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Review Article

Recent Developments in the Treatment of Intrauterine Adhesions Using Biomaterials Combined with Stem Cells

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ABSTRACT

Intrauterine Adhesions (IUA) significantly impact women's reproductive health, potentially leading to severe complications such as recurrent miscarriage and infertility. It is a significant public health issue among premenopausal women. Current treatment options are limited, and a definitive solution to prevent postoperative re-adhesions after IUA surgery has yet to be found. Although more studies demonstrate the effectiveness of stem cells in treating IUA, the drawbacks of stem cells themselves have become apparent. With the rapid development of bioengineering technology, significant developments have been made in addressing the problem of postoperative re-adhesions. Therefore, this paper primarily reviews the functions of current biomaterials combined with stem cells and their source cytokines in treating IUA. It also looks forward to research on composite multifunctional materials.

Keywords: Biomaterials; Stem cells; Intrauterine adhesions; Endometrial repair

Abbreviations: Abs: Apoptotic bodies; AME: Amniotic Membrane Extract; bFGF: Basic Fibroblast Growth Factor; BMSCs: Bone Marrow Mesenchymal Stem Cells; CS: Collagen Scaffold; DUM: Decellularized Endomematrix; EMT: Epithelial-Mesenchymal Transformation; ESCs: Endometrial Stromal Cells; ECM: Extracellular Matrix; Exos: Exosomes; HPMSCs: Human Placenta-Derived Mesenchymal Stem Cells; UCMSCs: Human Umbilical Cord Mesenchymal Stem Cells; hADMSCs: Human Adipose-Derived Mesenchymal Stem Cells; hAMSCs: Human Amniotic Mesenchymal Stem Cells; hSMSCs: Human Synovial-Derived Mesenchymal Stem Cells; HA: Hyaluronic Acid; HAECM: Human Amniotic Extracellular Matrix; IGF: Insulin-like Growth Factor; IUA: Intrauterine Adhesions; IL-1β: Interleukin-1β; MSCs: Mesenchymal Stem Cells; MenSCs: Menstrual blood mesenchymal Stem Cells; MSC/Alg-rCo III: Mesenchymal Stem Cell-loaded Alg-rCo III hydrogels; PPCNg: Polyethylene glycol citrate-co-N-isopropylacrylamide gelatin; PGS: Polyglyceryl Sebacate; rCo III: Recombinant type III collagen; TGF-β1: Transforming Growth Factor β1; HAECM: Human Amniotic Extracellular Matrix; VEGF: Vascular Endothelial Growth Factor

INTRODUCTION

Intrauterine Adhesions (IUAs), due to repeated intrauterine trauma and infection, were the leading cause of secondary infertility or abnormality of implantation, such as ectopic pregnancy, repeated pregnancy loss, and placental accreta [1-3]. Endometrial fibrosis, in which normal endometrial tissue was replaced mainly by non-vascular fibrous tissue and spindle myofibroblasts, and the boundary between the functional layer and base layer of endometrium disappeared, was the critical pathological feature of IUA [4-6]. Currently, hysteroscopic adhesion lysis is the only effective treatment. However, it was hard to predict the therapeutic outcome, and the recurrence rate was as high as 62.5% in severe cases [7,8]. Commonly used clinical auxiliary measures included

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placing an intrauterine device and Foley balloon, intrauterine gel injection, and oral estrogen, efficiently reducing adhesion recurrence [9]. However, they did not promote endometrial repair, improve the patient's reproductive function, or increase fertility [10,11]. Endometrial repair dysfunction was closely related to the damage and loss of stem cells that could be transdifferentiated into endometrial epithelial cells or paracrine cytokines [12]. Therefore, applying stem cells to treat IUA may be an effective strategy to restore fertility.

Mesenchymal Stem Cells (MSCs) had a high potential for self-renewal and multi-directional differentiation [13]. Current research focused on implanting different mesenchymal stem cells to inhibit injured endometrial fibrosis, promote endometrial functional regeneration, and restore patients' reproductive function. In-depth studies have found that MSCs played a repair-promoting function mainly through trans-differentiation into epithelial cells, paracrine various active factors, and participation in immune regulation [7,14,15].

Gan et al. [16], confirmed that human Amniotic Mesenchymal Stem Cells (hAMSCs) transplantation could inhibit proinflammatory TNF-α and IL-β, promote the levels of anti-inflammatory factors bFGF and IL-6, and then promote the regeneration of damaged endometrium. Yao et al. [17], proved that exosomes derived from Bone Marrow Mesenchymal Stem Cells (BMSCs) regulated the TGF-β1/Smad signal pathway to reverse Epithelial-Mesenchymal Transformation (EMT) and promote endometrial repair. Although MSCs showed great prospects for clinical application, their efficacy was chiefly limited by low colonization, survival, and utilization rates. With years of research, significant progress has been made in using biomaterials as carriers for MSCs and therapeutic factors, or as physical barriers to prevent re-adhesion, and immune regulators to inhibit inflammatory reactions. However, there are still limitations, such as how to improve targeted implantation rates, achieve precise controlled release, synthesize multifunctional composite materials, and complete clinical translation. This article mainly discussed the use of biomaterials as delivery systems for MSCs and therapeutic factors, physical barriers, and immune regulators to treat IUA. We also look forward to the research direction, which will likely change the traditional treatment mode to obtain better clinical results and provide valuable references for follow-up research.

LITERATURE REVIEW

Therapeutic delivery systems of MSCs

In order to approach the issues of low engraftment rate and survival rate in the therapy of MSCs, researchers have designed various types of biomaterials for delivery, which not only need to meet the specific requirements of the microenvironment and targeting the injured but also support the survival of MSCs and controlled the release without impairing the characteristic function, including hydrogels (Table 1), collagen scaffolds (Table 2), decellularized matrices (Table 3), and other unique materials (Table 3).

