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Review

Novel therapeutic strategies for Asherman's syndrome: Endometrial regeneration using menstrual blood-derived stem cells

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ABSTRACT

Endometrium is vital to the establishment of pregnancy through its cyclical regeneration, which, when disrupted, can lead to endometrial thinning and Asherman's syndrome (AS). AS is characterized by infertility, pelvic pain, menstrual irregularities, and placental complications. Currently, treatments such as hysteroscopic adhesiolysis and hormone replacement therapy have demonstrated variable efficacy with limited clinical evidence. Recent developments in cell therapy have introduced menstrual blood-derived mesenchymal stem cells (MenSCs) as a promising alternative therapeutic strategy. Menstrual blood offers a noninvasive, periodically available source of mesenchymal stem cells, MenSCs for endometrial regeneration. This review comprehensively examines the endometrial regenerative process, pathophysiology of AS, and therapeutic prospects of MenSCs, underscoring the need for continued research to optimize treatment strategies.

Contents

Abbreviations: ADCs, Adipose-derived mesenchymal stem cells; AFS, American Fertility Society; AMP, Adenosine monophosphate; AS, Asherman's syndrome; BMSCs, Bone marrow-derived mesenchymal stem cells; CCL, Chemokine ligand; CD, Clusters of Differentiation; CFU-F, Colony forming unit-fibroblast; CXCR4, C-X-C chemokine receptor type 4; eMSCs, endometrial mesenchymal stem cells; ESCs, Endometrial stromal cells; GCSF, Granulocyte colony-stimulating factor; HSG, Hysterosalpingography; HUVECs, Human umbilical vein endothelial cells; IFN, Interferon; IGFBP1, Insulin-like growth factor binding protein 1; IgG, Immunoglobulin G; IL, Interleukin; ISCT, The International Society for Cellular Therapy; IUA, Intrauterine Adhesion; MenSCs, Menstrual blood-derived mesenchymal stem cells; MSC, mesenchymal stem cells; NCAD, N-cadherin; NK cells, natural killer cells; PBMCs, peripheral blood mononuclear cells; scRNA-seq, single-cell RNA sequencing; SSEA-1, stage-specific embryonic antigen-1; SUSD2, sushi domain containing 2; TGF-β1, transforming growth factor-beta 1; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; UC-MSCs, umbilical cord-derived mesenchymal stem cells.

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1. Introduction

Endometrium is vital in the establishment of pregnancy [1]. This highly regenerative tissue undergoes cyclical processes of proliferation, differentiation, shedding, and regeneration throughout the menstrual cycle. This regenerative cycle occurs more than 400 times during a woman's reproductive lifespan [2–4]. Disruptions in this regenerative process result in endometrial thinning, which is associated with implantation defects and recurrent miscarriage [4]. Endometrial thinning is influenced by factors such as physical disruption caused by intrauterine manipulation [5], blood flow obstruction from uterine artery embolization, or endometrial chronic infection which can lead to endometrial thinning with intrauterine adhesions known as Asherman's syndrome (AS) [6].

Intrauterine adhesions can lead to infertility, pelvic pain, menstrual abnormalities, and placental abnormalities after conception, such as placental abnormalities, namely, placenta accreta, increta, and percreta [7]. In general clinical practice, hysteroscopic adhesiolysis is recommended for restoring uterine cavity and improving fertility in patients with symptomatic intrauterine adhesions; however, this surgical approach has low level of evidence in the clinical guideline [8], and no randomized controlled trial has precluded definitive conclusions regarding its efficacy. In some cases, the surgical intervention causes complications such as uterine perforation and recurrence of intrauterine adhesions, particularly in severe cases of AS [9]. Other treatments include hormone replacement therapy using estrogen [10] and intrauterine administration of platelet-rich plasma (PRP) or granulocyte colony-stimulating factor (G-CSF) for endometrial regeneration and tissue repair [11–13]. However, the consistency of the effects of these treatments is poor [14,15]. The lack of progress in the development of these treatments is thought to be partly due to the poorly understood physiological pathogenesis of the disease. Therefore, the underlying pathophysiology of AS should be elucidated, and more effective and appropriate treatments based on the pathophysiology are needed.

