975. doi:10.3389/fbioe.2022.986975
43. Sang W, Zhang R, Shi X, Dai Y. Advanced metallized nanofibers for biomedical applications. *Adv Sci*. 2023;10(27):e2302044. doi:10.1002/advs.202302044
44. Hanuman S, Nune M. Srividya hanuman, manasa nune. design and characterization of maltose-conjugated polycaprolactone nanofibrous scaffolds for uterine tissue engineering. *Regenera Engin Translat Med*. 2022;8:334–344. doi:10.1007/s40883-021-00231-0
45. Song S, Wu S, Meiduo D, Chen P, Li H, He H. Nano-biomaterial Fibrinogen/P(LLA-CL) for prevention of intrauterine adhesion and restoration of fertility. *J Biomed Mater Res A*. 2024;112(2):167–179. doi:10.1002/jbm.a.37604
46. Zhou L, Wang H, Shen D, et al. Stem cells implanted with nanofibrous mats for injured endometrial regeneration and immune-microenvironment remodeling. *Mater Today Bio*. 2023;23:100855. doi:10.1016/j.mtbio.2023.100855
47. Zhu H, Li H, Gao K, et al. Chorionic villi-derived nanofibers enhanced mesenchymal stem cell extracellular vesicle secretion and bioactivity for endometrium regeneration toward intrauterine adhesion treatment. *Nano Today*. 2023;52:101986. doi:10.1016/j.nantod.2023.101986
48. Cao Y, Qi J, Wang J, et al. Injectable "Homing-Like" bioactive short-fibers for endometrial repair and efficient live births. *Adv Sci*. 2024;11:e2306507. doi:10.1002/advs.202306507
49. Zheng Y, Du Y, Chen L, et al. Recent advances on shape memory polymeric nanocomposites for biomedical applications and beyond. *Biomater. Sci.* 2024;2024:D4BM00004H.
50. Luo L, Zhang FH, Wang LL, Liu YJ, Leng JS. Recent advances in shape memory polymers: multifunctional materials, multiscale structures, and applications. *Adv Funct Mater*. 2023;34(14):2312036. doi:10.1002/adfm.202312036
51. Dong C, Yang C, Younis MR, et al. Bioactive NIR-II light-responsive shape memory composite based on cuprorivaite nanosheets for endometrial regeneration. *Adv Sci*. 2022;9(12):e2102220. doi:10.1002/advs.202102220
52. Huang J, Zhang W, Yu J, et al. Human amniotic mesenchymal stem cells combined with PPCNg facilitate injured endometrial regeneration. *Stem Cell Res Ther*. 2022;13(1):17. doi:10.1186/s13287-021-02682-2
53. Alavije AA, Barati F, Barati M, Nazari H, Karimi I. Polyethersulfone/MWCNT nanocomposite scaffold for endometrial cell culture: preparation, characterization, and in vitro investigation. *Biomed Phys Eng Express*. 2021;7(2):025004. doi:10.1088/2057-1976/abd67f
54. Zhu Y, Li S, Li Y, Tan H, Zhao Y, Sun L. Antioxidant nanozyme microneedles with stem cell loading for in situ endometrial repair. *Chem Eng J*. 2022;449:137786. doi:10.1016/j.cej.2022.137786
55. Hanuman S, Pande G, Nune M. Current status and challenges in uterine myometrial tissue engineering. *Bioengineered*. 2023;14(1):2251847. doi:10.1080/21655979.2023.2251847
56. You S, Zhu Y, Li H, et al. Recombinant humanized collagen remodels endometrial immune microenvironment of chronic endometritis through macrophage immunomodulation. *Regen Biomater*. 2023;10:rbad033.

