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Evolution of biotechnological advances and regenerative therapies for endometrial disorders: a systematic review

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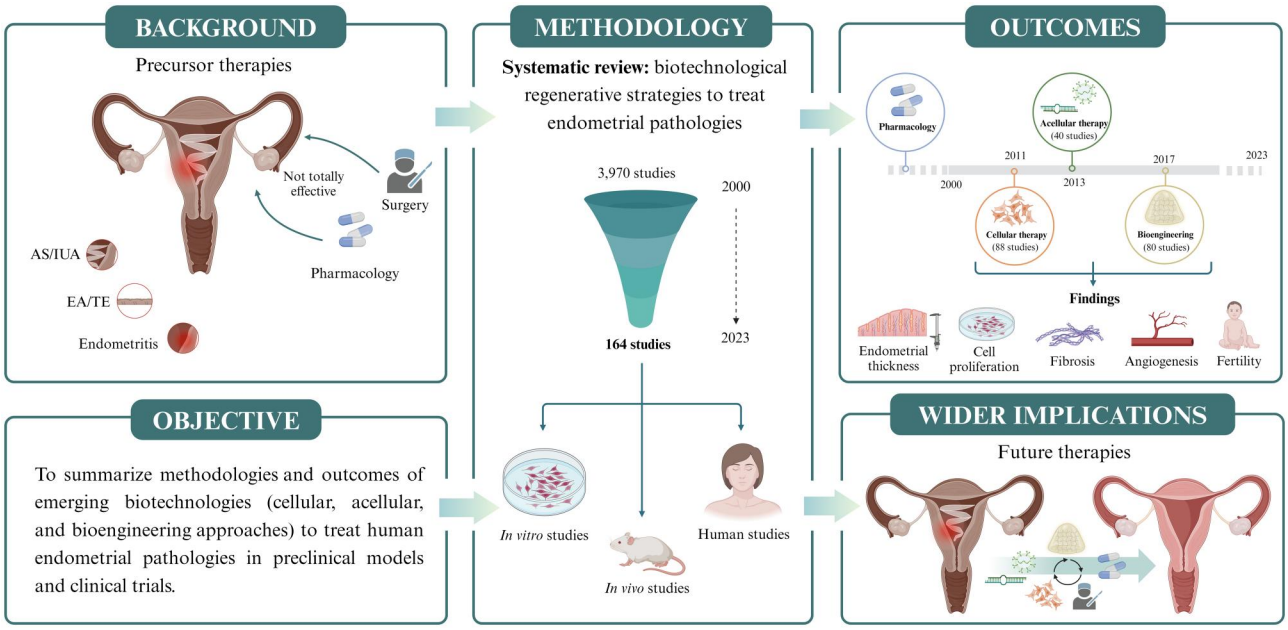
GRAPHICAL ABSTRACT



The emergence of new therapeutics and biotechnological advances for the treatment of endometrial pathologies. AS, Asherman syndrome; IUA, intrauterine adhesions; EA, endometrial atrophy; TE, thin endometrium. Created with BioRender.com

ABSTRACT

BACKGROUND: The establishment and maintenance of pregnancy depend on endometrial competence. Asherman syndrome (AS) and intrauterine adhesions (IUA), or endometrial atrophy (EA) and thin endometrium (TE), can either originate autonomously or arise as a result from conditions (i.e. endometritis or congenital hypoplasia), or medical interventions (e.g. surgeries, hormonal therapies, uterine curettage or radiotherapy). Affected patients may present an altered or inadequate endometrial lining that hinders embryo implantation and increases the risk of poor pregnancy outcomes and miscarriage. In humans, AS/IUA and EA/TE are mainly treated with surgeries or pharmacotherapy, however the reported efficacy of these therapeutic approaches remains unclear. Thus, novel regenerative techniques utilizing stem cells, growth factors, or tissue engineering have emerged to improve reproductive outcomes.

OBJECTIVE AND RATIONALE: This review comprehensively summarizes the methodologies and outcomes of emerging biotechnologies (cellular, acellular, and bioengineering approaches) to treat human endometrial pathologies. Regenerative therapies derived from human tissues or blood which were studied in preclinical models (*in vitro* and *in vivo*) and clinical trials are discussed.

SEARCH METHODS: A systematic search of full-text articles available in *PubMed* and *Embase* was conducted to identify original peer-reviewed studies published in English between January 2000 and September 2023. The search terms included: human, uterus, endometrium, Asherman syndrome, intrauterine adhesions, endometrial atrophy, thin endometrium, endometritis, congenital hypoplasia, curettage, radiotherapy, regenerative therapy, bioengineering, stem cells, vesicles, platelet-rich plasma, biomaterials, microfluidic, bioprinting, organoids, hydrogel, scaffold, sheet, miRNA, sildenafil, nitroglycerine, aspirin, growth hormone, progesterone, and estrogen. Preclinical and clinical studies on cellular, acellular, and bioengineering strategies to repair or regenerate the human endometrium were included. Additional studies were identified through manual searches.

OUTCOMES: From a total of 4366 records identified, 164 studies (3.8%) were included for systematic review. Due to heterogeneity in the study design and measured outcome parameters in both preclinical and clinical studies, the findings were evaluated qualitatively and quantitatively without meta-analysis. Groups using stem cell-based treatments for endometrial pathologies commonly employed mesenchymal stem cells (MSCs) derived from the human bone marrow or umbilical cord. Alternatively, acellular therapies based on platelet-rich plasma (PRP) or extracellular vesicles are gaining popularity. These are accompanied by the emergence of bioengineering strategies based on extracellular matrix (ECM)-derived hydrogels or synthetic biosimilars that sustain local delivery of cells and growth factors, reporting promising results. Combined therapies that target multiple aspects of tissue repair and regeneration remain in preclinical testing but have shown translational value. This review highlights the myriad of therapeutic material sources, administration methods, and carriers that have been tested.

WIDER IMPLICATIONS: Therapies that promote endometrial proliferation, vascular development, and tissue repair may help restore endometrial function and, ultimately, fertility. Based on the existing evidence, cost, accessibility, and availability of the therapies, we propose the development of triple-hit regenerative strategies, potentially combining high-yield MSCs (e.g. from bone marrow or umbilical cord) with acellular treatments (PRP), possibly integrated in ECM hydrogels. Advances in biotechnologies together with insights from preclinical models will pave the way for developing personalized treatment regimens for patients with infertility-causing endometrial disorders such as AS/IUA, EA/TE, and endometritis.

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Keywords: stem cell therapy / acellular therapy / bioengineering / endometrium / Asherman síndrome / intrauterine adhesions / endometrial atrophy / thin endometrium / endometritis / fertility restoration

Introduction

The human endometrium is the innermost mucosal layer of the uterus, which connects to the fallopian tubes and ovaries. This tissue, comprised mainly of stroma and uterine glands, is crucial for successful embryo implantation and adequate uterine function (Critchley *et al.*, 2020; Jain *et al.*, 2022). In addition, the endometrial layer prevents adhesion formation between opposed walls of the myometrium, thereby maintaining the integrity of the uterine cavity (Bergmann *et al.*, 2021; Navarro *et al.*, 2021).

Endometrial tissue undergoes cyclic breakdown, repair, and regeneration during each menstrual cycle. These physiological processes involve hormonal regulation, proliferation, decidualization, inflammation, hypoxia, apoptosis, haemostasis, and vasoconstriction (Critchley *et al.*, 2020). Cyclical endometrial remodelling and proliferation drive the hypothesis that a subset of somatic or adult endometrial stem cells are activated every menstrual cycle (Chan and Gargett, 2006; Cervelló *et al.*, 2007, 2010, 2013, 2015; Masuda *et al.*, 2012; Deane *et al.*, 2016; Santamaria *et al.*, 2016, 2018). Dysfunctional endogenous endometrial stem cell populations were related to certain gynaecological disorders (Santamaria *et al.*, 2018) and conditions, including Asherman syndrome (AS) or intrauterine adhesions (IUA), hereafter referred to as AS/IUA; endometrial atrophy (EA) or thin endometrium (TE), hereafter referred to as EA/TE; and endometritis.

Pathologies that directly affect the uterine lining, such as AS/IUA and EA/TE, may provoke a refractory endometrium characterized by a lack of proliferation and abnormal thickness, which in turn causes infertility. The earliest report of curettage causing IUA and amenorrhea was in 1894 (Fritsch, 1894). However, the term AS was only coined in 1950, when Dr Asherman described 29 cases of secondary amenorrhea following intrauterine trauma (Asherman, 1950). AS is characterized by the presence of IUA or endocervical adhesions with a consequent risk of hypomenorrhea or amenorrhea, reduced fertility, pregnancy loss, and abnormal placentation (de Miguel-Gómez *et al.*, 2021c). On the other hand, EA/TE is characterized by an endometrial thickness of less than 6–8 mm during the secretory phase, with no consensus among the various published studies. Endometrial thickness is measured by ultrasonography at the time of hCG administration in IVF cycles or after adequate estrogen exposure in artificially prepared frozen embryo transfer cycles (de Miguel-Gómez *et al.*, 2021c). Furthermore, certain interventions, such as curettage or radiotherapy (Kudesia and Kuokkanen, 2016), and conditions like congenital hypoplasia (Jayaprakasan and Ojha, 2022) or endometritis can cause endometrial damage, leading to AS/IUA or EA/TE in some cases.

Hysteroscopy is the gold standard for IUA surgery, which aims to restore the uterine cavity size and shape, thus normalizing endometrial function. Treatment options vary from adhesiolysis using scissors, to electrocautery or laser ablation for dense IUAs (Conforti *et al.*, 2013). However, these approaches have variable results and are often unsuccessful in severe cases (Hanstede *et al.*, 2015; Bosteels *et al.*, 2017).

In clinical practice, less invasive ultrasound-based signs of endometrial competence and reproductive success, including endometrial thickness, pattern, and blood flow are often preferred (Liu *et al.*, 2019a; Jacobs *et al.*, 2022; Mahutte *et al.*, 2022; Cakiroglu *et al.*, 2023). However, the anatomical normality of the uterus does not necessarily reflect appropriate function; women with damaged endometrium may achieve pregnancy (Dix and Check, 2010; Amui *et al.*, 2011; Check and Cohen, 2011; Cruz and Bellver, 2014; Ata *et al.*, 2023) while women considered to have a normal uterine morphology and good-quality embryos transferred may not have successful implantation or be able to maintain pregnancy (Cimadomo *et al.*, 2023). Notably, therapies designed to improve endometrial thickness and, ultimately, reproductive performance, were mainly tested in studies with small cohorts and/or poor methodology (Garcia-Velasco *et al.*, 2016; Ranisavljevic *et al.*, 2019; Liu *et al.*, 2019a). Further, conflicting outcomes for anatomical restoration and reproductive parameters were reported (Liu *et al.*, 2019a; Cakiroglu *et al.*, 2023; Shabiti *et al.*, 2023). Conventional hormone-based therapies involved high doses of estrogen, long-lasting secondary effects, and different routes of administration. Other therapies that targeted endometrial cellular receptors [e.g. systemic hCG, GnRH, or growth hormone], blood flow enhancers (e.g. aspirin, sildenafil, pentoxifylline, l-arginine, nitroglycerine, and tocopherol) (Garcia-Velasco *et al.*, 2016; Ranisavljevic *et al.*, 2019; Liu *et al.*, 2019a; Cakiroglu *et al.*, 2023) or utilized biomimetic electrical stimulation (Shabiti *et al.*, 2023) did not consistently restore uterine function or improve reproductive outcomes.

Due to the ineffective and inconsistent outcomes reported for these pharmacological treatments, emerging strategies that aim to change the current practices in reproductive medicine are based on new therapeutics and biotechnological advances (Francés-Herrero *et al.*, 2022a; Cakiroglu *et al.*, 2023). Cell therapy is defined as the transfer of autologous or allogeneic cellular material (via injection, instillation, or transplantation) for medical purposes (El-Kadiry *et al.*, 2021). In 2011, pioneering studies demonstrated the use and promise of autologous and heterologous stem cells to improve human endometrial thickness (Fig. 1). These were followed by studies exploring strategies with mesenchymal stem cells (MSCs) derived from human menstrual blood-derived (MenMSCs) and umbilical cord-derived stem cells (UCMSCs), among other cell sources. In 2013, non-invasive acellular therapies for endometrial regeneration were introduced with platelet-rich plasma (PRP) (Fig. 1), followed by microRNAs (miRNAs), extracellular vesicles (EVs), and other growth factors. In 2017, two independent groups used collagen scaffolds to improve endometrial reconstruction (Fig. 1). The number of next-generation bioengineering applications in reproductive medicine continues to rise, with new strategies based on silicone, hyaluronic acid (HA), and decellularized extracellular matrices (dECM). Here, we review how modern therapies and advances in biotechnology revolutionized treatments for endometrial disorders affecting human fertility (particularly, AS/IUA, EA/TE, and endometritis). The shifting trend of reports on pharmacotherapy, cellular and acellular therapies, and bioengineering strategies used to manage these disorders, published between 2000 and 2023, is illustrated in Fig. 1.

Prior to 2011, endometrial damage was conventionally managed with drugs (e.g. estrogens or aforementioned alternatives) alone, or in combination with hysteroscopic surgery or curettage (Conforti *et al.*, 2013). Pharmacotherapies targeting endometrial alterations emerged in the 1950s (Gonen and Casper, 1990) but, surprisingly, were not as exploited over the last 23 years as the other techniques discussed herein, in terms of research and publications. Indeed, we identified 15 years between 2000 and 2023 with no pharmacological study reported 6 years where only one study was published, and 3 years with two contemporary reports.

These sporadic reports focused on optimizing administration and dosing (Fanchin *et al.*, 2001; Guo *et al.*, 2017; Yi *et al.*, 2023). Due to the lack of significant progress in drug-mediated endometrial repair and regeneration, we considered the existing drug

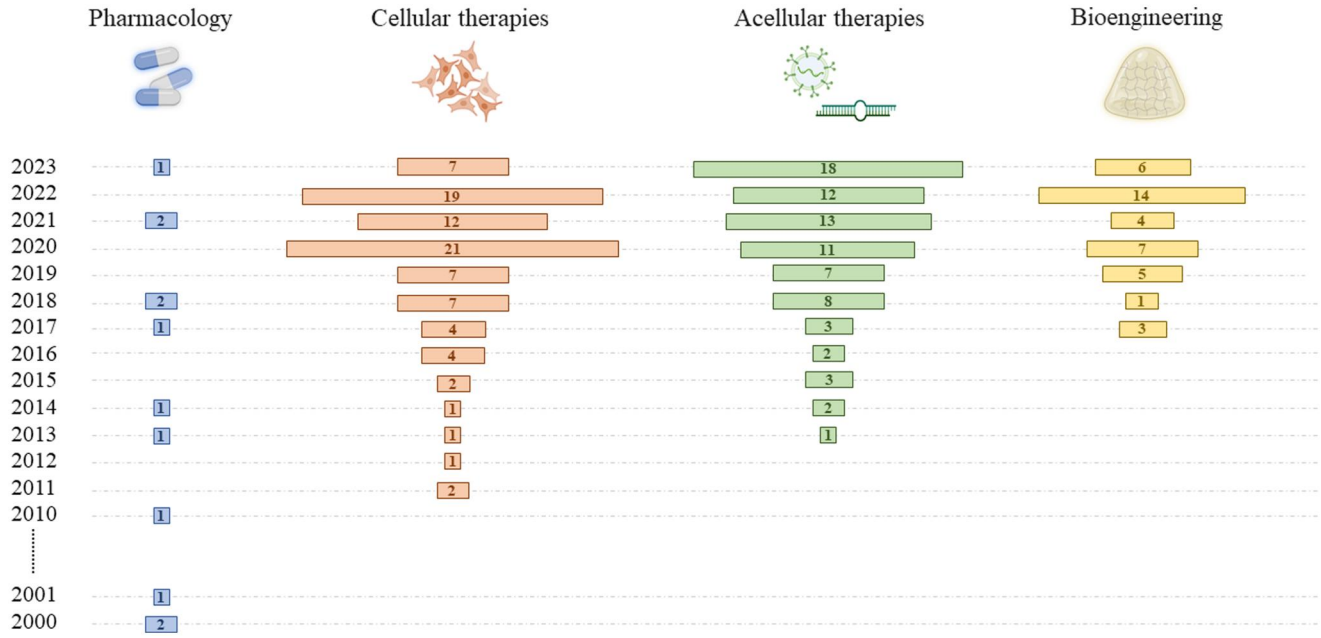

Figure 1. Evolution of reports on pharmacotherapy, cellular and acellular therapies, and bioengineering strategies used to manage endometrial disorders. The numbers in the bars indicate the annual sum of studies indexed in PubMed and Embase (1 January 2000 to 19 September 2023). The search queries for cellular, acellular, and bioengineering therapies are detailed in the Methods. Notably, there were no studies reported between 2002 and 2009.

treatments as precursors for the emerging therapies reviewed herein. Valuable advances in alternative management strategies for endometrial repair and regeneration are encouraging clinicians and scientists. These advances raise the possibility of combining effective biotechnologies with established treatments to improve the care of patients with endometrial factor infertility.