Recently, to address the limitations of existing therapies for AS, cell therapy has emerged as a novel therapeutic strategy. Mesenchymal stem cells (MSCs) are renowned for their self-renewal capabilities and multilineage differentiation potential and have been featured in the treatment for AS [15]. MSCs can be harvested from various tissues, including the bone marrow, adipose tissue, umbilical cord, placenta, and dental pulp [16]. Recently, menstrual blood has offered a periodic and less invasive source of MSCs [16,17]. MenSCs are gaining attention as an alternative to traditional MSCs because they can be harvested noninvasively and exhibit higher proliferative and differentiation potential [18]. Some early-stage clinical trials have used autologous MenSCs for the treatment of AS [19,20].

Therefore, this review aimed to describe the physiological regenerative functions of the endometrium and the detail pathogenesis of AS including consideration of the endometrial stem cell niche and referring to the latest findings. This review further focused on the therapeutic potential of MenSCs for this disease and the recent trend and prospects of therapeutic strategy.

2. Physiology of endometrium regeneration

2.1. Menstruation cycle

Endometrium is histologically divided into the basal and functional layers (Fig. 1). Functional layer, which is shed during menstruation, includes stromal and endothelial cells in vessels, such as spiral arteries, and the glandular epithelium, which extends from the basal layer, as well as the luminal epithelium that covers the surface layer [21]. The luminal epithelium is the first cell population that comes into contact with the fertilized egg during implantation. During the menstrual cycle, the endometrial structure, function, and biochemical environment are modulated by steroid hormones secreted by the ovaries.

Decidualization is the transformation of endometrial stromal cells (ESCs) into the secretory decidual cells and results from the activation of progesterone secreted by the ovary after ovulation and intracellular cyclic adenosine monophosphate signaling [22]. This process induces morphological changes in ESCs, transforming them from spindle-shaped to cobble stone-like cells, which secrete prolactin and insulin-like growth factor binding protein 1. If pregnancy is not established, estrogen and progesterone withdrawal lead to menstruation, during which the functional layer of the endometrium is shed as menstrual blood. Endometrial destruction is accompanied by repair and reepithelialization. Remarkably, this monthly regeneration of the endometrium does not result in scarring during repair, indicating the unique tissue repair mechanism within the basal and functional layers [23].