57. Fang Z, Lu C, Du W, et al. Injectable self-assembled dual-crosslinked alginate/recombinant collagen-based hydrogel for endometrium regeneration. *Int J Biol Macromol*. 2023;236:123943. doi:10.1016/j.ijbiomac.2023.123943
58. Wei S, Li Z, Xia H, et al. An endometrial biomimetic extracellular matrix (ECM) for enhanced endometrial regeneration using hyaluronic acid hydrogel containing recombinant human type III collagen. *Int J Biol Macromol*. 2024;268(Pt 1):131723. doi:10.1016/j.ijbiomac.2024.131723
59. Rezaeipour Y, Alizadeh P, Keshavarz M. Collagen scaffold impregnated with borosilicate bioactive glass for endometrial healing. *Appl Mater Today*. 2023;30:101727. doi:10.1016/j.apmt.2022.101727
60. Ding L, Li X, Sun H, et al. Transplantation of bone marrow mesenchymal stem cells on collagen scaffolds for the functional regeneration of injured rat uterus. *Biomaterials*. 2014;35(18):4888–4900. doi:10.1016/j.biomaterials.2014.02.046
61. Chen L, Li L, Mo Q, et al. An injectable gelatin/sericin hydrogel loaded with human umbilical cord mesenchymal stem cells for the treatment of uterine injury. *Bioeng Transl Med*. 2023;8(1):e10328. doi:10.1002/btm2.10328
62. Karadbhajne P, More A. Effect of hyaluronic acid-enriched media in embryo implantation. *Cureus*. 2022;14(7):e27083. doi:10.7759/cureus.27083
63. Lin Y, Dong S, Zhao W, et al. Application of hydrogel-based delivery system in endometrial repair. *ACS Appl Bio Mater*. 2020;3(11):7278–7290. doi:10.1021/acsabm.0c00971
64. Qi J, Li X, Cao Y, et al. Locationally activated PRP via an injectable dual-network hydrogel for endometrial regeneration. *Biomaterials*. 2024;309:122615. doi:10.1016/j.biomaterials.2024.122615
65. Kim YY, Park KH, Kim YJ, et al. Synergistic regenerative effects of functionalized endometrial stromal cells with hyaluronic acid hydrogel in a murine model of uterine damage. *Acta Biomater*. 2019;89:139–151. doi:10.1016/j.actbio.2019.03.032
66. Hu Q, Xie N, Liao K, et al. An injectable thermosensitive Pluronic F127/hyaluronic acid hydrogel loaded with human umbilical cord mesenchymal stem cells and asiaticoside microspheres for uterine scar repair. *Int J Biol Macromol*. 2022;219:96–108. doi:10.1016/j.ijbiomac.2022.07.161
67. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure. *Adv Drug Deliv Rev*. 2016;97:4–27. doi:10.1016/j.addr.2015.11.001
68. Badylak SF. The extracellular matrix as a biologic scaffold material. *Biomaterials*. 2007;28(25):3587–3593. doi:10.1016/j.biomaterials.2007.04.043
69. Lopez-Martinez S, Rodriguez-Eguren A, de Miguel-Gomez L, et al. Bioengineered endometrial hydrogels with growth factors promote tissue regeneration and restore fertility in murine models. *Acta Biomater*. 2021;135:113–125. doi:10.1016/j.actbio.2021.08.025
70. Giobbe GG, Crowley C, Luni C, et al. Extracellular matrix hydrogel derived from decellularized tissues enables endodermal organoid culture. *Nat Commun*. 2019;10(1):5658. doi:10.1038/s41467-019-13605-4
71. Li X, Wang Y, Ma R, et al. Reconstruction of functional uterine tissues through recellularizing the decellularized rat uterine scaffolds by MSCs in vivo and in vitro. *Biomed Mater*. 2021;16(3):035023. doi:10.1088/1748-605X/abd116
72. Ahn J, Sen T, Lee D, et al. Uterus-derived decellularized extracellular matrix-mediated endometrial regeneration and fertility enhancement. *Adv Funct Mater*. 2023;33:2214291. doi:10.1002/adfm.202214291