Table 1: Application of various hydrogels in the repair of endometrial injury.

Composition	Fabrication methods	Degree of crosslinking	Pore size	Highlight	Significant outcomes	Ref.
Hyaluronic acid, fibrinogen, thrombin	Chemical crosslinking using fibrinogen and thrombin	Low	Not provided	Excellent biocompatibility, supporting the survival and proliferation of cells, promoting release of adhesion molecules and increasing adhesive properties	Reducing fibrous tissue, promoting endometrial function recovery and embryo implantation	[18]
Hyaluronic acid, Glycidyl methacrylate	Chemical crosslinking using glycidyl methacrylate, Photo-crosslinking by exposing to 365 nm UV light	Low	Not provided	Facilitating the encapsulation and transportation of small molecules or cells, promoting the enrichment and maximization of the retention of MSCs	Promoting endometrial cell proliferation and angiogenesis, improving the implantation rate of embryos	[19]
Hyaluronic acid	Auto-crosslinking	Low	Not provided	Prolonged absorption time (7 to 14 days), resisting adhesion recurrence, regulating inflammatory response	Dual effects of anti-adhesion and endometrial regeneration	[20]
Hyaluronic acid	Auto-crosslinking	Low	Not provided	Few degradations and high viscosity, extended the gel's half-life, continuous isolation of the uterine cavity	Dual effects of anti-adhesive properties with endometrial regeneration stimuli	[21]

Hyaluronic acid	Auto-crosslinking	Low	Not provided	Few degradations and high viscosity, extended the gel's half-life, continuous isolation of the uterine cavity	Preventing adhesion, improving endometrial receptivity	[22]
Maleimide-modified hyaluronic acid, Methylfuran-modified hyaluronic acid	Diels-Alder click crosslinking	Low	Not provided	Suitable mechanical properties, good biocompatibility, and desirable degradation properties, minimally invasive administration, mechanical barriers and reservoirs for cytokines and bioactive mediators	Promoting endometrial regeneration and endometrial receptivity and fertility	[23]
Recombinant type III collagen, Sodium alginate, $CaCl_2$	Calcium chloride crosslinking	Low	Not provided	Excellent biocompatibility, maintaining stemness, promoting the proliferation, migration and viability of MSCs	Less collagen deposition and higher pregnancy rates and maintaining hormonal response	[24]
Natural polysaccharide	Chemical crosslinking	Low	Not provided	Three-dimensional polymeric network, mimicking microenvironment of tissues, supporting 3D tissue-like growth	Increasing number of glands and restoration of partial fertility	[25]
Arg-Gly-Asp peptide hydrogel, amniotic membrane extract	Physical crosslinking (hydrophobic interaction, hydrogen bonding)	Low	Not provided	Three-dimensional hydrophilic polymer network, good biocompatibility, promoting cell attachment and cell-matrix interactions, anti-inflammatory and wound healing	Improving the retention and viability of MSCs in the uterus	[26]
Pluronic F-127 diacrylate	Physical crosslinking (hydrophobic interaction)	Low	108.64 ± 5.84 μm	Injectability, biocompatibility and temperature sensitivity, stable chemical properties, extending half-lives of drugs	Elevating angiogenesis with IL-1β stimulation, and facilitating thin endometrium regeneration	[27]
Pluronic F-127 diacrylate, vitamin C	Physical crosslinking (hydrophobic interaction)	Low	Not provided	Vitamin C alleviating the cytotoxic effect of PF-127 and promotes cell survival and growth	Decreasing fibrotic areas and inflammation	[28]
Methacrylated gelatin (GelMA), methacrylated collagen (ColMA)	Cross-linked by 3D printing and blue light	Low	100 μm	Denser and interconnected microporous structure, appropriate swelling ratio, good anticavity adhesion effects and mechanical properties, and impressive stability, prolonged degradability	Reducing fibrosis area and promoting anti-adhesion	[37]

VitroGel MMP (polysaccharide, Matrix Metalloproteinase (MMP)-sensitive peptides)	Auto-crosslinking	Low	not provided	Simulating the natural extracellular matrix environment, promoting cell attachment and cell-matrix interactions	Restricting the area of fibrosis, and partially restoring fertility	[39]
Hyaluronic acid	Auto-crosslinking	Low	Not provided	Promoting the retention of ABs and continuous release	Promoting endometrial regeneration and fertility restoration	[10]
Methacrylate hyaluronic acid	Chemical crosslinking using methacrylate,	pAb	pAb	pAb	pAb	pAb
Photo-crosslinking by exposing UV irradiation	Low	Not provided	Good stability and biodegradability, achieving the sustained and long-term release of drugs	Repairing endometrial injury and promoting viable pregnancy	[42]	pAb
Sodium alginate hydrogel	Chemical crosslinking	Low	Not provided	Good biocompatibility, degradability, low cost and abundant sources	Facilitating collagen fiber remodeling and endometrial regeneration, enhancing endometrial receptivity	[43]
Chitosan, sodium glycerophosphate	Physical crosslinking	Low	Not provided	Antibacterial and anti-inflammatory, slow drug release and temperature sensitivity	Reducing the manifestations and extent of endometrium fibrosis	[44]
Poloxamer, heparin	Chemical crosslinking using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide and N-hydroxysuccinimide	Low	Not provided	Long-term release of drugs	Increasing the number of endometrial glands and reducing the area of fibrosis	[45]
Poloxamer, heparin	Chemical crosslinking using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide and N-hydroxysuccinimide	Low	Not provided	Low toxicity and good biocompatibility, temperature sensitivity, strong affinity to heparin-binding growth factor and, prolonging the half-life of drugs	Promoting the proliferation of endometrial glandular epithelial cells and luminal epithelial cells	[46]
Poloxamer, heparin, ε-polylysine	Physical crosslinking using ε-polylysine	Low	Not provided	Strong mucoadhesive and rheological ability, accelerating drug release and absorption	Promoting the proliferation of endometrial epithelial cell and glands, and angiogenesis, inhibiting the cellular apoptosis	[47]
Poloxamer, nanocomposite aloe	Chemical crosslinking using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide and N-hydroxysuccinimide	Low	Not provided	Have the biomimetic and biodegradable properties, temperature sensitivity, and low immunogenicity, control drug release	Increasing morphological recovery and decreasing uterine fibrosis rate	[48]