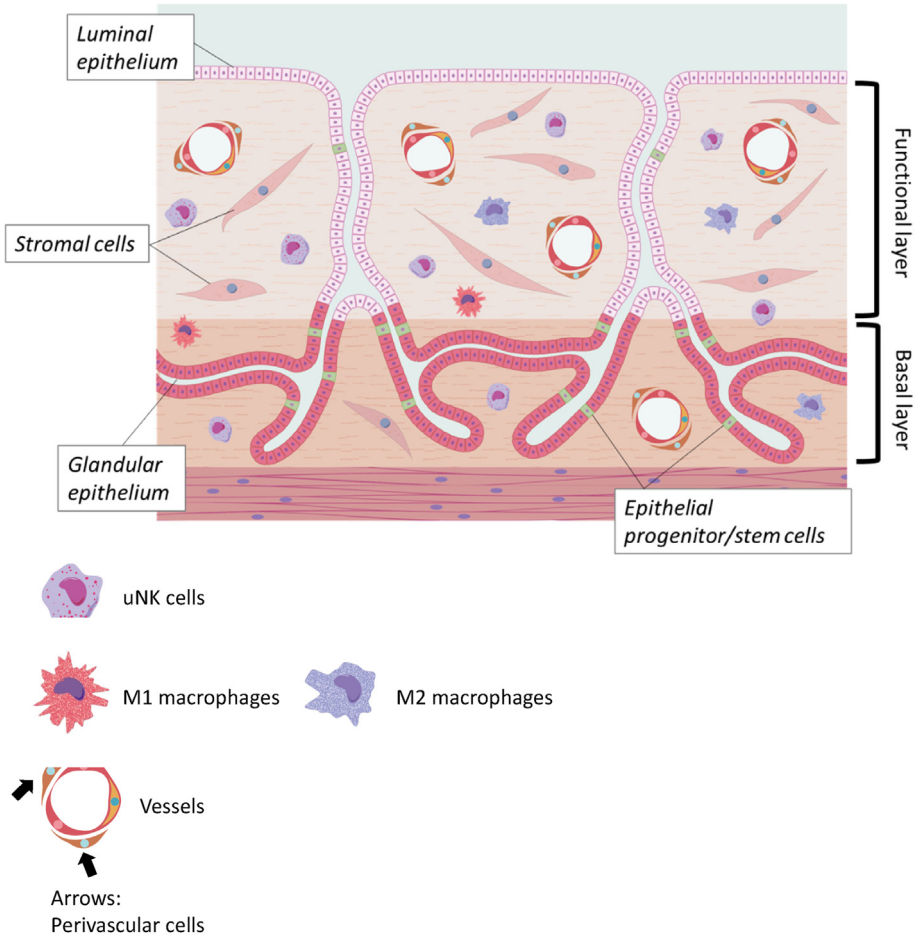

Fig. 1. Schematic diagram of the normal endometrium. Endometrium has two layers: basal and functional layers. The functional layer includes stromal cells, glandular epithelium, and luminal epithelium. Epithelial progenitor/stem cells exist in the basal layer, forming longitudinal and horizontal network. CD146, CD140b, and SUSD2-positive perivascular cells are present in both layers. Endometrium contains immune cells such as uNK cells, macrophages (M2>M1) for immunomodulation and homeostasis.

2.2. Epithelial stem/progenitor cells

Histologically, the endometrial epithelium lines the uterine cavity and includes tubular glands that radiate toward the myometrium through the endometrial stroma, displaying coiled and branched morphogenesis [24,25]. After shedding the functional layer during menstruation, the endometrial epithelium in the functional layer is generated depending on endometrial epithelial progenitor/stem cells present in the basal layer [21,26,27]. Despite knowledge on endometrial regeneration, the detailed mechanisms of endometrial regeneration during the menstrual cycle and the precise location of endometrial progenitor/stem cells remain unclear. Studies have tried to identify markers specific to the basal endometrial epithelium, where endometrial epithelial stem/progenitor cells are presumed to exist. These markers reported include stage-specific embryonic antigen-1 (SSEA-1) positive cells, identified in the endometrial epithelium of postmenopausal women [28,29], and N-cadherin (NCAD), a cell adhesion molecule.

Nguyen et al. proposed that human endometrial columnar epithelial cells possess a potential differentiation hierarchy, with the most primitive cells being NCAD-positive and SSEA-1-negative cells, existing at the base of the glands in the basal layer, close to the myometrium. During the migration of these primitive NCAD-positive and SSEA-1-negative cells from the basal portion of the gland through the basement membrane to the lumen, they gradually lose their NCAD activity and differentiate into NCAD-negative and SSEA-1-positive cells. Upon entering the functional layer, these cells are further downregulated and became fully differentiated NCAD- and SSEA-1 double-negative cells [30].

A recent study revealed that epithelial progenitor/stem cells in the basal layer form an extensive network in the longitudinal direction but horizontally, which may contribute to dynamic tissue repair [23] (Fig. 1). This intricate network is believed to maintain the integrity and function of the endometrium and thus ensure successful cyclical regeneration and preparation for potential implantation. This network of horizontal epithelial cells in the basal layer is maintained during menstruation [31]. In addition, these basal glands are branching, and most share branches with other glands in the basal layer. The number of glands sharing branches gradually increase with age. If iatrogenic damage causes the loss of the basal layer, the repair of the horizontal basal layer is assumed to occur from the remaining skipping lesion. This disruption of repair mechanisms in the horizontal network of the basal layer may contribute to AS onset. Thus, further basic studies are needed to determine which epithelial stem cell populations in this unique basal layer structure are responsible for the endometrial repair mechanism.