73. Arezoo N, Mohammad H, Malihezaman M. Tissue engineering of mouse uterus using menstrual blood stem cells (MenSCs) and decellularized uterine scaffold. *Stem Cell Res Ther*. 2021;12:475. doi:10.1186/s13287-021-02543-y
74. Izanlou S, Afshar A, Zare A, et al. Enhancing differentiation of menstrual blood-derived stem cells into female germ cells using a bilayer amniotic membrane and nano-fibrous fibroin scaffold. *Tissue Cell*. 2023;85:102215. doi:10.1016/j.tice.2023.102215
75. Chen X, Sun J, Li X, Mao L, Cui L, Bai W. Transplantation of oral mucosal epithelial cells seeded on decellularized and lyophilized amniotic membrane for the regeneration of injured endometrium. *Stem Cell Res Ther*. 2019;10(1):107. doi:10.1186/s13287-019-1179-z
76. Zhu X, Peault B, Yan G, Sun H, Hu Y, Ding L. Stem cells and endometrial regeneration: from basic research to clinical trial. *Curr Stem Cell Res Ther*. 2019;14(4):293–304. doi:10.2174/1574888X14666181205120110
77. Song YT, Liu PC, Tan J, et al. Stem cell-based therapy for ameliorating intrauterine adhesion and endometrium injury. *Stem Cell Res Ther*. 2021;12(1):556. doi:10.1186/s13287-021-02620-2
78. Gharibeh N, Aghebati-Maleki L, Madani J, Pourakbari R, Yousefi M, Ahmadian Heris J. Cell-based therapy in thin endometrium and Asherman syndrome. *Stem Cell Res Ther*. 2022;13(1):33. doi:10.1186/s13287-021-02698-8
79. Li X, Lv HF, Zhao R, Ying MF, Samuriwo AT, Zhao YZ. Recent developments in bio-scaffold materials as delivery strategies for therapeutics for endometrium regeneration. *Mater Today Bio*. 2021;11:100101. doi:10.1016/j.mtbio.2021.100101
80. Jiang X, Li X, Fei X, et al. Endometrial membrane organoids from human embryonic stem cell combined with the 3D Matrigel for endometrium regeneration in asherman syndrome. *Bioact Mater*. 2021;6(11):3935–3946. doi:10.1016/j.bioactmat.2021.04.006
81. Zhang D, Du Q, Li C, et al. Functionalized human umbilical cord mesenchymal stem cells and injectable HA/Gel hydrogel synergy in endometrial repair and fertility recovery. *Acta Biomater*. 2023;167:205–218. doi:10.1016/j.actbio.2023.06.013
82. Gao L, Huang Z, Lin H, Tian Y, Li P, Lin S. Bone marrow mesenchymal stem cells (BMSCs) restore functional endometrium in the rat model for severe asherman syndrome. *Reprod Sci*. 2019;26(3):436–444. doi:10.1177/1933719118799201
83. de Miguel-Gomez L, Ferrero H, Lopez-Martinez S, et al. Stem cell paracrine actions in tissue regeneration and potential therapeutic effect in human endometrium: a retrospective study. *BJOG*. 2020;127(5):551–560. doi:10.1111/1471-0528.16078
84. Wang L, Yang M, Jin M, et al. Transplant of insulin-like growth factor-1 expressing bone marrow stem cells improves functional regeneration of injured rat uterus by NF-kappaB pathway. *J Cell Mol Med*. 2018;22(5):2815–2825. doi:10.1111/jcmm.13574
85. Ho CH, Lan CW, Liao CY, Hung SC, Li HY, Sung YJ. Mesenchymal stem cells and their conditioned medium can enhance the repair of uterine defects in a rat model. *J Chin Med Assoc*. 2018;81(3):268–276. doi:10.1016/j.jcma.2017.03.013
86. Yuan L, Cao J, Hu M, et al. Bone marrow mesenchymal stem cells combined with estrogen synergistically promote endometrial regeneration and reverse EMT via Wnt/beta-catenin signaling pathway. *Reprod Biol Endocrinol*. 2022;20(1):121.