Silk sericin	Chemical crosslinking (deionizing dialysis)	Low	Not provided	Non-toxic, non-irritating, low immunogenicity, excellent biocompatibility and biodegradability, releasing drugs stably for a long time	Promoting the cell migration and infiltration ability of Endometrial Stromal Cells (ESCs), blocking endometrial fibrosis	[49]
Sodium alginate-hyaluronic acid	Cross-linked by 3D extrusion-based bioprinting and Calcium chloride	Low	504.95 ± 80.40 μm	Good biocompatibility, non-toxic, non-immunogenic and easy to degrade	Restoring the morphology and structure of endometrial wall, improving the reproductive outcome	[61]

Table 2: The recent application of CS in endometrial regeneration and repair.

Composition	Pore sizes	Area sizes	Highlight	Study design	Applications	Significant outcomes	Ref.
Collagen type I	Not provided	Not provided	(i) Good biocompatibility and tensile resistance; (ii) Low immunogenicity; (iii) Three-dimensional framework supporting tissue and cell adhesion, migration and differentiation	Rat models of uterine scars	huMSCs delivery	Facilitating collagen degradation in uterine scars, and regeneration of the endometrium, myometrium and blood vessels in uterine scars	[29]
Collagen type I	100 ~ 200 μm	2.5 × 0.5 cm		Rat models of IUA	huMSCs delivery	Inducing intrinsic endometrial cell proliferation and epithelium recovery, promoting endometrial regeneration and collagen remodeling, and enhancing the expression of estrogen receptor α and progesterone receptor	[30]
Collagen type I	Not provided	1.5 × 0.5 cm		Rat models of IUA	huMSCs delivery	Increasing the number of endometrial glands and reducing the area of fibrosis	[31]
Collagen	20 ~ 200 μm	4.0 × 6.0 cm		Phase I clinical trial in IUA patients	huMSCs delivery	Promoting endometrial proliferation, differentiation and angiogenesis, improving patient fertility	[33]
Collagen	0 ~ 110 μm	2.5 × 0.5 cm		Rat models of acute endometrial injury	ADSCs delivery	Promoting endometrial thickness and gland number and tissue angiogenesis, reducing fibrosis and restoring fertility	[35]
Collagen	Not provided	1.0 × 0.5 cm		Rat models of IUA	MenSCs delivery	Decreasing the collagen I, increasing the number of endometrial glands	[36]
Collagen type I	20 ~ 200 μm	1.5 × 0.5 cm		Rat models of uterine horn damage	bFGF delivery	Notably retrieving the structure and function of uterine horns, improving the pregnancy rate	[50]
Collagen type I	Not provided	2.5 × 1.0 cm		Rat models of IUA	Exosomes from UCMSCs delivery	Inducing endometrium regeneration, collagen remodeling, increasing the expression of the estrogen receptor α/ progesterone receptor, and restoring fertility	[52]

Table 3: The role of ECM and other materials in endometrial regeneration and repair.

Type	Composition	Fabrication methods	Pore sizes	Degree of crosslinking	Highlight	Roles	Significant outcomes	Ref.
ECM scaffold	Crosslinked decellularized rabbit uterus matrix (dUECM), naturally derived Genipin (GP) and Procyanidins (PC)	Chemical crosslinking+physical crosslinking	Not provided	High	Similar mechanical properties to the native uterus, reasonable enzymatic degradation rate, excellent biocompatibility, minimum xenogeneic host immune rejections, and best uterus regeneration and construction after xenotransplantation	NA	Promoting cell regeneration and uterine regeneration	[55]
	Decellularized Extracellular Matrix (ECM) from porcine dermis	Natural cross-linked state	Not provided	Low	Possessing extraordinary affinity to biological components and achieving precise matching of tissue regeneration and scaffold degradation rates to promote tissue repair, and maintaining the long-term release of drugs	ADSC-exos delivery	Improving endometrium thickness, angiogenesis, myometrium regeneration and finally restoring fertility	[57]
	Urinary Bladder Matrix (UBM)	Natural cross-linked state	1000 μm	Low	having ideal mechanical properties and higher biological activity, holding complete basement membrane and can achieve complete self-functional repair, exhibit natural resistance to infection	NA	Increasing numbers of glands and fewer fibrotic areas, promoting proliferation of cells and blood vessels, improving endometrial receptivity and fertility	[56]
	Human Amniotic Extracellular Matrix (HAECM), Poly Lactic-co-Glycolic Acid (PLGA)	physical crosslinking	100 ~ 300 μm	Low	Good biocompatibility, biodegradability, tolerance, low immunogenicity, as well as the preservation of abundant bioactive components	17β-estradiol delivery	Upregulating expression of growth factors in endometrial cells to achieve endometrium regeneration	[58]
	"Homing-like" bioactive Decellularized Extracellular matrix short-Fibers (DEFs)	Natural cross-linked state	Not provided	Low	Binding to endometrial cells through noncovalent dipole interactions and release bioactive growth factors *in situ*, attractting endometrial cells through the "homing-like" effect, promote cell adhesion, spreading, and proliferation	HESCs and HUVECs delivery	Accelerating endometrial restoration, angiogenesis, and receptivity, inhibiting endometrial collagen deposition and improving live birth rate	[64]
PGS	Poly (Glycerol Sebacate) (PGS) scaffold	Chemical crosslinking	75 ~ 150 μm	Low	Excellent elasticity and fatigue durability with a limited hysteresis under dynamic deformation	BMSCs delievry	Promoting the regeneration and differentiation of endometrium and improving embryo implantation	[38]
PPCNg	Poly (Polyethylene glycol Citrate-co-N-isopropylacrylamide) (PPCN), gelatin	Autocrosslinking/ Chemical crosslinking	Not provided	Low	Thermo-responsive biomaterial, maintaining the biological activity of cells and therapeutic factors and continuous release	AMSCs delivery	Increasing in the thickness of endometrial and decreasing fibrosis area, promoting fertility	[41]
Porous scaffolds	Gelatin methacrylated and Na-alginate	Chemical crosslinking+physical crosslinking	Not provided	Low	Porous structure, absorbable, slow degradation, good elasticity and sufficient mechanical strength, loading and controlling the release of drugs *in vivo*	bFGF delivery	Promoting neovascularization and repair damaged endometrium	[62]