In this review, we summarize the methodologies and main findings of studies evaluating endometrial repair and regeneration strategies based on stem cells, acellular components, and bioengineering approaches. The growing interest in these new strategies contrasts with the stagnant landscape of conventional pharmacological treatments. We present both preclinical and clinical evidence to guide the design of future studies and facilitate informed decision-making in patients undergoing infertility treatment with ART.

Methods

Protocol and registration

The protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and the systematic review following PRISMA 2020 guidelines (Page *et al.*, 2021). Our protocol is registered in the Open Science Framework (OSF) database (https://osf.io/th8yf/).

Study selection and eligibility criteria

The Population, Intervention, Comparison, and Outcome (PICO) framework was used to define the eligibility criteria for this systematic review. Briefly, we screened the study population (*in vitro, in vivo*, clinical models), intervention to regenerate the endometrium (therapy), comparison (regenerative parameters), and outcome (verification of endometrial regeneration and/or fertility restoration). We included original, rigorous, and accessible peer-reviewed full-text articles that reported the treatment of any cellular/acellular/bioengineering approach to treat endometrial diseases, and applied these regenerative treatments in preclinical or clinical cases.

Studies using cellular/acellular therapies derived from animal sources, or non-human biomaterials without human components, were not considered in this review. Reviews, opinion articles, technical articles, editorials, letters to the editor, personal opinions, books, book chapters, and untranslated documents were excluded.

Literature search results were exported to MS Excel™ 2016 and duplicates were identified using electronic and manual methods. Titles, abstracts, and full texts were screened independently and in duplicate by two authors (A.R.-E. and C.B.-F.). Questions or disagreements were resolved by discussion (A.R.-E., C.B.-F., A.P., and I.C.). The final list of included studies was approved by I.C.

Search strategy

A systematic search of relevant full-text articles available in *PubMed* and *Embase* was conducted by A.R.-E. and C.B.-F. The search was limited to full-text articles, in English, published between the first of January 2000 and 19th of September 2023. The search queries used for each database are presented in Supplementary Table S1. The following keywords were applied: human, uterus, endometrium, Asherman syndrome, intrauterine adhesions, endometrial atrophy thin endometrium, endometritis, congenital hypoplasia, curettage, radiotherapy, gynecologic surgery, regenerative therapy, bioengineering, stem cells, vesicles, platelet-rich plasma, biomaterials, microfluidic, bioprinting, organoids, hydrogel, scaffold, sheet, miRNA, sildenafil, nitroglycerine, aspirin, growth hormone, progesterone, and estrogen. When the full texts were not available, a request was sent to the corresponding author(s). Additional studies were identified by manually searching the references of selected articles and

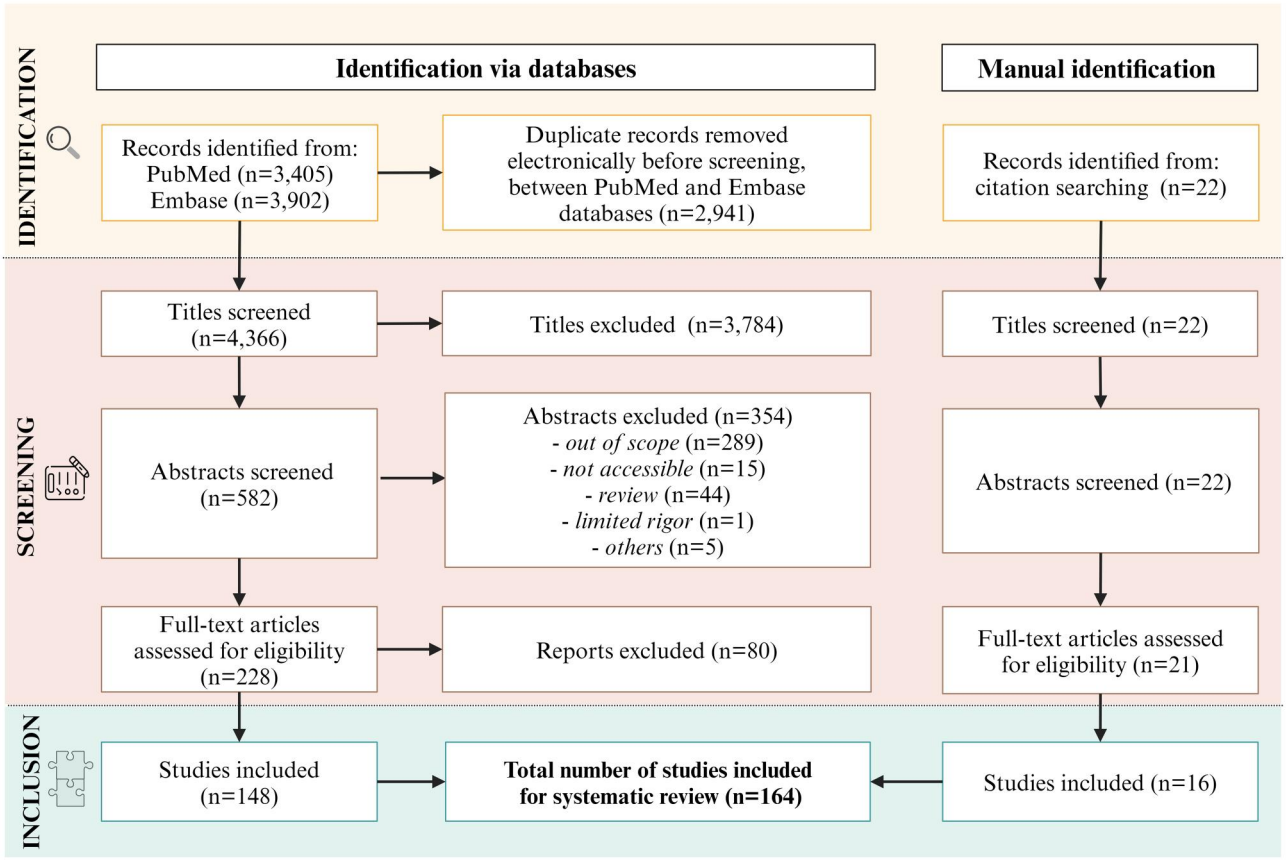

Figure 2. PRISMA flow diagram for the selection of studies in a systematic review of regenerative therapies in the management of endometrial disorders. Exact terms used for each database are detailed in Supplementary Table S1. Adapted from Francés-Herrero *et al.* (2022a). PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis. Created with BioRender.com.

complementary reviews. The systematic workflow is detailed in Fig. 2.

Data extraction and synthesis of results

Relevant findings are summarized in Table 1. Data were synthesized according to the reporting guidelines for Synthesis Without Meta-analysis (SWiM) in systematic reviews (Campbell *et al.*, 2020). Extracted data, including titles, authors, year of publication, and relevant outcomes were compiled into a shared Google Sheets spreadsheet and revised by M.G.-Á., E.F.-H., J.B., and E.S. Studies were grouped by the model (AS/IUA, EA/TE, endometritis), treatment type (cellular/acellular/bioengineering strategy), study type (*in vitro*, *in vivo*, clinical), source (autologous, heterologous, commercial, or other), route of administration (local instillation/injection, intravenous, subcutaneous, intraperitoneal, or other), and carriers (if applicable). Notably, the nomenclature used for classifications reflects the terminology reported by the original authors. Reproductive outcome measures, including endometrial thickness, uterine glands, expression of proliferation markers, fibrosis, regenerative markers, American Fertility Society (AFS) score, menstrual changes, and fertility outcomes, were extracted for all studies. A compilation of the human trial results is included in Table 2. Detailed comparisons of *in vitro* and *in vivo* studies are included in Supplementary Tables S2 and S3, respectively. A formal meta-analysis to compare treatment efficacy was not feasible due to the heterogeneity in measurements and methodology of studies included for systematic review.

Results

Search results

The search queries in *PubMed* and *Embase* yielded 4366 results (from a total of 7307 titles identified) after the removal of duplicates. Title screening excluded 86.6% (3784) reports. Abstract screening excluded 354 reports based on criteria presented in Fig. 2. Of the 228 full-text manuscripts (5.2%) that met the criteria for assessment, 148 studies (3.3%) were included for review. An additional 22 records were identified manually, of which, 16 were included. Among the final 164 articles considered for systematic review, there were 88 (53.6%) about stem cell therapies, 80 (48.8%) about acellular therapies, and 40 (24.4%) related to bioengineering. We included a total of 40 (24.4%) studies discussing *in vitro* models, 87 (53.0%) studying *in vivo* efficacy, and 58 (35.4%) clinical trials. Notably, the sum of these values is greater than the total because manuscripts were assessed with each category they corresponded with. Finally, none of the included studies evaluated direct treatments for congenital endometrial hypoplasia, endometrial damage after curettage, or radiotherapy with regenerative therapies.

Regenerative endometrial therapies: systematic summary of the literature

In the following sections, we summarize 164 investigations of potential human therapies to treat endometrial disorders, particularly AS/IUA, EA/TE, or endometritis. A comparison of the study designs is presented in Table 1. Figure 3 illustrates the sources of the human-based therapies for preclinical studies (*in vitro* and

Table 1. Comparison of study designs from preclinical and clinical studies evaluating cellular, acellular, and bioengineering-based treatments for endometrial disorders.

Therapy	Model	Type of study	Carrier	Source	Damage	Route of administration	Reference
BMMSC	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU instillation	(Du *et al.*, 2012)
	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU vs IV injection	(Cervelló *et al.*, 2015)
	AS/IUA	*In vivo* (mouse) + clinical trial	None	Heterologous	Scratching	IU instillation	(de Miguel-Gómez *et al.*, 2019)
	AS/IUA	Clinical	Collagen	Autologous	N/A	IU instillation	(Zhao *et al.*, 2017)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Nagori *et al.*, 2011)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Santamaria *et al.*, 2016)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Zhao *et al.*, 2013)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Arikan *et al.*, 2023)
	AS/IUA + EA/TE	Clinical	None	Autologous	N/A	IU injection	(Singh *et al.*, 2014)
	AS/IUA + EA/TE	Clinical	None	Autologous	N/A	IU injection	(Singh *et al.*, 2020)
BMMSC + EV	AS/IUA	*In vitro* + *in vivo* (mouse)	None	Commercial	LPS	IP injection	(Liu *et al.*, 2021)
	AS/IUA	*In vivo* (rat)	None	Commercial	Scratching	IU instillation	(Mansouri-Kivaj *et al.*, 2023)
BMMSC + PRP	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Tandulwadkar *et al.*, 2021)
BMMSC + CM	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU injection	(Ho *et al.*, 2018)
BMMSC + EV + miRNA	AS/IUA	*In vitro* + *in vivo* (mouse)	None	Heterologous	Ethanol	IU instillation	(Tan *et al.*, 2020)
EndoMSC	AS/IUA	*In vitro* + *in vivo* (rat)	Chitosan	Heterologous	Scratching	IU instillation	(He *et al.*, 2022)
	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU injection	(Song *et al.*, 2021)
	AS/IUA	*In vivo* (mouse)	None	Heterologous	None	IU instillation	(Park *et al.*, 2020b)
	EA/TE	*In vivo* (rat)	Collagen	Heterologous	Wall rejection	IU injection	(Li *et al.*, 2019a)
	AS/IUA	*In vivo* (rat)	Microneedles	Heterologous	Scratching	IU instillation	(Li *et al.*, 2022a)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	SC injection	(Wang *et al.*, 2018)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Sapozhak *et al.*, 2020)
EndoMSC + PRP	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Tersoglio *et al.*, 2020)
EndoMSC + PRP + Electric pulse	EA/TE	Clinical	None	Autologous	N/A	IU injection	(Efendieva *et al.*, 2023)
UCMSC	AS/IUA	*In vitro*	None	Heterologous	Mifepristone	N/A	(Sun *et al.*, 2018)
	AS/IUA	*In vitro*	None	Heterologous	Mifepristone	N/A	(Yang *et al.*, 2011)
	AS/IUA	*In vitro*	None	Heterologous	Mifepristone	N/A	(Shi *et al.*, 2020)
	AS/IUA	*In vivo* (mouse)	SF-SIS	Commercial	Scratching	IU instillation	(Zheng *et al.*, 2022b)
	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU injection	(Park *et al.*, 2020a)
	AS/IUA	*In vivo* (mouse)	None	Commercial	Electrocoagulation	IU injection	(Li *et al.*, 2022b)
	AS/IUA	*In vivo* (mouse)	None	Heterologous	Ethanol	IU instillation	(Xu *et al.*, 2022)
	AS/IUA	*In vivo* (rat)	PF-127	Commercial	Scratching	IU instillation	(Hu *et al.*, 2022b)
	AS/IUA	*In vivo* (rat)	ECM derived	Commercial	Ethanol	IU instillation	(Wang *et al.*, 2021a)
	AS/IUA	*In vivo* (rat)	Collagen	Heterologous	Scratching	IU instillation	(Xin *et al.*, 2019)
	AS/IUA	*In vivo* (rat)	Collagen	Heterologous	Scratching	IU instillation	(Liu *et al.*, 2020a)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Ethanol	IV injection	(Zhang *et al.*, 2018)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Ethanol	IU injection	(Li *et al.*, 2021)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IV injection	(Wang *et al.*, 2021b)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU injection	(Zheng *et al.*, 2022a)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Trichloroacetic acid	IP vs IV injection	(Sabry *et al.*, 2017)

(continued)

Table 1. (continued)