87. Xu B, Cao Y, Zheng Z, et al. Injectable mesenchymal stem cell-laden matrigel microspheres for endometrium repair and regeneration. *Adv Biol (Weinh)*. 2021;5(8):e2000202. doi:10.1002/adbi.202000202
88. Huang J, Li Q, Yuan X, Liu Q, Zhang W, Li P. Intrauterine infusion of clinically graded human umbilical cord-derived mesenchymal stem cells for the treatment of poor healing after uterine injury: a Phase I clinical trial. *Stem Cell Res Ther*. 2022;13:85. doi:10.1186/s13287-022-02756-9

89. Naeem A, Gupta N, Naeem U, Elrayess MA, Albanese C. Amniotic stem cells as a source of regenerative medicine to treat female infertility. *Human Cell*. 2023;36:15–25. doi:10.1007/s13577-022-00795-1
90. Mao Y, Yang Y, Sun C, et al. Human amniotic mesenchymal stem cells promote endometrium regeneration in a rat model of intrauterine adhesion. *Cell Biol Int*. 2023;47(1):75–85. doi:10.1002/cbin.11951
91. Gan L, Duan H, Xu Q, et al. Human amniotic mesenchymal stromal cell transplantation improves endometrial regeneration in rodent models of intrauterine adhesions. *Cytotherapy*. 2017;19(5):603–616. doi:10.1016/j.jcyt.2017.02.003
92. Yu J, Zhang W, Huang J, et al. Management of intrauterine adhesions using human amniotic mesenchymal stromal cells to promote endometrial regeneration and repair through Notch signalling. *J Cell Mol Med*. 2021;25(23):11002–11015. doi:10.1111/jcmm.17023
93. Fan Y, Sun J, Zhang Q, Lai D. Transplantation of human amniotic epithelial cells promotes morphological and functional regeneration in a rat uterine scar model. *Stem Cell Res Ther*. 2021;12(1):207. doi:10.1186/s13287-021-02260-6
94. Kharbikar BN, Mohindra P, Desai TA. Biomaterials to enhance stem cell transplantation. *Cell Stem Cell*. 2022;29(5):692–721. doi:10.1016/j.stem.2022.04.002
95. Xue Y, Baig R, Dong Y. Recent advances of biomaterials in stem cell therapies. *Nanotechnology*. 2022;33(13):10.1088/1361–6528/ac4520.
96. 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. doi:10.1016/j.bioactmat.2021.11.023
97. Solomonov A, Kozell A, Shimanovich U. Designing multifunctional biomaterials via protein self-assembly. *Angew Chem-Int Ed*. 2024;63(14):e202318365. doi:10.1002/anie.202318365
98. Zhang XS, Xie G, Ma HH, et al. Highly reproducible and cost-effective one-pot organoid differentiation using a novel platform based on PF-127 triggered spheroid assembly. *Biofabrication*. 2023;15(4):045014. doi:10.1088/1758-5090/acee21
99. Yang H, Wu S, Feng R, et al. Vitamin C plus hydrogel facilitates bone marrow stromal cell-mediated endometrium regeneration in rats. *Stem Cell Res Ther*. 2017;8:267. doi:10.1186/s13287-017-0718-8
100. Yao Q, Zheng YW, Lan QH, et al. Aloe/poloxamer hydrogel as an injectable beta-estradiol delivery scaffold with multi-therapeutic effects to promote endometrial regeneration for intrauterine adhesion treatment. *Eur J Pharm Sci*. 2020;148:105316. doi:10.1016/j.ejps.2020.105316
101. Li B, Zhang L, Xie Y, Lei L, Qu W, Sui L. Evaluation of pharmacokinetics and safety of a long-term estradiol-releasing stent in rat uterine. *Regen Ther*. 2022;21:494–501. doi:10.1016/j.reth.2022.10.001
102. Pérez-Gutiérrez L, Ferrara N. Biology and therapeutic targeting of vascular endothelial growth factor A. *Nat Rev Mol Cell Biol*. 2023;24(11):816–834. doi:10.1038/s41580-023-00631-w
103. Lei L, Lv Q, Jin Y, et al. Angiogenic microspheres for the treatment of a thin endometrium. *ACS Biomater Sci Eng*. 2021;7(10):4914–4920. doi:10.1021/acsbiomaterials.1c00615
104. Zhu X, Chen S, Zhang P, et al. Granulocyte-macrophage colony-stimulating factor promotes endometrial repair after injury by regulating macrophages in mice. *J Reprod Immunol*. 2023;160:104156. doi:10.1016/j.jri.2023.104156