Hydrogel-based therapeutic delivery: Hydrogels are known for their excellent water retention, outstanding biocompatibility, controllable mechanical properties, biodegradability, responsiveness to external factors such as temperature and light, and customizable structure and functions. They are considered an ideal carrier for delivering MSCs. Kim et al. [18], prepared a hyaluronic acid/fibrinogen gel with good injectability and biocompatibility. It encapsulated Endometrial Stromal Cells (ESCs) and thrombin, which enhanced gel formation and implantation effects and effectively released adhesive molecules. The gel-loaded EMSCs increased the endometrium thickness of IUA mice in a short period. They promoted successful embryo implantation and normal development, which were more effective than treating MSCs alone. Lin et al. [19-22], designed a cross-linked Hyaluronic Acid (HA) hydrogel loaded with human Placenta-derived Mesenchymal Stem Cells (PMSCs), providing structural and mechanical support for PMSCs, effectively boosting activity and longevity, prolonging the retention time. Compared to the PMSCs group, in addition to anti-adhesion, the PMSCs-HA hydrogel further decreased the fibrotic region, increased damaged endometrial thickness and glandular count, and a greater embryo implantation rate.

Based on the Diels-Alder reaction, Hu et al. [23], created an injectable hyaluronic acid hydrogel that contained human Umbilical Cord Mesenchymal Stem Cells (UCMSCs). With its suitable mechanical characteristics, strong biocompatibility, and optimal degradation performance, this hydrogel enables minimally invasive drug administration and smooth tissue integration. Research has demonstrated that in addition to having antifibrotic properties, UCMSC-rich injectable hydrogels promoted angiogenesis, induced macrophage recruitment, and polarized them into the M2 phenotype to facilitate endometrial regeneration and the restoration of fertility.

Type III collagen, a vital extracellular matrix component, accelerated cell proliferation and maintained MSC stemness. Given the bioinert nature of sodium alginate hydrogels and the absence of a cell adhesion component, the survival and proliferation of MSCs in the hydrogels were significantly fostered by introducing type III collagen. Shuai et al. [24], developed a complex alginate gel (MSC/Alg-rCoIII) containing recombinant type III collagen (rCo III) and UMSCs, finding that it improved the migration and vitality of ESCs and promoted the mesenchymal-to-epithelial transition of ESCs, thereby boosting endometrial thickening and improving fertility in mouse models.

ShakeGel™3D is a bioactive hydrogel with a three-dimensional polymer network that simulates the tissue microenvironment and microstructure to support 3D tissue-like growth *in vitro* and *in vivo*. By isolating autogenous Adipose-Derived Mesenchymal Stem Cells (ADMSCs) and then combining them with ShakeGel™3D to inject into the uterine cavity of IUA rats, Zhao et al. [25], showed that autogenous ADMSCs could be used in combination with ShakeGel™3D to maintain function and create a viable 3D growth environment. The combined transplantation of autologous ADMSCs and ShakeGel™3D promoted recovery of damaged endometrial tissue by increasing BMP7-Smad5 signalling, resulting in the thickening of the endometrium, an increase in the number of glands and a reduction in fibrosis, thereby restoring some fertility.

The RGD (Arg-Gly-Asp) peptide could mimic cell adhesion proteins and bind to integrins. RGD hydrogels have a three-dimensional hydrophilic polymer network with good mechanical properties and biocompatibility, which could promote cell attachment and cell-matrix interaction. Amniotic Membrane Extract (AME), obtained by hydration of freeze-dried amniotic membrane, and is rich in various growth factors and cytokines. It is used widely in regenerative medicine due to its anti-inflammatory and wound-healing properties. Hao et al. [26], designed an RGD hydrogel enriched with AME and evaluated the therapeutic effect of the material combined with Menstrual blood mesenchymal Stem Cells (MenSCs) transplantation. The results showed that AME promoted the proliferation and secretion of MenSCs *in vitro*, up-regulated the expression of BCL2, and down-regulated the expression of Caspase-3 and Caspase-8. Moreover, AME-rich hydrogels were biocompatible, improved the survival of MenSCs, and enhanced the effect of MenSCs on improving uterine morphology and endometrial tolerance.