Therapy	Model	Type of study	Carrier	Source	Damage	Route of administration	Reference
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU injection	(Tang *et al.*, 2016)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Ethanol	IV vs IV + IU injection	(Zhuang *et al.*, 2022)
	AS/IUA	*In vivo* (rat)	Hialuronic acid	Heterologous	Scratching	IU injection	(Zhang *et al.*, 2023a)
	AS/IUA	*In vivo* (rabbit)	None	Heterologous	Scratching	IU instillation	(Hua *et al.*, 2022)
	AS/IUA	*In vivo* (monkey)	Hialuronic acid	Commercial	Scratching	IU instillation	(Wang *et al.*, 2020c)
	EA/TE	*In vivo* (rat)	PF-127	Heterologous	Ethanol	IU instillation	(Zhou *et al.*, 2022)
	AS/IUA + EA/TE	Clinical	Collagen	Heterologous	N/A	IU instillation	(Zhang *et al.*, 2021b)
	AS/IUA + EA/TE	*In vitro* + *in vivo* (rat)	None	Heterologous	Ethanol	IU injection	(Zhang *et al.*, 2022a)
	AS/IUA + EA/TE	*In vivo* (rat)	Collagen	Heterologous	Others	IU injection	(Xu *et al.*, 2017a)
	AS/IUA	Clinical	Collagen	Heterologous	N/A	IU instillation	(Cao *et al.*, 2018)
	AS/IUA	Clinical	None	Heterologous	N/A	IU instillation	(Huang *et al.*, 2022a)
	AS/IUA	Clinical	None	Heterologous	N/A	IU instillation	(Kaczynski and Rzepka, 2022)
UCMSC + HOXA10	AS/IUA	*In vivo* (mouse)	None	Heterologous	Ethanol	IU injection	(Wu *et al.*, 2023)
UCMSC + Amniotic fluid	AS/IUA	*In vivo* (rat)	None	Heterologous	Talc powder	Non specified	(Aygün and Tümentemur, 2022)
UCMSC + EV	AS/IUA	*In vitro*	None	Heterologous	None	N/A	(Lv *et al.*, 2020)
	AS/IUA	*In vitro*	None	Heterologous	Mifepristone	N/A	(Wang *et al.*, 2020a)
	AS/IUA	*In vitro*	None	Heterologous	TGF-β1	N/A	(Li *et al.*, 2023b)
	AS/IUA	*In vitro*	None	Heterologous	Mifepristone	N/A	(Shi *et al.*, 2021)
	EA/TE	*In vivo* (rat)	None	Heterologous	Ethanol	IU instillation	(Zhang *et al.*, 2022b)
UCMSC + miRNA	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU instillation	(Sun *et al.*, 2021)
MenMSC	AS/IUA	*In vitro*	None	Heterologous	Mifepristone	N/A	(Zhu *et al.*, 2018)
	AS/IUA	*In vitro* + *in vivo* (mouse)	None	Commercial	Hydrothermal ablation	IU instillation	(Wang *et al.*, 2020b)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU instillation	(Hu *et al.*, 2019)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU injection	(Chang *et al.*, 2020)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Electrocoagulation	IU instillation	(Domnina *et al.*, 2016)
	AS/IUA	*In vivo* (rat)	ECM derived	Heterologous	Scratching	IU instillation	(Hao *et al.*, 2022)
	AS/IUA	*In vivo* (rat)	Collagen	Heterologous	LPS	IU instillation	(Hu *et al.*, 2022a)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Ethanol	IU vs IV injection	(Domnina *et al.*, 2018)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Ma *et al.*, 2020)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Tan *et al.*, 2016)
MenMSC + PRP	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU injection	(Zhang *et al.*, 2019)
AdiMSC	AS/IUA	*In vivo* (rat)	ECM derived	Heterologous	Ethanol	IU instillation	(Han *et al.*, 2020)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Lee *et al.*, 2020)
	TE/EA	Clinical	None	Autologous	N/A	IU injection	(Sudoma *et al.*, 2019)
AMSC	AS/IUA	*In vitro* + *in vivo* (mouse)	None	Heterologous	Scratching	IU instillation	(Li *et al.*, 2019b)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU injection	(Bai *et al.*, 2020)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU vs IV injection	(Ouyang *et al.*, 2020)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Wall rejection	IU + IP injection	(Fan *et al.*, 2021)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Ethanol	IU injection	(Yu *et al.*, 2021)
	AS/IUA	*In vivo* (rat)	None	Heterologous	LPS	IV injection	(Mao *et al.*, 2023a)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU instillation	(Gan *et al.*, 2017)
	AS/IUA	*In vivo* (rat)	PPCN	Heterologous	Ethanol	IU instillation	(Huang *et al.*, 2022b)
	EA/TE	*In vitro* + *in vivo* (mouse)	Hialuronic acid	Heterologous	Ethanol	IU instillation	(Lin *et al.*, 2022)

(continued)

Table 1. (continued)

Therapy	Model	Type of study	Carrier	Source	Damage	Route of administration	Reference
Embryonic MSC	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU injection	(Jun *et al.*, 2019)
	AS/IUA	*In vivo* (rat)	None	Commercial	Wall rejection	IU instillation	(Song *et al.*, 2015)
	AS/IUA	*In vivo* (rat)	None	Commercial	Scratching	IU instillation	(Jiang *et al.*, 2021)
iPSCs	AS/IUA	*In vivo* (rat)	Bioprinting	Heterologous	Scratching	IU instillation	(Ji *et al.*, 2020)
MSC	Endometritis	*In vitro*	None	Commercial	LPS	N/A	(Mani *et al.*, 2020)
PRP	AS/IUA	*In vitro*	None	Heterologous	N/A	N/A	(Aghajanova *et al.*, 2018)
	AS/IUA	*In vitro* + *in vivo* (mouse)	None	Heterologous	Scratching	IU instillation	(Kim *et al.*, 2022)
	AS/IUA	*In vitro* + *in vivo* (rat)	None	Heterologous	Scratching	IU instillation	(Mao *et al.*, 2023b)
	AS/IUA	*In vivo* (mouse)	None	Heterologous	Scratching	IU instillation	(Kim *et al.*, 2020)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Peng *et al.*, 2020)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Aghajanova *et al.*, 2021)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Shen *et al.*, 2022)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Chang *et al.*, 2023)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Pandey *et al.*, 2023)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Qiu *et al.*, 2023)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Javaheri *et al.*, 2020)
	AS/IUA	Clinical	None	Autologous	N/A	IU instillation	(Ahmed *et al.*, 2021)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Ibrahim *et al.*, 2018)
	AS/IUA	Clinical	None	Autologous	N/A	IU injection	(Ibrahim *et al.*, 2021)
	EA/TE	*In vitro*	None	Autologous	None	N/A	(Kuroda *et al.*, 2023)
	EA/TE	*In vitro* + Clinical	None	Autologous	N/A	IU instillation	(Wang *et al.*, 2019)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Zadehmodarres *et al.*, 2017)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Tandulwadkar *et al.*, 2017)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Molina *et al.*, 2018)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Eftekhar *et al.*, 2021)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Chang *et al.*, 2019)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Kusumi *et al.*, 2020)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Dogra *et al.*, 2022)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Enatsu *et al.*, 2021)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Russell *et al.*, 2022)
	EA/TE	Clinical	None	Commercial	N/A	IU instillation	(Gangaraju *et al.*, 2023)
	EA/TE	Clinical	None	Autologous	N/A	IU injection	(Apolikhina *et al.*, 2021)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Kim *et al.*, 2019)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Dzhincharadze *et al.*, 2021)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Chang *et al.*, 2015)
	EA/TE	Clinical	None	Autologous	N/A	IU instillation	(Nazari *et al.*, 2019)
	Endometritis	Clinical	None	Autologous	N/A	IU instillation	(Sfakianoudis *et al.*, 2019)
	Endometritis	Clinical	None	Autologous	N/A	IU instillation	(Li *et al.*, 2023b)
	AS/IUA + EA/TE	*In vitro* + *in vivo* (mouse)	None	Commercial	Scratching	IU instillation	(de Miguel-Gómez *et al.*, 2021b)
	AS/IUA + EA/TE	*In vivo* (mouse)	ECM derived	Heterologous	Ethanol	IU injection	(Rodríguez-Eguren *et al.*, 2022)
PRP + mitochondria	EA/TE	*In vivo* (rat)	None	Heterologous	Ethanol	IU instillation	(Kshersagar *et al.*, 2023)

(continued)

Table 1. (continued)

Therapy	Model	Type of study	Carrier	Source	Damage	Route of administration	Reference
EV	AS/IUA	*In vitro*	None	Heterologous	Oxygen/glucose deprivation + reoxygenation	N/A	(Liang *et al.*, 2020)
	AS/IUA	*In vitro*	None	Commercial	TGF-β1	N/A	(Zhou *et al.*, 2023)
	AS/IUA	*In vitro*	None	Heterologous	N/A	N/A	(Miller *et al.*, 2022)
	AS/IUA	*In vitro* + *in vivo* (mouse)	HP	Commercial	Ethanol	IU instillation	(Lin *et al.*, 2023)
	AS/IUA	*In vitro* + *in vivo* (mouse)	None	Heterologous	Scratching + LPS	IU instillation	(Yuan *et al.*, 2023)
	AS/IUA	*In vitro* + *in vivo* (rat)	Collagen	Heterologous	Scratching	IU injection	(Xin *et al.*, 2020)
	AS/IUA	*In vivo* (mouse)	None	Commercial	Scratching	IU injection	(Xu *et al.*, 2017b)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Trichloroacetic acid	Oral + IU + IP injection	(Ebrahim *et al.*, 2018)
	AS/IUA	*In vivo* (rat)	None	Heterologous	Scratching	IU instillation	(Zhang *et al.*, 2021a)
	AS/IUA	*In vivo* (rat)	ECM derived	Heterologous	Scratching	IU injection	(Zhu *et al.*, 2023)
	EA/TE	*In vitro*	None	Commercial	Hypoxia	N/A	(Wang *et al.*, 2022)
	Endometritis	*In vitro* + *in vivo* (mouse)	None	Heterologous	LPS	IP injection	(Wang *et al.*, 2023a)
EV + miRNA	AS/IUA	*In vitro* + *in vivo* (rat)	None	Heterologous	Ethanol	IV injection	(Wang *et al.*, 2023b)
	AS/IUA	*In vivo* (mouse)	None	Commercial	Scratching	IV injection	(Park *et al.*, 2022)
miRNA	AS/IUA	*In vitro*	None	Commercial	None	N/A	(Ning *et al.*, 2018)
	AS/IUA	*In vitro*	None	Heterologous	TGF-β1	N/A	(Li *et al.*, 2016a)
	AS/IUA	*In vivo* (rat)	None	Commercial	Scratching + LPS	IU injection	(Li *et al.*, 2016b)
	Endometritis	*In vitro*	None	Heterologous	LPS	N/A	(Zhao *et al.*, 2020)
G-CSF	AS/IUA	*In vitro* + *in vivo* (rat)	Dextran + PEG	Commercial	Scratching	IU instillation	(Wen *et al.*, 2022)
	TE/EA	Clinical	None	N/R	N/A	IU instillation	(Gleicher *et al.*, 2013)
	TE/EA	Clinical	None	N/R	N/A	IU instillation	(Kunicki *et al.*, 2014)
	TE/EA	Clinical	None	N/R	N/A	IU instillation	(Xu *et al.*, 2015)
	TE/EA	Clinical	None	N/R	N/A	IU instillation	(Shah *et al.*, 2014)
	TE/EA	Clinical	None	N/R	N/A	IU instillation	(Tehraninejad *et al.*, 2015)
MSC-CM	AS/IUA	*In vitro*	None	Commercial	None	N/A	(Wei *et al.*, 2022)
	AS/IUA	*In vitro* + *in vivo* (rat)	None	Heterologous	Ethanol	IU instillation	(Lin *et al.*, 2018)
	AS/IUA	*In vivo* (rat)	Hialuronic acid	Commercial	Electrocoagulation	IU injection	(Liu *et al.*, 2019b)
Apoptotic bodies	AS/IUA	*In vivo* (mouse)	Hialuronic acid	Heterologous	Scratching	IU instillation	(Xin *et al.*, 2021)
Natural Hydrogel	AS/IUA	*In vitro*	ECM derived	Commercial	None	N/A	(Chen *et al.*, 2020)
	AS/IUA	*In vivo* (rat)	ECM derived	Heterologous	Scratching	N/A	(Daryabari *et al.*, 2022)
	AS/IUA	*In vivo* (rat)	ECM derived	Commercial	Scratching	IU instillation	(Yao *et al.*, 2020b)
Synthetic hydrogel	AS/IUA	*In vitro* + *in vivo* (rat)	PHEMA	Commercial	Scratching	IU instillation	(Xie *et al.*, 2022)
	AS/IUA	*In vivo* (mouse)	Sodium alginate	Others	Ethanol	IU instillation	(Fang *et al.*, 2023a)
	AS/IUA	*In vivo* (rat)	Heparin-polaxamer	Commercial	Scratching	IU injection	(Zhang *et al.*, 2017)
	AS/IUA	Clinical	Hialuronic acid	N/R	N/A	IU instillation	(Pabuçcu *et al.*, 2019)
	AS/IUA	Clinical	Hialuronic acid	Commercial	N/A	IU instillation	(Guo *et al.*, 2022)
	AS/IUA	Clinical	Gel	Commercial	N/A	Transdermal injection vs oral	(Yi *et al.*, 2023)
	AS/IUA	Clinical	Silicone sheet	Commercial	N/A	IU instillation	(Azumaguchi *et al.*, 2019)
	AS/IUA	Clinical	Hialuronic acid	Commercial	N/A	IU injection	(Zhou *et al.*, 2021)
	Endometritis	*In vitro* + *in vivo* (rat)	rhCol III	Commercial	LPS	IU instillation	(You *et al.*, 2023)

AdiMSC, adipose mesenchymal stem cells; AS, Asherman syndrome; BMMSC, bone marrow-derived mesenchymal stem cells; CM, conditioned medium; EA, endometrial atrophy; ECM, extracellular matrix; EndoMSC, endometrial mesenchymal stem cells; EV, extracellular vesicle; G-CSF, granulocyte-colony stimulating factor; AMSC, amniotic mesenchymal stem cells; HP, poloxamer hydrogel; IP, intraperitoneal; iPSCs, induced-pluripotent stem cells; IU, intrauterine; IUA, intrauterine adhesion; IV, intravenous; LPS, lipopolysaccharide; MenMSC, menstrual blood-derived mensenchymal stem cells; miRNA, microRNA; MSC, mesenchymal stem cell; N/A, not applicable; PEG, polyethylene glycol; PHEMA, poly(hydroxyethylmethacrylate); PPCN, poly (polyethylene glycol citrate-co-N-isopropylacrylamide); PRP, platelet-rich plasma; rhCOl III, recombinant human collagen type III; RNA, ribonucleic acid; SC, subcutaneous; TE, thin endometrium; TGF-β1, transforming growth factor β1; UCMSC, umbilical cord-derived mesenchymal stem cells.

Table 2. Comparison of endometrial regeneration and reproductive outcomes from clinical trials of cellular, acellular, and bioengineering-based treatments for endometrial disorders.