2.3. Stromal stem cells

In the functional layers, stromal stem cells can also contribute to endometrial regeneration [17,32]. Remarkably, concurrent with endometrial tissue shedding during menstruation,

inflammatory factors, growth factors, proteolytic enzymes, and recruited leukocytes are mobilized to repair and reepithelialize the endometrium [33]. High expression levels of proteases and gene products involved in extracellular matrix synthesis are observed in the stromal cells of the shedding endometrial region [34,35]. These findings demonstrate that stromal cells in the functional layer are involved in the regeneration of the endometrium.

Previous researches using samples from endometrial biopsies have demonstrated that cell populations, including endometrial MSCs (eMSCs) exhibiting clonogenic, self-renewal, and differentiation capacities, are present in both the basal and functional layers [36,37]. Notably, eMSCs are predominantly located near the spiral arteries; in particular, CD146 and platelet-derived growth factor receptor-β (CD140b)-positive cells are perivascular cells present in both the basal and functional layers of the endometrium and fulfill the International Society for Cellular Therapy (ISCT) criteria for surface marker expression and differentiation potential. These cells represent 1.5 % of eMSCs and highly express genes involved in angiogenesis, steroid hormone/hypoxia responses, immunomodulation, inflammation, cell communication, and proteolysis/inhibition [38].

Masuda et al. also reported the sushi domain containing 2 (SUSD2) as a specific marker for eMSCs. SUSD2-positive cells were also found in perivascular locations in both endometrial basal and functional layers [39]. SUSD2-positive cells had substantially higher clonogenicity than SUSD2-negative cells, and SUSD2-positive cells met the ISCT criteria. Moreover, studies indicating that SUSD2-positive cells transplanted under the kidney capsule of immunodeficient mice could form stromal-like and vascular structures demonstrate that the two primary components of human endometrial stroma, stromal fibroblasts and blood vessels, may originate from SUSD2-positive cells [39]. Accordingly, CD140b+, CD146+, and SUSD2+ cells may be eMSC-specific stem cells, and eMSCs are essential in a remarkable regenerative mechanism without scarring [17,21,32].

The immunomodulatory properties of perivascular eMSCs have been studied. Transcriptional analyses of CD140b + CD146+ eMSCs have unveiled that perivascular eMSCs specifically express several immunomodulatory genes, distinguishing them from ESCs. These cells exhibit immunosuppressive functions, including the production of the anti-inflammatory cytokine interleukin (IL)-10, and express various immune-regulatory genes such as ILs (*IL15, IL33,* and *IL6ST*), tumor necrosis factor (TNF) and interferon (IFN)γ-related genes, prostaglandin E2 synthesis genes (*PLA2G4A, PTGS2/COX-2*, and *PTGES*), and Toll-like receptors (*TLR2* and *TLR3*) [38,40]. Furthermore, eMSCs seeded on gelatin-coated polyamide meshes in a nude rat wound-healing model initially increased the abundance of inflammatory M1 macrophages at the mesh–tissue interface. Subsequently, these eMSCs suppressed inflammation around the mesh filaments by promoting the switching of macrophages from the M1 phenotype to the wound-healing M2 phenotype [41]. These findings propose that eMSCs interact with the immune system and exert immunosuppressive effects through paracrine mechanisms and direct contact with target cells [42]. These eMSCs are also present in the functional layer, and shed with menstrual blood [43].

3. AS

3.1. Definition of AS

AS was first introduced by the Israeli gynecologist Joseph Asherman in 1948 to describe symptoms and diagnostic criteria for menstrual abnormalities resulting from intrauterine adhesions [12,44]. The terminology related to this condition varies, in which experts used terms such as AS, intrauterine adhesions (IUAs), and endometrial scarring are often used interchangeably to denote intrauterine adhesions associated with infertility. Some experts use the term AS to refer to endometrial scarring after pregnancy. In contrast, others consider all cases of IUAs, regardless of their cause, to fall under AS [45]. In addition, there is also a condition where the endometrium gets thin without adhesions in the uterine cavity. We defined this condition as thin endometrium in this review.