Pluronic F-127 (PF-127) is one of the thermosensitive biodegradable hydrogels approved by the U.S. Food and Drug Administration (USFDA) for clinical use. It is a liquid solution phase at a low temperature (4°C), which can be converted into a solid gel at body temperature. Moreover, it has a porous structure, which can load cell therapeutic factors at low temperatures. Zhou et al. [27], implanted UCMSCs encapsulated with PF-127 into the uterus of a rat model with thin endometrium. The results verified that embedding UCMSCs with PF-127 could prolong the retention time of UCMSCs and increase the endometrial thickness and the number of glands in the rat model with thin endometrium. Furthermore, local interleukin-1β (IL-1β) in the uterus can stimulate UCMSCs to release angiogenic factors, which may play a significant role in thin endometrial regeneration. PF-127 encapsulation has also been reported to hurt cell survival and proliferation, which can be improved by adding some membrane stabilizers to the gel preparation. It demonstrated [28], that Vitamin C (VC) reduced the toxicity of PF-127 and promoted the survival of encapsulated stem cells after the implantation of a mixture of PF-127, VC, and BMSCs into the uterus of a rat model of IUA. The implantation of the mixture promoted damaged endometrial repair and significantly reduced the pro-inflammatory cytokine IL-1β compared to the control group.

Scaffold-based therapeutic delivery: As one of the basic structural elements of Extracellular Matrix (ECM), collagen has been widely used in wound healing and tissue repair due to its rich source, biocompatibility, and biodegradability. Collagen not only serves as a framework for mechanical support but also as an additive that regulates cell behavior (Tables 2 and 3).

Collagen Scaffold (CS) arrived as highly organized, dynamically remodelled three-dimensional frameworks supported by tissue structure and so as a functional guide for cell adhesion, migration, and differentiation. Xu et al. [29], reported that the CS/UCMSC system promoted collagen degradation in uterine scars by up-regulating MMP-9 secreted by transplanted UCMSCs and increased blood vessels. Furthermore, uterine scars treated with scaffold/UC-MSCs showed almost complete recovery of receptive fertility.

Xin et al. [30], prepared a collagen scaffold with a porous structure that provided ideal physical support for the adhesion and proliferation of UCMSCs and applied it to endometrial regeneration. CS/UCMSCs promoted the proliferation of ESCs and inhibited apoptosis *in vitro* through paracrine. In a rat model of endometrial injury, CS/UCMSCs transplantation maintained standard tubular structure, induced endogenous endometrial epithelial recovery, enhanced the expression of estrogen receptor alpha and progesterone receptors, and improved the ability of the

regenerated endometrium to receive embryos. Liu et al. [31], also found that UCMSCs combined with CS could further modulate fibrosis, estrogen, and differentiation-related gene expression levels compared with hUCMSCs alone. In addition, protein levels of p transcription coactivator, stromal cell-derived factor-1, and C-X-C chemokine receptor type 4 with PDZ-binding motif upregulated. Wang et al. [32], used CS and UCMSCs to improve the regeneration of thin endometrium in a rat model, confirming that cell viability and the expression of stemness-related genes increased significantly, including organic cation/carnitine transporter 4 (Oct-4), Nanog homeobox (Nanog), and SRY-box transcription factor 2 (SOX2) increased.

Notably, CS combined with UCMSCs has also entered the clinical trial stage. Cao et al. [33], conducted a prospective, uncontrolled Phase I clinical trial involving 26 patients with recurrent IUA-induced infertility who received transplantation of a CS with 1×10^7 UCMSCs into the uterine cavity after hysteroscopic adhesion dissection and followed for 30 months. The results showed that the mean maximum endometrial thickness increased, and the IUA score was lower than before treatment. Histological studies showed up-regulated expression levels of ERα (Estrogen Receptor α), vimentin, Ki67, and vWF (von Willeophilia Factor) and down-regulated expression levels of ΔNP63, indicating improved endometrial proliferation, differentiation, and neovascularization after treatment. DNA Short Tandem Repeat (STR) analysis revealed that the regenerated endometrium contained only patient DNA. At the 30-month follow-up, 10 of the 26 patients were pregnant.

CS loaded with other sources of MSCs are also used to treat IUA, such as BMSCs [34], ADMSCs [35], and MenSCs [36]. Dai et al. [35], implanted ADMSCs composite porous stent (CS/ADMSCs) into the uterus can increase the thickness of the endometrium and the number of glands, and found that CS/ADMSCs can enhance tissue angiogenesis, reduce fibrosis, and restore fertility. Transcription analysis *in vitro* confirmed that CS/ADMSCs promote proliferation, angiogenesis, immunomodulation, and anti-fibrosis. Hu et al. [36], confirmed that human protein expression was detected in the uterus of IUA rats after CS/MenSCs transplantation 90 days. The number of endometrial glands increased, type I collagen significantly decreased, fibrosis area decreased, type I collagen decreased, and epithelium-associated protein CK18 increased. Surprisingly, human protein expression was detected in the uterus of IUA rats 90 days later, indicating that the survival time of MenSCs was significantly prolonged. There was the possibility of transdifferentiation.

The above studies suggested combining CS and MSCs may be an alternative for IUA. However, the scale and number of clinical studies were limited, and extensive clinical trials must confirm this treatment's long-term safety and feasibility.

Other potential therapeutic options: Feng et al. [37], used 3D printing technology to construct a composite hydrogel of methacrylate Gelatin Methacrylate (GelMA) and Collagen Methacrylate (ColMA) in different proportions through crosslinking reaction triggered by blue light, developing an effective and safe hydrogel for preventing IUA. It overcame the problem of cell proliferation and decreased vitality caused by UV crosslinking. The GelMA/ColMA/hAMSC hydrogel transplantation of IUA rat uterus significantly reduced the area of fibrosis and demonstrated good anti-adhesion properties.