Patients	Therapy	Endometrial thickness	Angiogenesis	Cell proliferation	Regenerative biomarkers	Fibrosis	Reproductive outcomes	Menstrual changes	Other remarks	Reference
AS/IUA	BMMSCs	↑ Endometrial thickness	N/R	↑ Ki67 expression	↑ Nanog, SSEA1, W5C5, CCNF1, ER-α, IGF-1 ↓ KLF4, LGR5	N/R	N/R	N/R	↑ Number of glands	(Zhao *et al.*, 2017)
	BMMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	✓ Single pregnancy	N/R	N/R	(Nagori *et al.*, 2011)
	BMMSCs	↑ Endometrial thickness	↑ Vascularity	N/R	N/R	N/R	↑ Pregnancy rate	↓ Menstruation volume	N/R	(Santamaria *et al.*, 2016)
	BMMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	N/R	↑ Menstruation	N/R	(Singh *et al.*, 2014)
	BMMSCs	↑ Endometrial thickness	N/R	N/R	↑ Jun, Serpine1, IL-4 expression ↓ CCNF1, CXCL-8 expression	N/R	N/R	N/R	↑ Number of glands	(de Miguel-Gómez *et al.*, 2019)
	BMMSCs	N/R	N/R	N/R	N/R	N/R	✓ Pregnancy	N/R	N/R	(Zhao *et al.*, 2013)
	BMMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	✓ Pregnancy	N/R	No adverse events	(Arikan *et al.*, 2023)
	UCMSCs	↑ Endometrial thickness	↑ vWF expression	↑ Ki67 expression	↑ ER-α expression	N/R	↑ Pregnancy rate	↑ Blood flow	No adverse events	(Cao *et al.*, 2018)
	UCMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	N/R	N/R	No adverse events	(Huang *et al.*, 2022a)
	UCMSCs	↑ Endometrial thickness	N/R	↑ Proliferation	N/R	N/R	N/R	↑ Blood flow	N/R	(Kaczynski and Rzepka, 2022)
	MenMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	✓ Pregnancy	N/R	N/R	(Tan *et al.*, 2016)
	MenMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	✓ Pregnancy	N/R	N/R	(Ma *et al.*, 2020)
	AdiMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	No differences	N/R	No adverse events	(Lee *et al.*, 2020)
	PRP	N/R	N/R	N/R	N/R	No differences in AFS score	No differences	N/R	N/R	(Peng *et al.*, 2020)
	PRP	No differences	N/R	N/R	N/R	N/R	No differences	N/R	No adverse events	(Aghajanova *et al.*, 2021)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	↓ Adhesions ↓ AFS score	N/R	↑ Blood flow	N/R	(Shen *et al.*, 2022)
	PRP	N/R	N/R	N/R	N/R	N/R	N/R	N/R	↑ Endometrial receptivity ↓ NK cells, CD8 T cells and Th1 cells	(Chang *et al.*, 2023)
	PRP	↑ Endometrial thickness	↑ Vascularity	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Pandey *et al.*, 2023)
	PRP	N/R	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Qiu *et al.*, 2023)
	PRP	N/R	N/R	N/R	N/R	No differences in AFS score	N/R	N/R	N/R	(Javaheri *et al.*, 2020)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Zadehmodarres *et al.*, 2017)

(continued)

Table 2. (continued)

Patients	Therapy	Endometrial thickness	Angiogenesis	Cell proliferation	Regenerative biomarkers	Fibrosis	Reproductive outcomes	Menstrual changes	Other remarks	Reference
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Molina *et al.*, 2018)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Eftekhar et al., 2021)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Chang *et al.*, 2019)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Kusumi *et al.*, 2020)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	No differences	N/R	N/R	(Dogra *et al.*, 2022)
	PRP	No differences	N/R	N/R	N/R	N/R	No differences	N/R	No adverse events	(Enatsu *et al.*, 2021)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Russell *et al.*, 2022)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Gangaraju *et al.*, 2023)
	PRP	No differences	↑ Vascularity	N/R	N/R	N/R	N/R	N/R	N/R	(Apolikhina *et al.*, 2021)
	PRP	No differences	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Kim *et al.*, 2019)
	PRP	No differences	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Dzhincharadze *et al.*, 2021)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Chang *et al.*, 2015)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Chemical pregnancy rate	N/R	No adverse events	(Nazari *et al.*, 2019)
	PRP	N/R	N/R	N/R	N/R	↓ Adhesions	No differences	↑ Menstrual duration and volume	N/R	(Ahmed *et al.*, 2021)
	PRP	N/R	N/R	N/R	N/R	↓ Adhesions	No differences	↑ Menstrual duration and volume	N/R	(Ibrahim *et al.*, 2018)
	PRP	N/R	N/R	N/R	N/R	↓ Adhesions	N/R	↑ Menstrual duration and volume	N/R	(Ibrahim *et al.*, 2021)
	SYNTHETIC HYDROGEL	N/R	N/R	N/R	N/R	No differences in adhesion recurrence No differences in AFS score	N/R	N/R	N/R	(Guo *et al.*, 2022)
	SYNTHETIC HYDROGEL	No differences	N/R	N/R	N/R	No differences in AFS score	No differences	↑ Blood flow	No differences in E2 concentration	(Yi *et al.*, 2023)
	SYNTHETIC HYDROGEL	N/R	N/R	N/R	N/R	↓ Adhesions	No differences	N/R	No adverse events	(Azumaguchi *et al.*, 2019)
	SYNTHETIC HYDROGEL	N/R	N/R	N/R	N/R	No differences in AFS score	N/R	No differences in menstrual patterns	N/R	(Zhou *et al.*, 2021)

(continued)

Table 2. (continued)

Patients	Therapy	Endometrial thickness	Angiogenesis	Cell proliferation	Regenerative biomarkers	Fibrosis	Reproductive outcomes	Menstrual changes	Other remarks	Reference
	SYNTHETIC HYDROGEL	↑ Endometrial thickness	N/R	N/R	N/R	N/R	✓ Pregnancy	N/R	N/R	(Pabuçcu *et al.*, 2019)
AS/IUA + EA/TE	BMMSCs	↑ Endometrial thickness	N/R	N/R	N/R	↓ Adhesions	↑ Pregnancy rate	N/R	No adverse events	(Singh *et al.*, 2020)
	UCMSCs	↑ Endometrial thickness	↑ Vascularity	↑ Ki67 expression	↑ ER-α, PR expression	↓ Adhesions	↑ Pregnancy rate	N/R	↑ Number of glands No adverse events	(Zhang *et al.*, 2021b)
EA/TE	EndoMSCs	N/R	N/R	N/R	N/R	N/R	✓ Single pregnancy	N/R	↑ Endometrial receptivity	(Sapozhak *et al.*, 2020)
	EndoMSCs + PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	↑ Immunological variables	(Tersoglio *et al.*, 2020)
	EndoMSCs + PRP + Electric pulse	↑ Endometrial thickness	↑ Vascularity	↑ CD34 expression	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Efendieva *et al.*, 2023)
	AdiMSCs	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Sudoma *et al.*, 2019)
	PRP	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Wang *et al.*, 2019)
	PRP	↑ Endometrial thickness	↑ Vascularity	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Tandulwadkar *et al.*, 2017)
	BMMSCs + PRP	↑ Endometrial thickness	↑ Vascularity	N/R	N/R	N/R	✓ Single pregnancy	N/R	N/R	(Tandulwadkar *et al.*, 2021)
	G-CSF	↑ Endometrial thickness	N/R	N/R	N/R	N/R	No differences	N/R	✓ Better morphology	(Jiang *et al.*, 2021)
	G-CSF	↑ Endometrial thickness	N/R	N/R	N/R	N/R	✓ Pregnancy	N/R	N/R	(Gleicher *et al.*, 2013)
	G-CSF	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Kunicki *et al.*, 2014)
	G-CSF	↑ Endometrial thickness	N/R	N/R	N/R	N/R	No differences	N/R	N/R	(Xu *et al.*, 2015)
	G-CSF	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	No adverse events	(Shah *et al.*, 2014)
	G-CSF	↑ Endometrial thickness	N/R	N/R	N/R	N/R	↑ Pregnancy rate	N/R	N/R	(Tehraninejad *et al.*, 2015)
Endometritis	PRP	N/R	N/R	N/R	N/R	N/R	✓ Achieved pregnancy	N/R	✓ No signs of endometritis	(Sfakianoudis *et al.*, 2019)
	PRP	N/R	N/R	N/R	N/R	N/R	N/R	N/R	Not improved endometritis	(Li *et al.*, 2023b)

AdiMSC, adipose mesenchymal stem cells; AFS, American Fertility Society; AS, Asherman's syndrome; BMMSC, bone marrow-derived mesenchymal stem cells; CCNF1, cyclin D1; CXCL-8, Interleukin 8; E2, estradiol; EA, endometrial atrophy; EndoMSC, endometrial mesenchymal stem cells; ER-α, estrogen receptor α; G-CSF, granulocyte-colony stimulating factor; IGF, insulin-like growth factor; IL, interleukin; KLF4, Kruppel-like factor 3; IUA, intrauterine adhesion; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; MenMSC, menstrual blood-derived stem cells; MSC, mesenchymal stem cells; NK, natural killer; Th1, type 1 T helper; N/R, not reported; PR, progesterone receptor; PRP, platelet-rich plasma; SSEA1, stage specific embryonic antigen-1; TE, thin endometrium; UCMSC, umbilical cord-derived mesenchymal stem cells; W5C5, sushi domain containing 2.

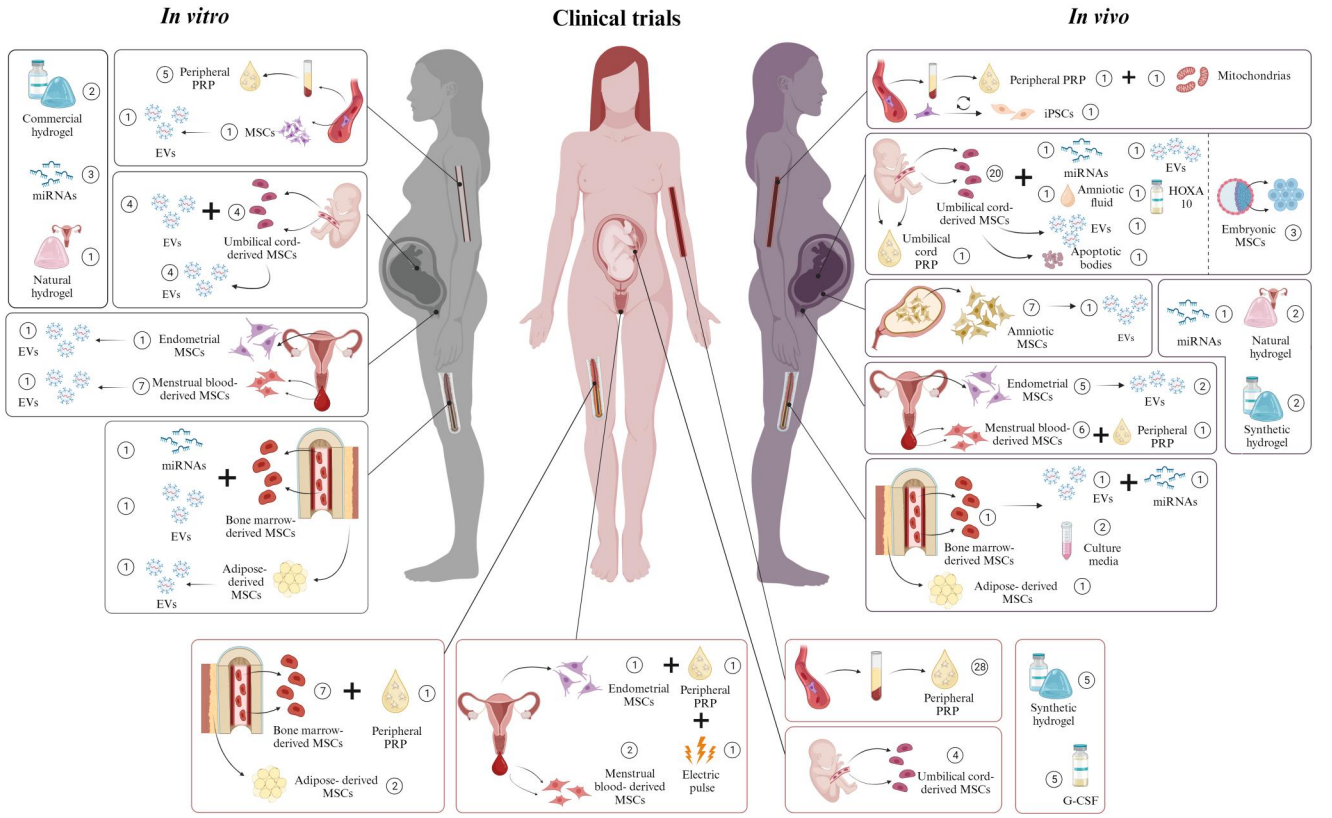

Figure 3. Overview of the source of the human-based therapies used for preclinical studies and clinical trials for endometrial disorders*. The numbers reflect the *in vitro* (left), *in vivo* (right), and clinical studies (center) included in Table 1. The arrows denote the therapy source, and the "+" symbol indicates cell/strategy combinations. *Asherman syndrome/intrauterine adhesions, endometrial atrophy/thin endometrium, and endometritis. EVs: extracellular vesicles, G-CSF, granulocyte-colony stimulating factor, iPSCs, induced pluripotent stem cells; miRNAs, microRNAs; MSCs, mesenchymal stem cells; PRP, platelet-rich plasma. Created with BioRender.com.

in vivo) and summarizes the clinical trials aiming to treat, reduce, and/or reverse endometrial disorders that were included in this review.

Cellular therapies

In 88 studies, human MSCs were used for endometrial regeneration. MSCs were obtained from the bone marrow (17.0%), endometrium (10.2%), umbilical cord (40.1%), menstrual blood (8.0%), or alternative sources (19.3%).

Bone marrow-derived MSCs

Bone marrow-derived MSCs (BMMSCs) are multipotent hematopoietic cells derived from spongy tissue of bone marrow (Wang *et al.*, 2016). To obtain these stem cells, marrow aspiration from the hip bone or peripheral blood must be carried out, followed by the isolation of the cell population of interest (Fitzsimmons *et al.*, 2018).

Fifteen studies have reported the use of BMMSCs in preclinical or clinical trials. Specifically, two studies employed *in vitro* models of AS/IUA (Tan *et al.*, 2020; Liu *et al.*, 2021), which also evaluated their regenerative potential *in vivo*. While one utilized commercial BMMSCs (Liu *et al.*, 2021), the other opted for heterologous cells, all of which remained in preclinical testing.

Both mouse (Du *et al.*, 2012; Cervelló *et al.*, 2015; de Miguel-Gómez *et al.*, 2019; Tan *et al.*, 2020; Liu *et al.*, 2021) and rat models of AS/IUA (Ho *et al.*, 2018; Mansouri-Kivaj *et al.*, 2023) were employed to test this therapy. Endometrial damage was induced by different techniques such as scraping (Du *et al.*, 2012; Cervelló *et al.*, 2015; Ho *et al.*, 2018; de Miguel-Gómez *et al.*, 2019; Mansouri-Kivaj *et al.*, 2023), local ethanol application (Tan *et al.*, 2020), or intraperitoneally injected lipopolysaccharide (LPS) (Liu *et al.*, 2021). The BMMSCs were administered via different routes. Local instillation was predominantly favored (Du *et al.*, 2012; de Miguel-Gómez *et al.*, 2019; Tan *et al.*, 2020; Mansouri-Kivaj *et al.*, 2023), over its combination with tail vein injection (Cervelló *et al.*, 2015), local (Ho *et al.*, 2018) or intraperitoneal injection (Liu *et al.*, 2021). Notably, De Miguel-Gómez and colleagues conducted a comparative study evaluating the effects of BMMSCs in *in vivo* models and patients (de Miguel-Gómez *et al.*, 2019).

All clinical trials reported autologous BMMSC therapies for AS/IUA (Nagori *et al.*, 2011; Zhao *et al.*, 2013, 2017; Santamaria *et al.*, 2016; de Miguel-Gómez *et al.*, 2020; Tandulwadkar *et al.*, 2021; Arikan *et al.*, 2023), as well as EA/TE (Singh *et al.*, 2014, 2020). Six clinical trials employed local injection (Nagori *et al.*, 2011; Singh *et al.*, 2014, 2020; Santamaria *et al.*, 2016; Tandulwadkar *et al.*, 2021; Arikan *et al.*, 2023), while others opted for intrauterine instillation (Zhao *et al.*, 2013, 2017; de Miguel-Gómez *et al.*, 2020) or delivery via a collagen assembly carrier (Zhao *et al.*, 2017).