105. Liu J, Ying Y, Wang S, et al. The effects and mechanisms of GM-CSF on endometrial regeneration. *Cytokine*. 2020;125:154850. doi:10.1016/j.cyto.2019.154850
106. Wen J, Hou B, Lin W, et al. 3D-printed hydrogel scaffold-loaded granulocyte colony-stimulating factor sustained-release microspheres and their effect on endometrial regeneration. *Biomater Sci*. 2022;10(12):3346–3358. doi:10.1039/D2BM00109H
107. Zeng J, Xiong S, Zhou J, et al. Hollow hydroxyapatite microspheres loaded with rhCXCL13 to Recruit BMSC for osteogenesis and synergetic angiogenesis to promote bone regeneration in bone defects. *Int J Nanomed*. 2023;18:3509–3534. doi:10.2147/IJN.S408905
108. Kim JH, Kang KW, Park Y, Kim BS. CXCR2 inhibition overcomes ponatinib intolerance by eradicating chronic myeloid leukemic stem cells through PI3K/Akt/mTOR and dipeptidylpeptidase IV (CD26). *Heliyon*. 2023;9(11):e22091. doi:10.1016/j.heliyon.2023.e22091
109. Sanz-Ortega L, Andersson A, Carlsten M. Harnessing upregulated E-selectin while enhancing SDF-1α sensing redirects infused NK cells to the AML-perturbed bone marrow. *Leukemia*. 2024;38:579–589. doi:10.1038/s41375-023-02126-1
110. Zheng X, Pan X, Pang Q, Shuai C, Ma L, Gao C. Selective capture of mesenchymal stem cells over fibroblasts and immune cells on E7-modified collagen substrates under flow circumstances. *J Mater Chem B*. 2018;6(1):165–173. doi:10.1039/C7TB02812A
111. Xin L, Zheng X, Chen J, et al. An acellular scaffold facilitates endometrial regeneration and fertility restoration via recruiting endogenous mesenchymal stem cells. *Adv Healthc Mater*. 2022;11(21):e2201680. doi:10.1002/adhm.202201680
112. Jiang P, Tang X, Wang H, et al. Collagen-binding basic fibroblast growth factor improves functional remodeling of scarred endometrium in uterine infertile women: a pilot study. *Sci China Life Sci*. 2019;62(12):1617–1629. doi:10.1007/s11427-018-9520-2
113. Sadtler K, Estrellas K, Allen BW, et al. Developing a pro-regenerative biomaterial scaffold microenvironment requires T helper 2 cells. *Science*. 2016;352(6283):366–370. doi:10.1126/science.aad9272
114. Wang J, Chang CY, Yang X, et al. Leukemia inhibitory factor, a double-edged sword with therapeutic implications in human diseases. *Mol Ther*. 2023;31(2):331–343. doi:10.1016/j.ymthe.2022.12.016
115. Xue B, Liu D, Song M, et al. Leukemia inhibitory factor promotes the regeneration of rat uterine horns with full-thickness injury. *Wound Repair Regen*. 2019;27(5):477–487. doi:10.1111/wrr.12729
116. Le TTV, Lam HM, Hoang TTD, Tran H. Platelet-rich plasma as an ideal biomaterial for improving pregnancy of infertility mice. *J Sci Advan Mater Dev*. 2023;8(3):100571. doi:10.1016/j.jsamd.2023.100571
117. Kshersagar J, Kawale AA, Tardalkar K, et al. Activated platelet-rich plasma accelerate endometrial regeneration and improve pregnancy outcomes in murine model of disturbed endometrium. *Cell Tissue Bank*. 2023;25(2):453–461. doi:10.1007/s10561-023-10101-4
118. Khayati S, Dehnavi S, Sadeghi M, Afshari JT, Esmaeili SA, Mohammadi M. The potential role of miRNA in regulating macrophage polarization. *Heliyon*. 2023;9(11):e21615. doi:10.1016/j.heliyon.2023.e21615
119. Liang T, Zhang R, Liu X, et al. Recent advances in macrophage-mediated drug delivery systems. *Int J Nanomed*. 2021;16:2703–2714. doi:10.2147/IJN.S298159
120. Ji JQ, Wang HH, Ming YN, Li J, Song XH, Lin KQ. Exosomes from ectopic endometrial stromal cells promote M2 macrophage polarization by delivering miR-146a-5p. *Int Immunopharmacol*. 2024;128:111573. doi:10.1016/j.intimp.2024.111573