Polyglyceryl Sebacate (PGS) is a representative synthetic elastomer with controllable degradation, high plasticity, and excellent biocompatibility. It is widely used in various biomedical applications due to its strong elasticity, which can maintain and restore various deformations in soft tissues and dynamic mechanical environments without causing mechanical stimulation of the surrounding environment. Xiao et al. [38], constructed a PGS scaffold loaded with BMSCs. The 3D structure provided by this scaffold was conducive to the attachment and growth of BMSCs and could significantly prolong the retention time of BMSCs in the injured rat uterine model. The study found that levels of Transforming Growth Factor β1 (TGF-β1), essential Fibroblast Growth Factor (bFGF), Vascular Endothelial Growth Factor (VEGF), and Insulin-like Growth Factor (IGF) in damaged endometrium near PGS/BMSCs constructs were higher than in other groups. In addition, the transplantation of PGS/BMSCs was more helpful in restoring the shape of the damaged uterus.

Wu et al. [39], used a new material, VitroGel, modified with MMP-sensitive peptides, to load MenSCs, with a balanced consideration that MenSCs could stay long enough to perform their functions while not lasting too long to avoid any biosafety concerns. MenSCs combined with VitroGel reduced the expression of inflammatory factors, increased the expression of anti-inflammatory factors, limited the area of endometrial fibrosis, reduced uterine adhesion, and partially restored fertility.

Polyethylene glycol Citrate-co-N-isopropylacrylamide gelatin (PPCNg) is a temperature-sensitive biological material composed of PPCN mixed with gelatin. It rapidly changes from liquid to gel at 37°C. Studies have shown that transplantation of PPCNg combined with human Synovial-Derived Mesenchymal Stem Cells (hSMSCs) can effectively promote the cartilage differentiation of hSMSCs by improving the nutrient supply and providing cell growth space at the injured site [40]. We previously reported that transplantation using PPCNg combined with Amniotic Mesenchymal Stem Cells (hAMSCs) could further improve the utilization of hAMSCs, promote the regeneration of injured endometrium, and ultimately restore reproductive ability [41]. In addition, its temperature-sensitive properties significantly reduced its unnecessary loss during performance. We are currently using PPCNg as the next phase of our exploration of the vaginal delivery system as the most non-invasive and cost-effective way to treat IUA.

Current research aimed to enhance the effectiveness of the combined delivery of different biological materials, which could support MSC proliferation, migration, differentiation, and survival in addition to optimizing the endometrial environment and promoting physical barrier repair of damaged endometrium. While stem cell therapy techniques have demonstrated impressive outcomes in managing IUA, treatment hurdles remain due to their complexity and cost. More significantly, mesenchymal stem cells continue to be immunogenic, tumorigenic, and uncontrollable. In order to encourage further treatment of IUA, research is currently gradually shifting to the delivery of therapeutic factors that offer better stability and controllability. This approach can lessen or eliminate the risk of immune rejection and tumor formation brought on by stem cell transplantation, and it is anticipated to simplify the procedure and lower treatment costs.

Therapeutic delivery systems of active substances derived MSCs

Hydrogel-based delivery system: Stem cell-derived cytokines such as apoptotic bodies, exosomes, EGF, KGF, SDF-1α, FGF1,

and estrogen can effectively treat IUA. However, the clinical application's lack of sustained release and targeting function significantly affects its efficacy. With the organic combination of biomaterials, the release rate and site could be controlled without affecting its biological activity. Hydrogel is an effective carrier of MSCs and cytokines because of its good biocompatibility, biofunction, biodegradability, and injectability. Xin et al. [10], used hyaluronic acid hydrogel to support Apoptotic Bodies (ABs) derived from UCMSCs. They found ABs-induced macrophage immune regulation, cell proliferation, and angiogenesis *in vitro*. In mouse models of acute endometrial injury and rat models of IUAs, *in situ*, hydrogel containing ABs injection effectively reduced fibrosis promoted endometrial regeneration, and restored fertility. Liu et al. [42], loaded Mesenchymal Stem Cell Secretory (MSC-Sec) into a cross-linked Hyaluronic Acid gel (HA gel) and established HA gel/MSCs-Sec sustained release system, which was found to repair the endometrial injury and promote pregnancy in rats. Liang et al. [43], mixed the Exosomes (Exos) from Decidual Stromal Cells (DSCs) with Sodium Alginate Hydrogel (SAH) scaffolds. They injected them into the uterine cavity of IUA mice, finding it promoted the dissolution of collagen fibers, initiated the epithelial transformation of stroma, enhanced endometrial receptivity, and restored fertility. Sun et al. [44], constructed an injectable thermosensitive hydrogel (CS/GP) that contained Exos modified by Tumor Necrosis Factor (TNF) stimulator gene 6 (TSG6). CS/GP can continuously release TSG6-modified Exos and effectively inhibit the activation of inflammatory M1-like macrophages in the initial stage of inflammation and maintain the macrophage phenotype (M1/M2) balance during the repair stage, finally alleviating the occurrence of IUA.

Poloxamer is a nonionic triblock copolymer that is water-soluble, mild, non-toxic, and non-irritating. The poloxamer hydrogel added with heparin and aloe can realize sol-gel transformation at 37°C, increase its affinity for cytokines, and prolong its release *in vivo*. Zhang et al. [45], embedded 17-β- estradiol in heparin-poloxamer hydrogel and implanted it into the uterine cavity of rats, realizing the local slow release of estrogen and facilitating the regeneration and repair of damaged endometrium, which was related to activating PI3K/Akt and ERK1/2 signalling pathways to inhibit endoplasmic reticulum stress. Xu et al. [46], prepared thermosensitive heparin-modified poloxamer with affinity to KGF(KGF-HP). They found that KGF-HP hydrogel could prolong the detention time of KGF in the uterus of damaged rats, verifying that KGF promoted epithelial cell proliferation and angiogenesis by regulating autophagy.