Endometrial MSCs

Endometrial MSCs (EndoMSCs) have been characterized as precursors for epithelial or stromal cells in the endometrium (Cervelló *et al.*, 2011; Gargett *et al.*, 2016; de Miguel-Gómez *et al.*, 2021a). Endometrial biopsy stands as the prevalent method for EndoMSC procurement (Hong, 2022).

EndoMSC-based treatments were reported in nine of the included studies, only one of which examined their effect in an *in vitro* model of AS/IUA (He *et al.*, 2022).

The majority of the reports were conducted in animal models, using heterologous EndoMSCs to treat AS/IUA (Wang *et al.*, 2018; Park *et al.*, 2020b; Song *et al.*, 2021; He *et al.*, 2022; Li *et al.*, 2022a) and EA/TE (Li *et al.*, 2019a). There was a preference for rat models (Wang *et al.*, 2018; Li *et al.*, 2019a, 2022a; He *et al.*, 2022) over mice (Park *et al.*, 2020b; Song *et al.*, 2021). Uterine damage was induced either by scraping (Wang *et al.*, 2018; Song *et al.*, 2021; He *et al.*, 2022; Li *et al.*, 2022a) or wall rejection (Li *et al.*, 2019a). The treatment was administered by local instillation (Park *et al.*, 2020b; He *et al.*, 2022; Li *et al.*, 2022a), local injection (Li *et al.*, 2019a; Song *et al.*, 2021), or subcutaneous administration (Wang *et al.*, 2018). The use of chitosan (He *et al.*, 2022), collagen (Li *et al.*, 2019a), or microneedles (Li *et al.*, 2022a) as carriers of EndoMSC treatment was also described.

Only autologous EndoMSC-based therapies were reported for patients with EA/TE (Sapozhak *et al.*, 2020; Tersoglio *et al.*, 2020; Efendieva *et al.*, 2023). Notably, these studies combined EndoMSCs with autologous PRP (Tersoglio *et al.*, 2020) or electrical impulses (Efendieva *et al.*, 2023). Among clinical trials, local instillation has emerged as the preferred administration route (Sapozhak *et al.*, 2020; Tersoglio *et al.*, 2020) over local injection (Efendieva *et al.*, 2023).

Umbilical cord-derived MSCs

UCMSCs are multipotent stem cells that can differentiate into various cell types (Lee *et al.*, 2004). The primary source of UCMSCs is generally the blood within the umbilical cord, a cord-like structure that connects a fetus to the placenta. However, recent evidence shows they can also be isolated from Wharton's jelly (Huang *et al.*, 2023), the connective tissue of the umbilical cord.

UCMSCs were the most common type of MSCs applied to treat endometrial disorders (36 studies). In *in vitro* models, several groups applied heterologous UCMSCs alone (Yang *et al.*, 2011; Sun *et al.*, 2018; Shi *et al.*, 2020) or in combination with EVs (Lv *et al.*, 2020; Wang *et al.*, 2020a; Shi *et al.*, 2021; Li *et al.*, 2023a) to revert AS/IUA. Conversely, one study employed both *in vitro* and *in vivo* models to study EA/TE treatments (Zhang *et al.*, 2021b). Mifepristone was the predominant choice for inducing AS/IUA *in vitro* (Yang *et al.*, 2011; Shi *et al.*, 2020), although a recent report also documented the use of transforming growth factor beta (TGF-β) (Li *et al.*, 2023a).

In animal models, UCMSCs were administered for the treatment of AS/IUA (Yang *et al.*, 2011; Zhang *et al.*, 2018; Sun *et al.*, 2021; Wang *et al.*, 2021b) and EA/TE (Xu *et al.*, 2017a; Zhang *et al.*, 2022a, 2022b; Zhou *et al.*, 2022). These treatments were evaluated in various animal species, including rats (Tan *et al.*, 2016; Liu *et al.*, 2020a; Li *et al.*, 2021; Hu *et al.*, 2022b), mice (Park *et al.*, 2020b; Sun *et al.*, 2021; Li *et al.*, 2022b; Xu *et al.*, 2022; Zheng *et al.*, 2022b; Wu *et al.*, 2023), rabbits (Hua *et al.*, 2022), and primates (Wang *et al.*, 2020c). The majority of the studies (31 studies) opted for heterologous UCMSCs, while a few employed commercial UCMSCs (five studies). Uterine damage in preclinical models was induced by endometrial scraping (Xin *et al.*, 2019; Liu *et al.*, 2020a; Wang *et al.*, 2020c; Hu *et al.*, 2022b; Zhang *et al.*, 2023a) or ethanol application (Zhang *et al.*, 2018; Li *et al.*, 2021; Xu *et al.*, 2022; Zhou *et al.*, 2022; Zhuang *et al.*, 2022). Alternative methods employing trichloroacetic acid (Sabry *et al.*, 2017), electrocoagulation (Li *et al.*, 2022b), and talcum powder (Aygün and Tümentemur, 2022) were also reported. The UCMSCs were mainly administered via local instillation (Xin *et al.*, 2019; Liu *et al.*, 2020a; Wang *et al.*, 2020c; Zhou *et al.*, 2022; Hu *et al.*, 2022b) followed by local endometrial (Xu *et al.*, 2017a; Li *et al.*, 2022b; Zhang *et al.*, 2022a; Zheng *et al.*, 2022a) or intravenous injection (Zhang *et al.*, 2018; Wang *et al.*, 2021b). Some studies compared the efficacy of administration routes (Sabry *et al.*, 2017; Zhuang *et al.*, 2022), while another did not specify the methodology (Aygün and Tümentemur, 2022). Interestingly, isolated studies combined UCMSCs with EVs (Zhang *et al.*, 2022b) or miRNAs (Sun *et al.*, 2021) for regenerative therapy. Additionally, some research groups evaluated the use of collagen (Xin *et al.*, 2019; Liu *et al.*, 2020) or other biomaterial matrices as carriers of UCMSCs for endometrial treatment (Wang *et al.*, 2021a; Zhou *et al.*, 2022).

In four clinical trials, UCMSCs were instilled into the uterine cavity of women with AS/IUA or EA/TE (Cao *et al.*, 2018; Zhang *et al.*, 2021b; Huang *et al.*, 2022a; Kaczynski and Rzepka, 2022). Among these, two groups evaluated the use of collagen as a vehicle for delivering UCMSCs to the endometrium (Cao *et al.*, 2018; Zhang *et al.*, 2021b).

Menstrual blood-derived MSCs

MenMSCs are multipotent stem cells that can be isolated from menstrual blood and have the ability to differentiate into endometrial epithelial or stromal cells (Bozorgmehr *et al.*, 2020). The notable advantage of these stem cells lies in the non-invasive collection approach, from used tampons or menstrual cups (Zhang *et al.*, 2023b).

Among the 11 studies evaluating MenMSCs to treat AS/IUA, two were *in vitro* studies (Zhu *et al.*, 2018; Wang *et al.*, 2020b). One of these studies used heterologous MenMSCs (Zhu *et al.*, 2018) while the other employed a commercial source.

The eight *in vivo* studies all employed heterologous MenMSCs (Domnina *et al.*, 2016, 2018; Hu *et al.*, 2019, 2022a; Chang *et al.*, 2020; Hao *et al.*, 2022) in rat (Domnina *et al.*, 2016, 2018; Hu *et al.*, 2019, 2022a; Chang *et al.*, 2020) or murine models (Wang *et al.*, 2020b). Endometrial damage was mainly induced by scraping (Hu *et al.*, 2019; Zhang *et al.*, 2019; Chang *et al.*, 2020; Hao *et al.*, 2022). Less frequently reported methods included electrocoagulation (Domnina *et al.*, 2016), LPS injection (Hu *et al.*, 2022a), ethanol infusion (Domnina *et al.*, 2018), and hydrothermal ablation (Wang *et al.*, 2020b). As for the treatment administration routes in these models, local instillation (Domnina *et al.*, 2016; Hu *et al.*, 2019, 2022a; Wang *et al.*, 2020b; Hao *et al.*, 2022), local injection (Zhang *et al.*, 2019; Chang *et al.*, 2020), and combined intravenous and intrauterine infusions (Domnina *et al.*, 2018) were reported. Interestingly, two groups incorporated MenMSCs into carriers for preclinical models of AS/IUA (Hao *et al.*, 2022; Hu *et al.*, 2022a).

Notably, only two human trials are reported (Tan *et al.*, 2016; Ma *et al.*, 2020), with autologous MenMSCs transplanted by local instillation (Tan *et al.*, 2016) or local injection (Ma *et al.*, 2020) to avoid the risk of incompatibility.

Other MSCs

Alternative reservoirs of MSCs, such as the placenta or adipose tissue, offer potential sources for acquiring placental amniotic mesenchymal stem cells (AMSCs), embryonic stem cells, adipose-derived stem cells (AdiMSCs) or induced pluripotent stem cells (iPSCs) (Fitzsimmons *et al.*, 2018; Miatmoko *et al.*, 2023). Numerous applications of these MSCs in regenerative medicine are currently being researched (17 studies).

Two groups tested heterologous human AMSCs *in vitro* (Li *et al.*, 2019b; Lin *et al.*, 2022) and nine rodent models were reported (Gan *et al.*, 2017; Li *et al.*, 2019b; Bai *et al.*, 2020; Yu *et al.*, 2021). While most of these studies did not include a carrier to

control AMSCs distribution, cell retention was enhanced with Poly(polyethylene glycol citrate-co-N-isopropylacrylamide) (PPCN) in one of the AS/IUA mouse models (Huang et al., 2022b) or HA hydrogel in the EA/TE model reported (Lin et al., 2022). Notably, combined administration routes (Ouyang et al., 2020; Fan et al., 2021), intravenous injection (Mao et al., 2023a), local injection (Bai et al., 2020; Yu et al., 2021) or instillation alone (Gan et al., 2017; Li et al., 2019b; Lin et al., 2022; Huang et al., 2022b) were selected. Therapies based on AMSCs have not yet progressed to clinical trials.

Embryonic stem cells were tested in three studies modelling AS/IUA in rodents. In rats, the endometrial damage was induced by wall rejection (Song et al., 2015) or scratching (Jiang et al., 2021), and treated with embryonic organoids by local instillation. In the mouse model, the damage induced by endometrial scratching was successfully reverted using embryonic stem cells (Jun et al., 2019). Therapies based on embryonic stem cells have not yet progressed to clinical trials.

AdiMSCs were delivered in a human amniotic membrane-derived scaffold to treat ethanol-induced uterine damage in a rat model of AS/IUA (Han et al., 2020). They have also been tested to clinically treat EA/TE (Sudoma et al., 2019) or AS/IUA (Lee et al., 2020). In both clinical trials, autologous AdiMSCs were administered locally without any carrier (Sudoma et al., 2019; Lee et al., 2020).

Finally, iPSCs were loaded into a bioprinted scaffold to revert AS/IUA in a rat model (Ji et al., 2020) and there was one report of commercial MSCs (with an unspecified source) used to treat LPS-induced endometritis *in vitro* (Mani et al., 2020). Therapies based on iPSCs have not yet progressed to clinical trials.

Acellular therapies

We classified 80 reports of acellular therapies for endometrial disorders into four main categories: PRP (50.0%), EVs (including exosomes and microvesicles; 25.7%), miRNAs (10.0%), and alternatives (13.8%).

Platelet-rich plasma

PRP is a fraction of blood, usually collected from peripheral blood through conventional venipuncture or sourced from allogeneic sources such as healthier donors (Liao et al., 2020) or the umbilical cord blood after delivery (Rebulla et al., 2016). The PRP is easily obtained via gradient density centrifugation and provides supraphysiologic platelet concentrations for clinical use. PRP is currently the leading acellular therapy to treat endometrial pathologies, with 40 reports included in this review.

Of the six studies testing PRP *in vitro* (Aghajanova et al., 2018; Wang et al., 2019; de Miguel-Gómez et al., 2021b; Kim et al., 2022; Kuroda et al., 2023; Mao et al., 2023b), half used PRP from a heterologous source; however, autologous PRP was more often employed than commercial plasma (de Miguel-Gómez et al. 2021b).

For animal trials, PRP was employed in models of AS/IUA (Aghajanova et al., 2018; Zhang et al., 2019; Kim et al., 2020, 2022; Mao et al., 2023b), EA/TE (Wang et al., 2019; Kshersagar et al., 2023; Kuroda et al., 2023), or both AS/IUA and EA/TE at the same time (de Miguel-Gómez et al., 2021b; Rodríguez-Eguren et al., 2023). Heterologous human adult PRP was explored more often than human umbilical cord-derived PRP (Rodríguez-Eguren et al., 2023) and commercial plasma (de Miguel-Gomez et al. 2021b). PRP efficacy was evaluated in rats (Zhang et al., 2019; Kshersagar et al., 2023; Mao et al., 2023b) and mice (Kim et al., 2020, 2022; de Miguel-Gómez et al., 2021b; Rodríguez-Eguren et al., 2023). Endometrial damage was induced by scratching (Zhang et al., 2019; Kim et al., 2020, 2022; de Miguel-Gómez et al., 2021b; Mao et al., 2023b) and ethanol infusion (Kshersagar et al., 2023; Rodríguez-Eguren et al., 2023). Groups conducting preclinical studies opted for local instillation (Kim et al., 2020, 2022; de Miguel-Gómez et al., 2021b; Kshersagar et al., 2023; Mao et al., 2023b) or local endometrial injection (Zhang et al., 2019; Rodríguez-Eguren et al., 2023). Notably, local delivery in a decellularized porcine endometrium-derived hydrogel enhanced the regenerative effects of umbilical cord-derived PRP (Rodríguez-Eguren et al., 2023). Further, intrauterine infusion of thrombin-activated PRP and mitochondria was evaluated to treat EA/TE in a rat model (Kshersagar et al., 2023).

In humans, PRP was applied to treat AS/IUA (Ibrahim et al., 2018, 2021; Javaheri et al., 2020; Peng et al., 2020; Aghajanova et al., 2021; Ahmed et al., 2021; Tandulwadkar et al., 2021; Shen et al., 2022; Chang et al., 2023; Pandey et al., 2023; Qiu et al., 2023), EA/TE (Chang et al., 2015, 2019; Tandulwadkar et al., 2017; Zadehmodarres et al., 2017; Molina et al., 2018; Kim et al., 2019; Nazari et al., 2019; Kusumi et al., 2020; Tersoglio et al., 2020; Apolikhina et al., 2021; Dzhincharadze et al., 2021; Eftekhar et al., 2021; Enatsu et al., 2021; Dogra et al., 2022; Russell et al., 2022; Efendieva et al., 2023; Gangaraju et al., 2023), and endometritis (Sfakianoudis et al., 2019; Li et al., 2023b). Notably, except for one study (Gangaraju et al., 2023), all of the aforementioned groups adopted autologous PRP instead of commercial PRP. The primary modes of treatment delivery were intrauterine instillation (Zadehmodarres et al., 2017; Molina et al., 2018; Kusumi et al., 2020; Peng et al., 2020; Tersoglio et al., 2020; Aghajanova et al., 2021; Enatsu et al., 2021) followed by local injection (Ibrahim et al., 2018, 2021; Javaheri et al., 2020; Apolikhina et al., 2021; Tandulwadkar et al., 2021; Shen et al., 2022; Efendieva et al., 2023).

Extracellular vesicles

EVs are heterogeneous cell-derived membranous structures, comprising exosomes secreted by the endosomes or microvesicles budding from the membrane (van Niel et al., 2018). They are replete with proteins, lipids, nucleic acids, and metabolites that confer therapeutic properties. EVs can be isolated based on their size, surface charge, or immunoaffinity; ultracentrifugation is currently considered the gold standard technique (Tan et al., 2024).