121. Park M, Oh HJ, Han J, Hong SH, Park W, Song H. Liposome-mediated small RNA delivery to convert the macrophage polarity: a novel therapeutic approach to treat inflammatory uterine disease. *Mol Ther Nucleic Acids*. 2022;30:663–676. doi:10.1016/j.omtn.2022.11.018

122. Bandopadhyay S, Mandal S, Ghorai M, et al. Therapeutic properties and pharmacological activities of asiaticoside and madecassoside: a review. *J Cell Mol Med*. 2023;27(5):593–608. doi:10.1111/jcmm.17635
123. Essa Ali SH, Hussain N, Kakar KU, et al. Tocopherol as plant protector: an overview of Tocopherol biosynthesis enzymes and their role as antioxidant and signaling molecules. *Acta Physiol Plant*. 2022;44:20. doi:10.1007/s11738-021-03350-x
124. Shahrook S, Ota E, Hanada N, Sawada K, Mori R. Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):11459. doi:10.1038/s41598-018-29616-y
125. Lee D, Ahn J, Koo HS, Kang Y-J. Intrauterine botulinum toxin A administration promotes endometrial regeneration mediated by IGFBP3-dependent OPN proteolytic cleavage in thin endometrium. *Cell Mol Life Sci*. 2023;80:26. doi:10.1007/s00018-022-04684-6
126. Ma JY, Zhan H, Li W, et al. Recent trends in therapeutic strategies for repairing endometrial tissue in intrauterine adhesion. *Biomater Res*. 2021;25(1):40. doi:10.1186/s40824-021-00242-6
127. Zhang SS, Xu XX, Xiang WW, et al. Using 17β-estradiol heparin-poloxamer thermosensitive hydrogel to enhance the endometrial regeneration and functional recovery of intrauterine adhesions in a rat model. *FASEB J*. 2020;34(1):446–457. doi:10.1096/fj.201901603RR
128. Kaygusuzoglu E, Caglayan C, Kandemir FM, et al. Zingerone ameliorates cisplatin-induced ovarian and uterine toxicity via suppression of sex hormone imbalances, oxidative stress, inflammation and apoptosis in female Wistar rats. *Biomed Pharmacother*. 2018;102:517–530. doi:10.1016/j.biopha.2018.03.119
129. Xu XX, Zhang SS, Lin HL, et al. Metformin promotes regeneration of the injured endometrium via inhibition of endoplasmic reticulum stress-induced apoptosis. *Reprod Sci*. 2019;26(4):560–568. doi:10.1177/1933719118804424
130. Xu BF, Zhou MJ, Liu MY, et al. Bioactive injectable and self-healing hydrogel via cell-free fat extract for endometrial regeneration. *Small*. 2023;19(30):2300481. doi:10.1002/smll.202300481
131. Lin JY, Wang Z, Huang JL, et al. Microenvironment-protected exosome-hydrogel for facilitating endometrial regeneration, fertility restoration, and live birth of offspring. *Small*. 2021;17(11):2007235. doi:10.1002/smll.202007235
132. Nie N, Gong L, Jiang D, et al. 3D bio-printed endometrial construct restores the full-thickness morphology and fertility of injured uterine endometrium. *Acta Biomater*. 2023;157:187–199. doi:10.1016/j.actbio.2022.12.016
133. Feng M, Hu S, Qin W, Tang Y, Guo R, Han L. Bioprinting of a blue light-cross-linked biodegradable hydrogel encapsulating amniotic mesenchymal stem cells for intrauterine adhesion prevention. *ACS Omega*. 2021;6(36):23067–23075. doi:10.1021/acsomega.1c02117
134. Li S, Liu S, Wang X. Advances of 3D printing in vascularized organ construction. *Int J Bioprint*. 2022;8(3):588. doi:10.18063/ijb.v8i3.588
135. Li Q, Yu H, Zhao F, et al. 3D printing of microenvironment-specific bioinspired and exosome-reinforced hydrogel scaffolds for efficient cartilage and subchondral bone regeneration. *Adv Sci*. 2023;10(26):e2303650. doi:10.1002/advs.202303650
136. Lu S, Wang X, Li W, Zu Y, Xiao J. Injectable 3D-printed porous scaffolds for adipose stem cell delivery and endometrial regeneration. *Adv Funct Mater*. 2023;33(34):2303368. doi:10.1002/adfm.202303368