The rapid renewal of endometrial mucus leads to poor retention and malabsorption of therapeutic drugs in the uterine cavity, mainly affecting the curative effect. Therefore, Xu et al. [47], prepared a kind of mucosal adhesive hydrogel, that is, ε-Poloxamer (HP) was added as a functional excipient based on prim modified Poloxamer (HP), and the rheological property and mucosal adhesion of EPL-HP hydrogel were controlled by changing the content of EPL in the formula. This hydrogel had strong mucosal adhesion and accelerated drug release behaviour, boosting the proliferation of damaged endometrial epithelial cells and angiogenesis and inhibiting apoptosis. Compared with HP hydrogel alone, the EPL-HP hydrogel with a suitable KGF release curve is more likely to have application prospects. In the following research, considering that the synthetic biomaterials in the hydrogel system may have toxic effects on the cells in direct contact, the hydrogel containing Aloe-Poloxamer (AP) was designed [48], which has bionic and biodegradability, temperature sensitivity, and low immunogenicity. E2 was encapsulated into acellular uterine-derived nanoparticles (uECMNPs) and further embedded in AP hydrogel to form an E2@uECMNPs/AP system. Promoting the expression of Ki67, cytokeratin, and estrogen receptors, inhibiting TGF- β and TNF-α levels, preventing endometrial fibrosis and re-adhesion, and promoting the recovery of uterine morphology and structure in IUA rats.

Sericin is a polymer biomaterial with excellent biocompatibility. FGF-1 factor is closely related to angiogenesis and wound healing. However, its short half-life and low concentration at the injured site limit the use of FGF-1. Guan et al. [49], constructed FGF1 sericin hydrogel material (FGF1-SS hydrogel), which not only had the function of a physical support barrier but also released FGF1 stably and continuously, prolonged the half-life and local concentration of FGF1. Animal experiments showed that FGF1-SS promoted the migration and infiltration of ESCs, increased the number of uterine glands and the uterine wall thickness, inhibited fibrosis formation through the TGF-β/Smad pathway, and improved fertility.

CS delivery system: Given the problems of isolated cytokine administration, such as easy diffusion, short half-life, and severe side effects, Li et al. [50], reported that a collagen-targeting essential Fibroblast Growth Factor (bFGF) delivery system was constructed by a collagen membrane loaded with bFGF fused a Collagen-Binding Domain (CBD) to the N-terminal, which limits the diffusion of bFGF from collagen. In this system, the release of bFGF was controlled by collagen degradation to maintain an effective concentration at the target site, improve the regeneration capacity of rat endometrium and muscle cells, promote blood vessel formation, and improve pregnancy outcomes in rats. At the same time, some scholars also studied the effect of collagen combined with vascular endothelial growth factor on uterine remodelling after full-thickness injury in scarred rats [51]. The results showed that the local concentration of vascular endothelial growth factor in the scarred uterus increased, and the biological effects were prolonged. Xin et al. [52], also constructed an exomes and CS system (CS/Exos). The results showed that local transplantation of CS/Exos regulated the endometrium by promoting M2 macrophage polarization, inhibiting pro-inflammatory responses, enhancing anti-inflammatory responses, and regulating collagen remodelling to promote fertility recovery. There was evidence that mobilizing endogenous MSC recruitment could overcome the traditional limitations. Xin et al. [53], explored an acellular biomaterial called Strom-Derived Factor-1α (SDF-1α)/E7-modified Collagen Scaffold (CES), in which CES implantation promoted endogenous MSCs recruitment through macrophage coordination in a rat IUA model to perform immune regulation functions and alter the local microenvironment.

Extracellular Matrix (ECM) delivery system: As an ideal biomaterial, a decellularized Extracellular Matrix (dECM) with a 3D structure that simulates the structure and composition of a natural extracellular matrix provides a survival environment for various cytokines and controls their release rate. Miyazaki et al. [54], prepared decellularized endomematrix (DUM) from rat uterus by aortic infusion with detergents. Furthermore, DUM placement onto a partially excised uterus yielded recellularization and regeneration of uterine tissues, and pregnancy achievement was nearly comparable to that of the intact uterus. Natural tissue dECM has poor mechanical properties and rapid degradation, compromising the curative effect. Optimizing mechanical strength and degradation while maintaining microstructure and

minimizing immune rejection is still challenging. Yao et al. [55], chose a decellularized rabbit uterus matrix (dUECM) crosslinked by Genipin (GP) and Procyanidins (PC) to enhance the mechanical properties and prolong the degradation rate. The crosslinked dUECM of GP and PC was applied to rats undergoing circular hysterectomy. The results showed that it had excellent cell recellularization and infiltration ability. Notably, while the efficacy of crosslinked dUECM highly depends on the degree of crosslinking, careful evaluation of crosslinking conditions to balance the role of crosslinked dECM in the mechanical and biological support of tissue regeneration is indispensable.