Twenty-two reports described preclinical EV-based treatments to reverse the effects of endometrial disorders. Fifteen *in vitro* assays were reported for models of AS/IUA (Wang et al., 2020a; Miller et al., 2022), EA/TE (Wang et al., 2022), and endometritis (Wang et al., 2023a). The use of heterologous EVs was more common (Tan et al., 2020; Miller et al., 2022; Li et al., 2023a) than the use of commercial EVs (Liu et al., 2021; Wang et al., 2022; Lin et al., 2023; Zhou et al., 2023). Agents such as mifepristone (Wang et al., 2020a; Shi et al., 2021) and TGF-β (Zhou et al., 2023) or processes such as oxygen/glucose deprivation (Liang et al., 2020) and hypoxia (Wang et al., 2022) were selected to induce endometrial damage *in vitro*.

Six studies combined *in vitro* and *in vivo* approaches (Xin et al., 2020; Lin et al., 2021, 2023; Wang et al., 2023a, 2023b; Yuan et al., 2023). The remaining studies were mainly *in vivo* models of AS/IUA (Zhang et al., 2021a; Park et al., 2022; Mansouri-Kivaj et al., 2023); EA/TE and endometritis models were under-reported. EV therapies were tested in rats (Ebrahim et al., 2018; Xin et al., 2020; Zhang et al., 2021a, 2022b; Mansouri-Kivaj et al., 2023; Zhu et al., 2023; Wang et al., 2023b), and mice (Xu et al., 2017b; Tan et al., 2020; Liu et al., 2021; Park et al., 2022; Lin et al., 2023; Wang et al., 2023a; Yuan et al., 2023). Endometrial damage was usually

induced by scratching (Xu *et al.*, 2017b; Xin *et al.*, 2020; Zhang *et al.*, 2021a; Park *et al.*, 2022; Mansouri-Kivaj *et al.*, 2023; Yuan *et al.*, 2023; Zhu *et al.*, 2023) or ethanol (Tan *et al.*, 2020; Zhang *et al.*, 2022b; Lin *et al.*, 2023). A few studies reported using LPS alone (Liu *et al.*, 2021), or in combination with mechanical damage (Yuan *et al.*, 2023) or trichloroacetic acid (Ebrahim *et al.*, 2018). EV therapies were mainly delivered via local instillation (Tan *et al.*, 2020; Zhang *et al.*, 2021a, 2022b; Lin *et al.*, 2023; Yuan *et al.*, 2023) or endometrial injection (Xu *et al.*, 2017b; Xin *et al.*, 2020; Liu *et al.*, 2021; Zhu *et al.*, 2023). Less common EV administration routes included intravenous techniques (Park *et al.*, 2022; Wang *et al.*, 2023b), intraperitoneal injection alone (Liu *et al.*, 2021; Wang *et al.*, 2023a), or in combination with instillation (Ebrahim *et al.*, 2018). Notably, independent groups recently applied hydrogel carriers derived from decellularized amniotic membrane (Zhu *et al.*, 2023), poloxamer (Lin *et al.*, 2023), or collagen (Xin *et al.*, 2020).

Finally, there were no reports of EV-based treatments for endometrial pathologies in humans.

miRNAs

miRNAs are evolutionarily conserved, small non-coding single-stranded RNAs, generally 21–22 nucleotides length, that repress gene expression with translational inhibition or mRNA degradation (Li *et al.*, 2017). Typically, miRNAs achieve these regulatory effects by binding to specific recognition sites on target mRNAs via complementary base pairing (Frith *et al.*, 2014). miRNAs participate in various cellular processes, including but not limited to aging and apoptosis, in addition to diverse signaling pathways (Li *et al.*, 2017).

miRNA-based therapies were reported in eight articles, predominantly about *in vitro* testing for AS/IUA (Li *et al.*, 2016a, 2016b; Ning *et al.*, 2018; Tan *et al.*, 2020; Sun *et al.*, 2021; Park *et al.*, 2022; Wang *et al.*, 2023b) and endometritis (Zhao *et al.*, 2020). These studies reported the use of either heterologous miRNAs (Li *et al.*, 2016a; Tan *et al.*, 2020; Zhao *et al.*, 2020; Sun *et al.*, 2021; Wang *et al.*, 2023b) or commercially designed miRNAs (Ning *et al.*, 2018); there were no reports of autologous miRNA treatments. To date, endometrial cell damage has been induced with TGF-β (Li *et al.*, 2016a) or LPS (Zhao *et al.*, 2020).

Regarding *in vivo* trials, rat (Li *et al.*, 2016b; Wang *et al.*, 2023b) and mouse models (Tan *et al.*, 2020; Sun *et al.*, 2021; Park *et al.*, 2022) were reported. Heterologous miRNA sources were more prevalent than commercial ones. Endometrial damage was induced by scratching (Sun *et al.*, 2021; Park *et al.*, 2022), ethanol (Tan *et al.*, 2020), or a combination of mechanical damage and LPS (Li *et al.*, 2016b). miRNAs were administered intravenously (Park *et al.*, 2022; Wang *et al.*, 2023b), by local instillation (Tan *et al.*, 2020; Sun *et al.*, 2021) or endometrial injection (Li *et al.*, 2016a).

Notably, there were no reports using miRNA to treat endometrial pathologies in humans.

Alternative acellular therapies

Eleven reports did not fit into the aforementioned classifications of acellular therapies.

During *in vitro* cell culture, stem cells release a myriad of growth factors and paracrine effectors into the medium. Thus, centrifugation of spent medium concentrates an interesting cocktail of biomolecules for use in regenerative medicine (Goonoo and Bhaw-Luximon, 2019).

Four studies focused on treating AS/IUA with conditioned medium. Two employed *in vitro* designs (Lin *et al.*, 2018; Wei *et al.*, 2022) and three used *in vivo* models (Ho *et al.*, 2018; Lin *et al.*, 2018; Liu *et al.*, 2019b). Endometrial damage induced by either electrocoagulation (Liu *et al.*, 2019b), scratching (Ho *et al.*, 2018), or ethanol (Lin *et al.*, 2018) was treated with injection or instillation of conditioned medium. There was one report using an HA hydrogel as a carrier (Liu *et al.*, 2019b).

Moreover, glycoproteins, such as granulocyte colony stimulating factor (G-CSF), interact with the extracellular matrix (ECM) of the stem cell niche, reducing the attachment of stem cells to the stroma and promoting their mobilization into the bloodstream (Rettig *et al.*, 2012). Treatment with commercial G-CSF was reported in six studies. Five patients with EA/TE were treated with local instillation of G-CSF (Gleicher *et al.*, 2013; Kunicki *et al.*, 2014; Shah *et al.*, 2014; Tehraninejad *et al.*, 2015; Xu *et al.*, 2015). The regenerative effect of G-CSF instillation using a bioprinted scaffold and microspheres to repair damage by endometrial scraping was recently evaluated in a rat model of AS/IUA (Wen *et al.*, 2022). Another acellular therapy tested in a mouse model of AS/IUA involved apoptotic bodies carried by HA hydrogels (Xin *et al.*, 2021).

Bioengineering tools

We classified 40 reports of bioengineering-based therapies into dECM hydrogels (20%) and other biomaterials (80%).

Extracellular matrix-derived hydrogels

The use of bioengineering strategies offers the ability to sustain cells and/or active ingredients of treatments at the target site, extending a favourable environment that improves the regeneration rate.

Hydrogels derived from dECM, designed to control treatment delivery and retain the characteristics of the native milieu, are prominent bioengineering tools. Eight preclinical studies used dECM carriers to deliver endometrial treatments. Among these, one study delivered commercial estradiol-loaded microspheres in an amniotic membrane-derived hydrogel to treat AS/IUA *in vitro* (Chen *et al.*, 2020).

The remaining studies aimed to reverse AS/IUA in rat models (Han *et al.*, 2020; Yao *et al.*, 2020a; Wang *et al.*, 2021a; Daryabari *et al.*, 2022; Hao *et al.*, 2022; Zhu *et al.*, 2023). One study applied a porcine endometrial dECM-derived hydrogel to sustain local delivery of PRP in a murine model of AS/IUA or EA/TE (Rodríguez-Eguren *et al.*, 2023). Notably, heterologous biomaterials (Han *et al.*, 2020; Daryabari *et al.*, 2022; Hao *et al.*, 2022; Rodríguez-Eguren *et al.*, 2023; Zhu *et al.*, 2023) were used more frequently than commercial materials (Chen *et al.*, 2020; Yao *et al.*, 2020b; Wang *et al.*, 2021a). *In vivo* endometrial damage was induced by scratching (Yao *et al.*, 2020a; Daryabari *et al.*, 2022; Hao *et al.*, 2022; Zhu *et al.*, 2023) and ethanol (Han *et al.*, 2020; Wang *et al.*, 2021a; Rodríguez-Eguren *et al.*, 2023), then treated by local instillation (Han *et al.*, 2020; Yao *et al.*, 2020b; Wang *et al.*, 2021a); Hao *et al.*, 2022 more frequently than local injection (Rodríguez-Eguren *et al.*, 2023; Zhu *et al.*, 2023). Finally, we identified two studies that did not report how the hydrogels were administered (Chen *et al.*, 2020; Daryabari *et al.*, 2022).

Other biomaterials

Most of the biomaterials used to carry cells or treatments to the endometrium were not dECM-derived. Instead, these natural or synthetic biomaterials often served as scaffolds or carriers promoting cell growth and differentiation. In this regard, the biomaterial choice depended on the specific application and the therapeutic agents being used (Francés-Herrero *et al.*, 2022a).

Thirty-two studies used alternative matrices. We identified nine reports administering collagen matrices embedded with

UCMSCs by instillation (Cao et al., 2018; Li et al., 2019a; Xin et al., 2019; Liu et al., 2020a; Zhang et al., 2021b), BMMSCs (Zhao et al., 2017), MenMSCs (Hu et al., 2022a), EndoMSCs (Li et al., 2019a), or exosomes (Xin et al., 2020).

Collagen scaffolds prevailed in *in vivo* studies modelling AS/IUA (Xu et al., 2017a; Xin et al., 2019, 2020; Liu et al., 2020a; Hu et al., 2022a) and EA/TE (Xu et al., 2017a; Li et al., 2019a). As for animal models, both local injection (Xu et al., 2017a; Li et al., 2019a; Xin et al., 2020) and local instillation were employed (Xin et al., 2019; Liu et al., 2020b; Hu et al., 2022a). Local instillation of commercial recombinant humanized type III collagen successfully treated LPS-induced endometritis *in vitro* and *in vivo* (You et al., 2023).

There were three clinical trials treating AS/IUA or EA/TE after local instillation of the treatment (Zhao et al., 2017; Cao et al., 2018; Zhang et al., 2021b).

HA-based hydrogels accounted for eight studies in rodent models of AS/IUA (Liu et al., 2019b; Xin et al., 2021; Zhang et al., 2023a) and *in vitro* and *in vivo* EA/TE models (Lin et al., 2022). We identified one study using HA-based hydrogels to treat AS/IUA in *Rhesus macaques* (Wang et al., 2020c). In most of the preclinical models, HA-based hydrogel treatments were instilled (Wang et al., 2020c; Xin et al., 2021; Lin et al., 2022) or locally injected (Liu et al., 2019b; Zhang et al., 2023a). Similarly, among three clinical trials of AS/IUA, HA hydrogels were instilled in the cavity (Pabuçcu et al., 2019; Guo et al., 2022) or injected (Zhou et al., 2021).

Other clinical trials instilled silicone sheets or contraceptive uterine devices wrapped in oxidized regenerated cellulose to treat AS/IUA (Azumaguchi et al., 2019). Another study compared reproductive outcomes following transdermal and oral applications of an estrogen gel (Yi et al., 2023).

Pluronic-F127 hydrogel-embedded UCMSCs were tested *in vivo* with HA for AS/IUA (Hu et al., 2022b) or without HA for EA/TE (Zhou et al., 2022). Other *in vivo* treatments for AS/IUA included a commercial aloe-poloxamer hydrogel (Yao et al., 2020a), UCMSCs in a silk fibroin small-intestinal submucosa-derived hydrogel (Zheng et al., 2022b), AMSCs in a PPCN-gelatine mixture (Huang et al., 2022b), sodium alginate (oxidized or not) with recombinant type III collagen (Fang et al., 2023b), and a silicone patch (Li et al., 2022a). Estradiol was administered in a poly(hydroxyethylmethacrylate) (PHEMA) hydrogel (Xie et al., 2022) and human iPSCs were embedded in bioprinted scaffolds (Ji et al., 2020).

Non dECM-derived hydrogels were also used to deliver stem cells in *in vivo* models of EA/TE (Li et al., 2019a) and a clinical trial on AS/IUA (Zhao et al., 2017); EVs (Lin et al., 2023) or G-CSF (Wen et al., 2022) in preclinical models. Notably, commercialized synthetic hydrogels reversed AS/IUA in both rats (Zhang et al., 2017) and humans (Guo et al., 2022).

State-of-the-art applications of regenerative therapies in the endometrium

In the dynamic field of regenerative medicine, clinical translation entails progressing from rigorously validated *in vitro* platforms and *in vivo* animal models to human trials. Comparing the study variables and outcomes of each research stage may help clinicians feel more equipped at navigating challenges arising with endometrial conditions. Meanwhile, learning how each therapeutic approach evolved helps prioritize resources and accelerate clinical integration. Figure 4 summarizes the frequency of relevant outcome measures *in vitro*, *in vivo* and in clinical trials.

In vitro *discoveries*

In vitro systems are indispensable to validate and refine potential treatments. These models bridge initial experimental discoveries with more complex *in vivo* assays in animals and humans. *In vitro* systems provide a controlled environment where researchers can study biological processes (e.g. fibrosis and inflammation), cellular pathways, and target interactions to gain a better understanding of endometrial function, repair, and regeneration. A comparison of *in vitro* findings is presented in Supplementary Table S2.

Cell proliferation metrics provide insights on cell division and growth, demonstrating how treatments help regenerate tissues. Co-cultures of endometrial cells and UCMSCs (Sun et al., 2018) or MenMSCs (Zhu et al., 2018) enhanced proliferation (evidenced by Ki67 expression) and cell viability [evidenced by Cell Counting Kit 8 (CCK8) expression] (Zhang et al., 2022a). On the other hand, platelet-derived growth factor (PDGF) improved cell migration and invasiveness of MenMSCs (Wang et al., 2020b). Conditioned medium from UCMSCs (Wei et al., 2022), or their EVs (Wang et al., 2020b), induced overexpression of the cell proliferation marker miR-29a in endometrial epithelial cells (Tan et al., 2020).

Wound healing assays helped determine if treatments accelerated endometrial repair and regeneration. Therapies combining UCMSCs and EVs enhanced the division of mifepristone-damaged endometrial cells (Wang et al., 2020a), while commercial exosomes achieved similar outcomes (Miller et al., 2022). Furthermore, peripheral (Kim et al., 2022; Kuroda et al., 2023) and umbilical cord-derived PRP (de Miguel-Gómez et al., 2021b) expedited endometrial wound healing.

Fibrosis, defined by the excessive deposition of ECM proteins, such as collagen, is the leading characteristic of AS/IUA. Fibrosis may be reversed during its early stages or proceed to an irreversible displacement of functional endometrial tissue. Notably, MenMSCs-conditioned medium reduced expression of the fibrosis-related protein Gli2 (Lin et al., 2018) and led to miR-326-mediated suppression of α-smooth muscle actin (α-SMA), collagen 1 (COL1)A1, and fibronectin, which inactivated the TGF-β1/SMAD3 pathway in EndoMSCs from patients with AS/IUA (Ning et al., 2018).