137. Li J, Wang C, Wang Z, et al. A robotic system with robust remote center of motion constraint for endometrial regeneration surgery. *Chin J Mech Eng*. 2022;35:76. doi:10.1186/s10033-022-00731-2
138. Fitzgerald HC, Dhakal P, Behura SK, Schust DJ, Spencer TE. Self-renewing endometrial epithelial organoids of the human uterus. *Proc Natl Acad Sci U S A*. 2019;116(46):23132–23142. doi:10.1073/pnas.1915389116
139. Kim JJ. A new endometrial organoid: synthetically engineered matrix enhances epithelial-stromal interactions. *Nat Rev Endocrinol*. 2024;20(1):3–4. doi:10.1038/s41574-023-00917-1
140. Berg HF, Hjelmeland ME, Lien H, et al. Patient-derived organoids reflect the genetic profile of endometrial tumors and predict patient prognosis. *Commun Med*. 2021;1:20. doi:10.1038/s43856-021-00019-x
141. Frances-Herrero E, Juarez-Barber E, Campo H, et al. Improved models of human endometrial organoids based on hydrogels from decellularized endometrium. *J Pers Med*. 2021;11(6). doi:10.3390/jpm11060504
142. Murphy AR, Campo H, Kim JJ. Strategies for modelling endometrial diseases. *Nat Rev Endocrinol*. 2022;18(12):727–743. doi:10.1038/s41574-022-00725-z
143. Horejs C. Organ chips, organoids and the animal testing conundrum. *Nat Rev Mater*. 2021;6(5):372–373. doi:10.1038/s41578-021-00313-z
144. Young RE, Huh DD. Organ-on-a-chip technology for the study of the female reproductive system. *Adv Drug Deliv Rev*. 2021;173:461–478. doi:10.1016/j.addr.2021.03.010
145. Rogal J, Schlunder K, Loskill P. Developer's guide to an organ-on-chip model. *ACS Biomater Sci Eng*. 2022;8(11):4643–4647. doi:10.1021/acsbiomaterials.1c01536
146. Yin Z, Wang J, Cui W, Tong C. Advanced biomaterials for promoting endometrial regeneration. *Adv Healthc Mater*. 2023;12(16):e2202490. doi:10.1002/adhm.202202490
147. Ma H, Liu M, Li Y, et al. Intrauterine transplantation of autologous menstrual blood stem cells increases endometrial thickness and pregnancy potential in patients with refractory intrauterine adhesion. *J Obstet Gynaecol Res*. 2020;46(11):2347–2355. doi:10.1111/jog.14449
148. Shen M, Duan H, Lv R, Lv C. Efficacy of autologous platelet-rich plasma in preventing adhesion reformation following hysteroscopic adhesiolysis: a randomized controlled trial. *Reprod Biomed Online*. 2022;45(6):1189–1196. doi:10.1016/j.rbmo.2022.07.003
149. Sfakianoudis K, Simopoulou M, Nitsos N, et al. Successful implantation and live birth following autologous platelet-rich plasma treatment for a patient with recurrent implantation failure and chronic endometritis. *Vivo*. 2019;33(2):515–521. doi:10.21873/invivo.11504
150. Molina A, Sánchez J, Sánchez W, Vielma V. Platelet-rich plasma as an adjuvant in the endometrial preparation of patients with refractory endometrium. *JBRA Assist Reprod*. 2018;22(1):42–48. doi:10.5935/1518-0557.20180009
151. Cao Y, Sun H, Zhu H, et al. Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial. *Stem Cell Res Ther*. 2018;9(1):192. doi:10.1186/s13287-018-0904-3
152. Pang WJ, Zhang Q, Ding HX, Sun NX, Li W. Effect of new biological patch in repairing intrauterine adhesion and improving clinical pregnancy outcome in infertile women: study protocol for a randomized controlled trial. *Trials*. 2022;23(1):510. doi:10.1186/s13063-022-06428-0
153. Zhou Q, Shi X, Saravelos S, et al. Auto-cross-linked hyaluronic acid gel for prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a randomized controlled trial. *J Minim Invasive Gynecol*. 2021;28(2):307–313. doi:10.1016/j.jmig.2020.06.030