Bladder Matrix (UBM) is a derived extracellular matrix biomaterial with a complete basement membrane advantage. It can achieve complete self-functional repair for the body. Zhang et al. [56], transplanted UBM into the uterus of IUA rats, finding that the transcription level of proinflammatory cytokines (TNF-α) decreased, the expression of anti-inflammatory cytokines (bFGF) and endometrial receptor factor 3 increased, and the number of embryos increased. Jin et al. [57], generated ECM from the porcine dermis and combined it with adipose stem cells-derived exosomes (ECM@ADSC-Exos). They found that ECM@ADSC-exos showed good cytocompatibility and promoted cell proliferation, migration, and angiogenesis. In the IUA rat model, ECM@ADSC-exos promotes endometrial regeneration, enhances local angiogenesis, promotes myometrial repair, and maintains fertility.

The decellularized Amnion Membrane (AM) preserved abundant bioactive components. Chen et al. [58], developed an innovative drug delivery system, the Human Amniotic Extracellular Matrix (HAECM) scaffold, in which 17 β-estradiol (E2)-supported microspheres (E2-MS) were dispersed in the scaffold to reduce the initial burst of E2 release and prolong the release, consistent with the female menstrual cycle. It was found in the application that the E2-MS-HAECM scaffold had good biocompatibility, providing more biological guidance for cells and up-regulating the expression of EGF and IGF-1 to achieve endometrial regeneration.

Cytokines are challenging to target to the damaged part of the uterus. Its release speed and concentration are difficult to control. In order to solve these problems, scholars have further combined cytokines with biomaterials with different functions to establish a targeted delivery system to ensure that drugs can be delivered to the damaged part in a targeted manner and then released stably to maintain the curative effect, and finally realize the treatment of IUA in a low-cost and efficient way, restoring the fertility of female.

Independent application status of biomaterials in IUA

Many biomaterials have anti-inflammatory, antibacterial, anti-oxidative stress, and immune microenvironment regulation functions, holding excellent application potential in treating and promoting endometrial repair. The functional research and related mechanism exploration of these materials can provide more clues and opportunities for endometrial regeneration, seeking a more economical, convenient, and effective therapy for IUA.

DISCUSSION

Huiyi et al. [59], introduced multiple groups into the hydrogel system through self-polymerization and amidation, forming a multi-network SA/PDA/CMCS-Arg injectable hydrogel through a non-toxic ion-triggering system. It regulated the reactive oxygen species scavenging and antibacterial activity mediated by multifunctional groups in the microenvironment and inflammatory environment, thereby reducing the degree of tissue fibrosis and inflammation and repairing endometrial tissue. Li et al. [60], developed an acellular amniotic membrane gel made from Amniotic Membrane (AM) through decellularization, freeze-drying, and enzymatic digestion processes. IUA rats were injected with DAM gel immediately after surgery, significantly reducing fibrosis and increasing microvessel density, improving fertility. Based on 3D bioprinting technology, Nie et al. [61], constructed a double-layer Endometrial Construct (EC) of sodium alginate-haluronic acid (Alg-HA) hydrogel. The upper layer is a single layer of Endometrial Epithelial Cells (EEC), and the lower layer is a mesh-like microstructure loaded with Endometrial Stromal Cells (ESC). It simulated the morphology and structure of the endometrial wall and significantly improved reproductive outcomes in the surgical area after implantation (75%, 12/16). Droplet microfluidic technology is used to manufacture polymers and composite particles with complex structures whose composition, porosity, and shape can be easily adjusted. Cai et al. [62], designed a novel drug-loaded porous scaffold based on a microfluidic droplet template that combines the properties of GelMA, an artificial biocompatible material, and NA-alginate, a natural polysaccharide material, with compressibility and delivery of drugs, proved to promote neovascularization and repair damaged endometrium after implanted in a rat model of IUA. Cell-free fat extract is a substance extracted from adipose tissue that removes the cellular component, leaving only the extracellular matrix and dissolved biological factors. Xu et al. [63], innovatively synthesized a bioactive injectable hydrogel using thiolated polyethylene (PEG), Cu^{2+}, and free fat extract (CEFFE, CF). It reduced cell apoptosis, promoted vascular regeneration *in vitro*, and induced endometrial cells to self-repair *in situ*, and improved fertility. Cao et al. [64], innovatively designed an injectable "homing-like" bioactive acellular extracellular matrix short fiber (DEF) derived from pig skin, which effectively attracted endometrial cells to adhere, spread, and proliferate on its surface and further released bioactive growth factors *in situ*, thereby improving endometrial tolerance and achieving efficient live births.

CONCLUSION

Exploring new multifunctional biomaterials combined with therapeutic factors or stem cells to target the damaged sites and release them slowly to maintain local drug concentration and thereby promote endometrial regeneration is the most potential therapeutic strategy for IUA. The uterine injection is a commonly used method of drug administration at present. However, its clinical application value is minimal because it is invasive. Drugs without combined materials have many challenges regarding non-specific colonization and liver metabolism when entering the body *via* a vein. In contrast, local vaginal administration is entirely non-invasive and safe. The pelvic vein can be used due to the rich blood supply to increase the concentration of the drug in the uterus. We previously compared the effects of temperature-sensitive material PPCNg combined with hAMSCs in the treatment of IUA *via* the vagina and uterine cavity, respectively, finding that vaginal administration of PPCNg/hAMSCs can effectively inhibit fibrosis and promote epithelial repair. In summary, we believe that the combination of drugs or stem cells with new biomaterials and vaginal administration is likely to become the leading research direction of IUA therapy.

DATA AVAILABILITY

All data (or sources thereof) relevant to this study are included in the

article, and further inquiries can be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

Xiao Yang, Xiyue Huang, Ling Wei: Collecting studies, writing the manuscript. Qiuhong Chen, Quanhong Shi, Shasha Wu: Contributed to manuscript preparation and revising. Wenwen Zhang, Peng Jiang, Yanhua Mao, Changjiang Li, Yingfeng Zhang, Congcong SuN: Contributed to writing and revising the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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