The first step of tissue regeneration is mitigating inflammatory processes that might impede tissue repair. MSCs downregulated proinflammatory markers [IL-6, IL-8, Toll-like receptor 4 (TLR-4), p-JNK, and p-ERK1/2] and increased expression of IκB-α, IL-10, and TGF-β1 (Mani et al., 2020). Similarly, MenMSCs upregulated vascular endothelial growth factor (VEGF), β-catenin, and p-AKT (Zhu et al., 2018). UCMSCs inhibited apoptosis and promoted VEGF expression (Yang et al., 2011). Alternatively, UCMSC-derived EVs repressed IL-2, tumor necrosis factor α (TNF-α), and interferon γ (IFNγ) (Wang et al., 2020a) while upregulating miR-145-5p (Li et al., 2023a). Overexpression of miR-29b or miR-643 activated the NF-kB pathway (Zhao et al., 2020) and enhanced maternally expressed gene 3 (MEG3) expression (Li et al., 2016a) which, in turn, halted the fibrotic progression that drives AS/IUA. On the other hand, PRP upregulated epidermal growth factor receptor (EGF-R) and inhibited TGF-α in epithelial endometrial cells. PRP was also found to downregulate ferroptosis, autophagy, and pyroptosis pathways in Ishikawa cells (Mao et al., 2023b).

In vivo *implications*

Animal models of AS/IUA and EA/TE help decipher the underlying pathophysiology and reproductive implications of endometrial pathologies while providing a complex living platform to evaluate treatment safety and efficacy. Restoration of

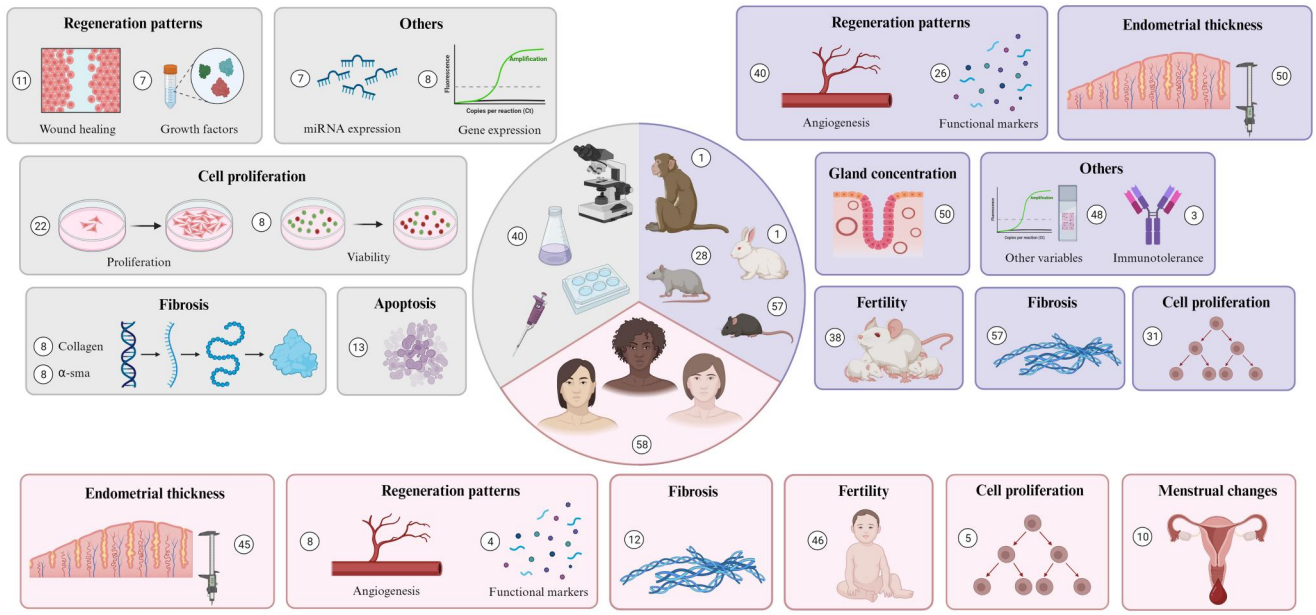

Figure 4. Overview of the outcome measures to evaluate endometrial repair and regeneration in the scientific literature. The numbers beside the human (pink), *in vitro* (grey) and *in vivo* (purple) parameters reflect the number of studies included in Table 2, Supplementary Tables S2 and S3, respectively. The main parameters evaluated in the *in vitro* studies include regeneration patterns (wound healing and growth factors expression), cell proliferation (proliferation and viability), fibrosis (collagen and α-smooth muscle actin), apoptosis, and others (micro RNA expression or gene expression). *In vivo* studies mainly assess regeneration patterns (angiogenesis and other functional markers), cell proliferation, gland concentration, endometrial thickness, fibrosis, fertility, and other parameters (immunotolerance, gene expression, proteins). Human trials parameters include endometrial thickness, regeneration patterns, fibrosis, fertility, cell proliferation and menstrual changes. miRNA, microRNA. Created with BioRender.com.

endometrial function can be evaluated *in vivo*, using parameters such as endometrial thickness, the number of uterine glands, the extent of fibrosis, cell proliferation, angiogenesis, expression of regenerative markers (such as PDGF, EGF, and HOXA10), and pregnancy outcomes. A comparison of studies (mainly performed in rodents) reporting these *in vivo* outcomes is presented in Supplementary Table S3.

UCMSCs, EndoMSCs, and BMMSCs embedded in 3D scaffolds (e.g. collagen) promoted endometrial thickening and uterine gland proliferation in rodents (Li *et al.*, 2019a; Zhou *et al.*, 2022; Zhang *et al.*, 2023a) over an extended period of time (Xin *et al.*, 2019; Wang *et al.*, 2021a; Hu *et al.*, 2022a). Other treatments that similarly restored endometrial function included MenMSCs and estrogen combined in a collagen matrix (Liu *et al.*, 2020a); AMSCs, with or without a PPCN carrier (Bai *et al.*, 2020; Huang *et al.*, 2022b); PRP (Rodríguez-Eguren *et al.*, 2023); microRNAs (Tan *et al.*, 2020; Park *et al.*, 2022) and EVs (Wang *et al.*, 2020a). EVs embedded in hydrogels proved to be a viable strategy for endometrial regeneration (Lin *et al.*, 2023). Combining cellular and acellular therapies, such as MenMSCs and PRP (Zhang *et al.*, 2019), UCMSCs and HOXA10 (Wu *et al.*, 2023), or UCMSCs and EVs, also favored endometrial gland proliferation (Ebrahim *et al.*, 2018). Notably, supplementing sodium alginate hydrogel with recombinant type III collagen boosted its pharmacodynamic properties, as evidenced by improved endometrial thickness 7 days after treatment (Fang *et al.*, 2023b).

MSC-based therapies (Zheng *et al.*, 2022b), MenMSCs, EVs (Zhang *et al.*, 2021a), and estrogen-loaded hydrogels (Hao *et al.*, 2022) all diminished local fibrosis. MenMSCs also reduced EGF and PDGF-BB (Wang *et al.*, 2018) whereas BMMSC and EV treatments repressed α-SMA (Mansouri-Kivaj *et al.*, 2023). Acellular therapies based on miRNAs (Park *et al.*, 2022) and EVs (Wen *et al.*, 2022) decreased fibrotic markers such as collagen (Kim *et al.*, 2022; Zhang *et al.*, 2022b; Lin *et al.*, 2023; Mao *et al.*, 2023a). Bioengineering-based strategies supplying estrogens via synthetic hydrogels made from aloe-poloxamer (Yao *et al.*, 2020a), heparin-poloxamer (Zhang *et al.*, 2017) or chemical sources (Xie *et al.*, 2022; Hu *et al.*, 2022b) also reduced fibrosis *in vivo*. Finally, EndoMSCs reversed the pro-fibrotic effect of chitosan hydrogels (He *et al.*, 2022).

Endometrial tissue proliferation is necessary to regenerate the layered structure and function of the uterus. Local administration of UCMSCs (Xin *et al.*, 2019), MenMSCs (Hao *et al.*, 2022), BMMSCs (Cervelló *et al.*, 2015) and AMSCs (Lin *et al.*, 2022) enhanced cell proliferation rates and tissue regeneration markers [e.g. pan-cytokeratin, cytokeratin (CK) 18, proliferating cell nuclear antigen, prominin-1 (CD133), and Ki67]. Similarly, acellular therapies based on PRP (de Miguel-Gómez *et al.*, 2021b), EVs with or without BMMSCs (Liu *et al.*, 2021), or MenMSCs (Wang *et al.*, 2020a) also improved endometrial proliferation. Finally, several studies found larger proportions of Ki67-positive cells when hydrogels were loaded with estrogens (Liu *et al.*, 2020a; Xie *et al.*, 2022) compared to when they were applied alone (Liu *et al.*, 2020a; Fang *et al.*, 2023b).

Angiogenesis supports delivery of nutrients and growth factors to proliferating cells, playing a key role in tissue repair and regeneration. While most MSC-based therapies improve endometrial vascularization and promote VEGF expression (Li *et al.*, 2019b; Mansouri-Kivaj *et al.*, 2023; Mao *et al.*, 2023a), MenMSCs, alone or combined with EVs, did not increase the number of blood vessels (Zhang *et al.*, 2021a). Alternatively, PRP therapies enhanced angiogenesis (Zhang *et al.*, 2019), particularly when derived from human umbilical cord blood (Rodríguez-Eguren *et al.*, 2023).

Several promising bioengineering strategies supported endometrial repair by promoting angiogenesis, modulating inflammation, and restoring cell/tissue homeostasis. Local instillation of human-induced MSCs loaded in a bioprinted scaffold partially

restored angiogenesis and endometrial structure, as evidenced by the presence of a cluster of differentiation (CD)31 endothelial cells and cytokeratin in the epithelial cells of an AS/IUA rat model (Ji et al., 2020). Similarly, the levels of estrogen receptors, cytokeratin, vimentin, CK19, CD34, and human nuclear antigen were restored to basal levels following local treatment with UCMSCs in a collagen scaffold (Liu et al., 2020a), MenMSCs (Hu et al., 2019), and H9-ESC organoids (Jiang et al., 2021). UCMSCs embedded in a synthetic hydrogel (F127-CHO) modulated CD31 and insulin-like growth factor (IGF)-1 levels (Hu et al., 2022b). Treatment with AMSCs in PPCN led to an overexpression of cytokeratins (ie, CK7 and CK19), while AMSCs alone modulated inflammatory cytokines [reduced TNF-α and IL-1β and upregulated b-fibroblast growth factor and IL-6] (Gan et al., 2017). BMMSC therapy upregulated anti-inflammatory cytokines (ie, thrombospondin 1) while downregulating IGF-1 (Cervelló et al., 2015). Finally, estrogens delivered in a heparin-poloxamer hydrogel restored tissue homeostasis through GRP78, Caspase 12, and CHOP (Zhang et al., 2017).

Patients seeking treatment for AS/IUA and EA/TE are often trying to achieve pregnancy. *In vivo* models help ascertain if treatments can efficiently restore endometrial competence for embryo implantation and term pregnancy. Local treatment with MenMSCs (Zhang et al., 2021a); UCMSCs or their EVs (Zhang et al., 2022b); AMSCs (Ouyang et al., 2020); and BMMSCs (Jun et al., 2019) increased the litter size in rodent models of endometrial disorders. Fertility was also restored following treatment with MenMSCs and PRP (Zhang et al., 2019), UCMSCs in a collagen scaffold (Xin et al., 2019), or MSC-derived EVs embedded in hydrogel (Lin et al., 2023). Notably, acellular treatments alone were sufficient to restore fertility (Xin et al., 2021). Specifically, umbilical cord-derived PRP improved fertility outcomes (Rodríguez-Eguren et al., 2023), embryo weight, and litter size (Kim et al., 2022).

Clinical translation

Clinical trials aim to test the safety, efficacy, and dynamics of promising regenerative therapies. Outcome measures of studies evaluating treatments for human endometrial repair and regeneration include endometrial thickness, the number of uterine glands; degree of adhesions, fibrosis, or inflammation; proliferation rates, angiogenesis, expression of regenerative biomarkers (such as PDGF, EGF, and HOXA10); and pregnancy outcomes. A comparison of clinical trials reporting these outcomes is presented in Table 2.

MenMSCs (Ma et al., 2020) and BMMSCs (Singh et al., 2014; Santamaria et al., 2016; Arikan et al., 2023) supported endometrial growth for 6–9 months (Singh et al., 2020). Endometrial thickening was promoted by EndoMSCs alone (Tersoglio et al., 2020) or combined with PRP (Efendieva et al., 2023); UCMSCs alone (Kaczynski and Rzepka, 2022; Huang et al., 2022a) or embedded in a collagen scaffold (Cao et al., 2018; Zhang et al., 2021b). Notably, treatments including collagen scaffolds were associated with a favorable prognosis because they raised endometrial gland concentration (Zhao et al., 2017). The outcome of autologous PRP treatment remains controversial–some authors observed increased endometrial thickness (Tandulwadkar et al., 2017; Chang et al., 2019; Dogra et al., 2022) while others did not (Aghajanova et al., 2021; Enatsu et al., 2021). G-CSF therapies (Gleicher et al., 2013; Xu et al., 2015) and synthetic hydrogels (Tehraninejad et al., 2015; Pabuçcu et al., 2019) also promoted endometrial thickening and improved pregnancy rates (Kunicki et al., 2014).

In patients with fibrotic pathologies, PRP reduced the scarring and AFS score (Zhang et al., 2021b) or was ineffective (Javaheri et al., 2020; Peng et al., 2020). In patients with endometritis, PRP significantly repressed endometrial CD138, reflecting a diminished immune response (Li et al., 2023b).

Restoration of endometrial function was commonly verified by histological and molecular analyses. Notably, BMMSC therapy led to overexpression of Ki67, Nanog, stage-specific embryonic antigen (SSEA), estrogen receptor (ER) α, and IGF-1 coupled with the suppression of Kruppel-like factor (KFL) 4 and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) in endometrial biopsies of AS patients (Zhao et al., 2017). Alternatively, UCMSC therapy enhanced proliferation and angiogenesis by upregulating ERα, Ki67, and the von Willebrand factor (vWF) in patients with AS/EA (Cao et al., 2018; Zhang et al., 2021b) and increased blood flow (Cao et al., 2018). Despite CD133-positive BMMSC therapy reestablishing menstrual patterns, the effect progressively declined after 3 months (Santamaria et al., 2016). However, combined therapy with PRP and BMMSCs improved endometrial vascularity (Tandulwadkar et al., 2021).

Pregnancy rates and deliveries were generally improved by therapies based on BMMSCs (Santamaria et al., 2016), MenMSCs (Ma et al., 2020), AdiMSCs (Sudoma et al., 2019), or UCMSCs (Cao et al., 2018; Zhang et al., 2021b). Only one clinical trial reported no differences in pregnancy outcomes following therapy with AdiMSCs (Lee et al., 2020). While several studies reported that autologous peripheral PRP improved rates of implantation, clinical pregnancy (Chang et al., 2015, 2019; Nazari et al., 2019; Eftekhar et al., 2021), ongoing pregnancy (Tandulwadkar et al., 2017), and live births (Russell et al., 2022), other studies found that PRP did not consistently improve pregnancy rates (Aghajanova et al., 2021; Ahmed et al., 2021; Enatsu et al., 2021; Dogra et al., 2022; Li et al., 2023b). Notably, fertility was restored by combining cellular and acellular therapies, such as BMMSCs and PRP (Tandulwadkar et al., 2021), or EndoMSCs and PRP (Tersoglio et al., 2020; Efendieva et al., 2023).

Discussion

Conventional hysteroscopy and pharmacology: precursor therapies

In current clinical practice, visualizing suboptimal endometrial thickness, pattern, or morphology by ultrasonography often leads to cancelling or postponing embryo transfers. If the endometrium does not improve after estrogen exposure, diagnostic hysteroscopy is typically performed to evaluate the extent of endometrial tissue damage from AS/IUA, previous gynaecological surgeries, and pelvic radiation. Depending on the clinical findings, these procedures may be followed with antibiotics to treat infections, insertion of physical barriers (e.g. Foley balloons) to reduce the risk of further adhesion formation (Guo et al., 2023; Hanstede et al., 2023), or alternative pharmacotherapies. The problem remains that even experienced clinicians may have difficulty restoring uterine anatomy or endometrial function (Hanstede et al., 2015; Bosteels et al., 2017).

Despite there being no international consensus on what is considered an optimal endometrium and a recent study suggesting that TE does not affect embryo transfer outcomes (Ata et al., 2023), most groups agree that patients with a TE (<6–8 mm at secretory phase) following adequate estrogen exposure have poor reproductive outcomes. Specifically, patients with TE are reported to present lower implantation, clinical pregnancy, and live birth rates coupled with higher risks of miscarriage (Liu et al., 2019a; Jacobs et al., 2022; Mahutte et al., 2022; Cakiroglu et al., 2023) and obstetric complications from defective implantation or maternal placental malperfusion (Mouhayar et al., 2019;

Herman *et al.*, 2022; Liao *et al.*, 2022; Fang *et al.*, 2023a). In these cases, additional pharmacotherapy with hormones (estrogen, hCG, GnRH, growth hormone) and/or blood flow enhancers (e.g. aspirin, sildenafil, pentoxifylline, L-arginine, nitroglycerine, and tocopherol) is contemplated to improve reproductive performance (Garcia-Velasco *et al.*, 2016; Liu *et al.*, 2019a; Cakiroglu *et al.*, 2023). Estrogen therapy can be adjusted to higher doses, longer durations, or alternative administration routes. Notably, combining certain blood flow enhancers for at least 6 months proved to be beneficial (Lédée-Bataille *et al.*, 2002; Letur-Konirsch and Delanian, 2003; Acharya *et al.*, 2009).

Many existing pharmacotherapy studies exhibited methodological flaws related to the study design and population, or had heterogenous protocols for drug administration or patient management, leading to discrepancies of the therapeutic benefits, particularly in terms of endometrial thickness and reproductive outcomes (Ranisavljevic *et al.*, 2019; Liu *et al.*, 2019a). These results led to the proposal of experimental approaches which aimed to increase the endometrial blood flow, using electrical stimulation (Bodombossou-Djobo *et al.*, 2011; Shabiti *et al.*, 2023) or botulinum toxin (Lee *et al.*, 2023), which did not improve endometrial thickness. Thus, alternative biotechnological regenerative therapies for endometrial pathologies warrant further investigation in prospective studies.

The evolution of endometrial regeneration

Cellular therapies

The first stem cell transplantation was reported in 1965, when Thomas and Epstein transplanted BMMSCs to treat acute leukemia (Thomas *et al.*, 1975). Mounting evidence from successful autologous or allogenic MSC treatments shows regenerative functions of MSCs in several tissues (De Luca *et al.*, 2019). Since 2011, there have been 88 studies describing stem cell therapies (based on BMMSCs, EndoMSCs, UCMSCs, MenMSCs, and others MSCs) to treat endometrial pathologies. This elevated number of publications reflects the pressing clinical need to optimize efficacy of these therapies using well-designed randomized clinical trials (RCTs).

Among the MSC therapies tested in humans, the most efficient were those derived from the bone marrow and umbilical cord. While both improved endometrial thickness and regenerative parameters (proliferation and/or angiogenesis), recent studies have focused on UCMSCs. UCMSCs are collected non-invasively from tissues typically discarded after delivery (Rodríguez-Eguren *et al.*, 2022) and have potent anti-inflammatory and immunosuppressive properties (Bartolucci *et al.*, 2017; Huang *et al.*, 2022a). Endometrial treatments with UCMSCs embedded in biomaterials were immunotolerated and sustained the *in vivo* responses for longer than UCMSCs alone (Xin *et al.*, 2019; Park *et al.*, 2020a; Wang *et al.*, 2020c, 2021a; Zheng *et al.*, 2022a). While there have not been any reports of treatments with BMMSCs embedded in hydrogels, preclinical studies have shown that intrauterine administration of MenMSCs increased endometrial thickness, angiogenic factors and fertility rates, similar to UCMSCs or BMMSCs (Hu *et al.*, 2019; Hao *et al.*, 2022). MenMSC therapy recently progressed to clinical testing (Ma *et al.*, 2020) and is promising due to the non-invasive collection of menstrual blood, straightforward processing and high yield of MenMSCs, opportunity for large-scale donor recruitment, and broad autologous or heterologous applications (de Pedro *et al.*, 2023).

Acellular therapies

The paracrine signaling of adult stem cells involves secreted cytokines and growth factors that modulate cell proliferation, inflammation, and tissue repair (Gnecchi *et al.*, 2008). Leveraging these paracrine factors in the acellular therapies described herein shifted the paradigm for tissue regeneration (Baraniak and McDevitt, 2010). Excluding specific growth factors, such as G-CSF (Gleicher *et al.*, 2013), PRP is the most widely established acellular therapy for endometrial disorders. PRP is an easily-obtained blood derivative that, once activated, releases multiple proteins, growth factors, and biomolecules with regenerative properties (Cecerska-Heryć *et al.*, 2022). Several clinical trials have shown PRP thickens the endometrium (Zadehmodarres *et al.*, 2017), reduces scarring and adhesions (Shen *et al.*, 2022), modulates local inflammation (Sfakianoudis *et al.*, 2019), and increases pregnancy rates (Molina *et al.*, 2018). However, a recent study reported there was no improvement in live birth rates following PRP treatment (Aghajanova *et al.*, 2021). This disparity may have been influenced by the route of administration (Dogra *et al.*, 2022), substantial differences in processing techniques, and variance in patient age and/or comorbidities (Rodríguez-Eguren *et al.*, 2022). These issues may, in part, be addressed by using allogeneic PRP derived from younger sources, such as the umbilical cord blood (Rodríguez-Eguren *et al.*, 2023).

Research on the applications of the MSCs secretome, particularly the EVs, are gaining momentum in rodents, showing promise for fertility restoration (Mansouri-Kivaj *et al.*, 2023) and recovering endometrial function (Wang *et al.*, 2020c). While EVs produced better outcomes than the stem cells they originated from (Zhang *et al.*, 2022b), it is important to remember they require longer processing with special equipment for ultracentrifugation, making them less feasible to acquire.

Bioengineering strategies

The interest in uterine bioengineering approaches was amplified following the initial therapies reported in 2017, with 60% of studies published within the last 2 years. Many strategies based on synthetic and natural hydrogels (e.g. collagen, ECM-derived) have emerged, using hydrogels as delivery systems for the sustained local release of cells, small molecules, or drugs. Notably, the majority of *in vivo* studies employed natural and synthetic hydrogels as carriers for estrogen (Hao *et al.*, 2022; Xie *et al.*, 2022), stem cells (Hu *et al.*, 2019; Xin *et al.*, 2019; Wang *et al.*, 2021a), or apoptotic bodies (Xin *et al.*, 2021). On the contrary, clinical trials used synthetic hydrogels alone (Azumaguchi *et al.*, 2019; Zhou *et al.*, 2021; Pang *et al.*, 2022), often as carriers of biological products (Cao *et al.*, 2018). Hydrogel delivery systems have numerous applications in gynecological therapies and merit further investigation.

We highlight endometrial dECM-derived hydrogels for their resemblance to the native microenvironment and various preclinical applications. Our group has demonstrated that tissue-specific dECM-derived hydrogels support xenogenic follicle (Francés-Herrero *et al.*, 2023) and embryo cultures (Francés-Herrero *et al.*, 2021b), enhance patient-derived endometrial organoid proliferation (Francés-Herrero *et al.*, 2021a) and differentiation (Gómez-Álvarez *et al.*, 2023), as well as sustain local delivery of growth factors (López-Martínez *et al.*, 2021) or human umbilical cord-derived PRP in treatments for endometrial pathologies (Rodríguez-Eguren *et al.*, 2023). Independent preclinical studies have also revealed the potential of dECM scaffolds in endometrial regeneration (Yoshimasa *et al.*, 2023). Finally, the regenerative efficacy of dECM scaffolds loaded with stem cells

(Hellström et al., 2016), growth factors (López-Martínez et al., 2021), or PRP (Rodríguez-Eguren et al., 2023) is boosted when the strategies are employed synergistically.

One of the major limitations of deriving hydrogels from human endometrial ECM is obtaining sufficient uterine tissue for mass production of dECM hydrogels. However, given that ECM matrices are highly conserved across mammalian species (Bernard et al., 1983; Francés-Herrero et al., 2022b), animal tissue-specific ECM has the potential to become a valuable resource for biomedical research and clinical applications. For example, a recent study described a novel xenogeneic dECM-hydrogel derived from porcine heart tissue to treat human infarctions (Traverse et al., 2019).

New perspectives: what does the future hold?

This review discussed the benefits of relatively new therapies for endometrial regeneration. Treatments based on MSCs, acellular components, and diverse biomaterials are being tested for patients with AS/IUA, EA/TE, and endometritis. While MSCs may have applications in reproductive medicine, their procurement requires invasive procedures (especially in the case of BMMSCs) and they are associated with a higher risk of tumorigenesis and immunoreactivity (Ramaswamy Reddy et al., 2018). In contrast, acellular therapies may face greater regulatory hurdles (Thomas Pashuck and Stevens, 2012) and show lower retention, but have higher yields and long-term stability (Xie et al., 2020). The ability of tissue-specific dECM-derived hydrogels and other biomaterials to interact with the target tissue and participate in the healing process was recently evaluated (Francés-Herrero et al., 2022b), but there is limited standardization across hydrogel batches.

While the benefits of using autologous sources are evident (e.g. reduced risk of rejection or immune reactivity), significant drawbacks do exist. Some disadvantages include the restricted availability contingent on the patient, the potential invasiveness of tissue or cell harvesting, and subsequent post-processing requirements. These issues suggest the consideration of alternative origins. Commercial sources are consistent and held to high-quality standards. As their high costs and lack of customization remain considerable inconveniences, heterologous sources are positioned as potential solutions, the reasoning being that the costs are lower and there is flexibility to personalize therapies. Nevertheless, the limitations of heterologous sources include fewer quality controls, less standardization, availability and accessibility.

The paradigm of biomedical research has shifted towards developing personalized therapies. Combining stem cell-based therapies that promote cell renewal and differentiation, acellular therapies that modulate inflammation and promote tissue repair, and biomaterials that concentrate these actions at the target site might be the key for developing future therapies to restore endometrial function, and ultimately, improving reproductive success of patients with uterine-factor infertility. Based on the existing evidence, cost, accessibility and availability of the therapies we presented herein, we propose the development of triple-hit regenerative strategies, potentially combining high-yield MSCs (e.g. BMMSCs or UCMSCs) with acellular treatments (PRP), possibly integrated in ECM hydrogels. These approaches have individually demonstrated their efficacy and have the potential to drastically shift clinical management of endometrial strategies if their synergistic impact is confirmed. Finally, multicenter RCTs are required to evaluate the safety and efficacy of the biotechnological treatments presented throughout this review, before they can be fully implemented into clinical practice (Bhide et al., 2018).

Cutting-edge technologies, such as bioprinting or the creation of artificial organs, may revolutionize the field, enabling the manufacturing of personalized tissues and minimizing the chances of organ rejection. Additionally, the integration of artificial intelligence is expected to merge various clinical parameters and biomarkers. The development of predictive machine learning models may be able to identify subtle changes in endometrial patterns associated with patient-specific responses to therapies, and thus, contribute to more targeted strategies. Overall, the continuous growth and innovation in regenerative medicine will continue to unravel new treatment options in the imminent future, facilitating the clinical management of endometrial pathologies.

Limitations

This systematic review aimed to synthesize the mounting evidence of regenerative treatments for endometrial pathologies tested in the preclinical and clinical settings. Noteworthy limitations of this review include not identifying other potentially relevant studies due to the selection of keywords, the subjective nature of the filtering process, language barriers, publication biases, and the limitations of references. In total, we included 148 articles through our search queries and manually incorporated 16 additional records that were either not indexed in the databases or did not match our original queries. The heterogeneity of the methodologies and outcome measures of the included studies led to challenges in pooling data and prevented the feasibility of meta-analysis to determine which treatments were most effective.

Conclusion

Endometrial pathologies, particularly AS/IUA, EA/TE, and endometritis may lead to infertility. There is an ongoing international effort to develop effective treatments based on stem cell approaches, acellular components, and biomaterials (natural or synthetic) as traditional pharmacotherapy produced variable outcomes for endometrial repair/regeneration and fertility restoration. Emerging therapies combine cellular, acellular, and bioengineering approaches to expedite tissue regeneration by simultaneously restoring homeostasis, modulating inflammation, enhancing cell proliferation, and facilitating tissue remodeling. Many combined therapies remain experimental but show potential for clinical translation.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Authors' roles

Conceptualization: I.C., A.R.-E., C.B.-F., M.G.-Á., E.F.-H., J.B., E.S., and A.P.; systematic literature search, selection, and data curation: A.R.-E., C.B.-F.; data review: I.C., A.R.-E., and C.B.-F.; manuscript and figure preparation: I.C., A.R.-E., C.B.-F., M.G.-Á., and E.F.-H.; manuscript review: I.C., M.G.-Á., E.F.-H., J.B., E.S., and A.P. All authors have agreed to the published version of the manuscript.

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Conflict of interest

E.S. is a grant recipient or holds a contract with the Foundation for Embryonic Competence.

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Abbreviations list

α-SMA	α-Smooth muscle actin
AdiMSC	Adipose-derived mesenchymal stem cell
AFS	American Fertility Society
AMSC	Placental amniotic mesenchymal stem cell
AS	Asherman syndrome
BMMSC	Bone marrow-derived mesenchymal stem cell
CCK8	Cell Counting Kit 8
CD	Cluster of differentiation
CD133	Prominin-1
COL1	Collagen 1
dECM	Decellularized extracellular matrices
EA	Endometrial atrophy
ECM	Extracellular matrix
EGF-R	Epidermal growth factor receptor
EndoMSC	Endometrial mesenchymal stem cell
ER	Estrogen receptor
EV	Extracellular vesicle
G-CSF	Granulocyte colony stimulating factor
GnRH	Gonadotrophin releasing hormone
HA	Hyaluronic acid
IFNγ	Interferon γ
IGF	Insulin-like growth factor
IL	Interleukin
iPSC	Induced pluripotent stem cells
IUA	Intrauterine adhesions
KFL	Kruppel-like factor
LGR5	Leucine-rich repeat-containing G-protein coupled receptor 5
LPS	Lipopolysaccharide
MEG3	Maternally expressed gene 3
MenMSC	Menstrual blood-derived mesenchymal stem cell
mRNA	Messenger RNA
MSC	Mesenchymal stem cell
OSF	Open Science Framework
PDGF	Platelet-derived growth factor
PHEMA	Poly(hydroxyethylmethacrylate)
PICO	Population, Intervention, Comparison, and Outcome
PPCN	Poly(polyethylene glycol citrate-co-*N*-isopropylacrylamide)
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRP	Platelet-rich plasma
SSEA	Stage-specific embryonic antigen
SWiM	Synthesis Without Meta-analysis
TE	Thin endometrium
TGF-β	Transforming growth factor beta
TLR-4	Toll-like receptor 4
TNF-α	Tumor necrosis factor α
UCMSC	Umbilical cord-derived mesenchymal stem cell
VEGF	Vascular endothelial growth factor
vWF	Von Willebrand factor

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Review