In this review, AS will collectively refer to intrauterine adhesions and associated conditions, irrespective of their relationship to pregnancy. In the American Fertility Society (AFS) Classification, the severity of intrauterine adhesions, primary pathology of AS, is classified as grade I (mild), II (moderate), or III (severe) based on a combined score of menstrual patterns and findings on hysteroscopy or hysterosalpingography (Fig. 2). Because adhesions directly affect reproductive outcomes, the quality of the adhesions (filmy or dense) and adhesions' location inside the uterus also need to be described [46].

3.2. Epidemiology of AS

The exact prevalence of AS is unclear owing to the lack of a standardized definition for intrauterine adhesions associated infertility. However, a study estimated that the prevalence of repeated implantation failure due to thin endometrium, including

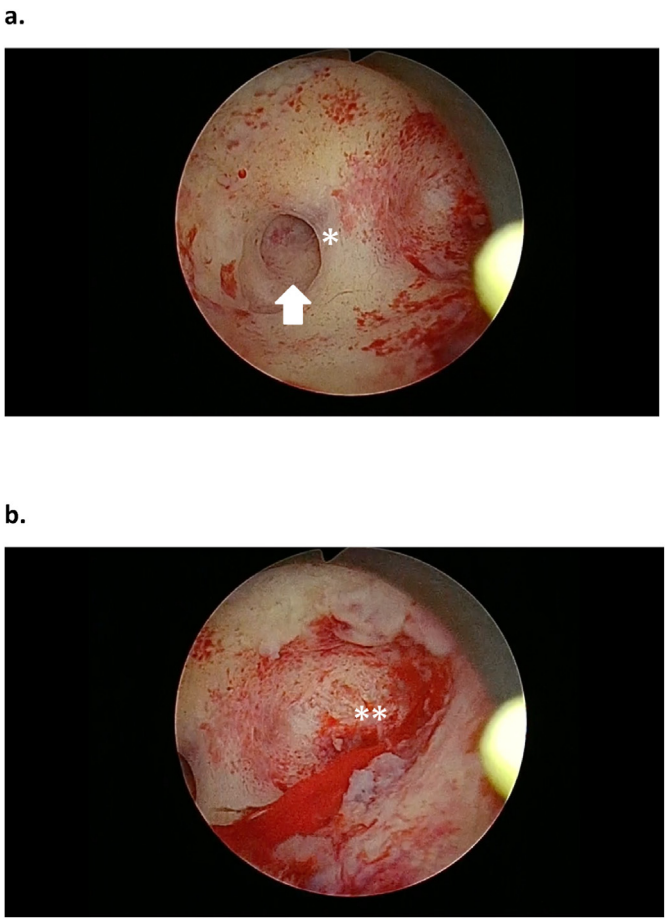

Fig. 2. Hysteroscopic images of AS (American Fertility Society classification grade I). a. Right side of the uterine fundus (Arrow). Adhesions are observed near the right fallopian tube opening (*). b. There is adhesion covering the entire left side of the uterine fundus (**), obstructing the left fallopian tube opening.

AS, is 1 %–5% in patients requiring infertility treatments [15,47]. According to a report published by the World Health Organization (WHO), approximately 17.5 % of the adult population is affected by infertility [48]. For example, In Japan, the annual number of marriages over the past few years has been approximately 500,000, and 22.7 % of couples married were undergoing testing/treatment for infertility [49] Thus, annually, 1000–2000 women in Japan may present with repeated implantation failure due to thin endometrium. Considering the incidence of AS after intrauterine procedures, intrauterine adhesions developed in approximately 20 % of women after undergoing surgery for abortion or miscarriage [15,50,51]. In addition, intrauterine adhesions were found in approximately 40 % of women who received intrauterine treatment for placental remnants after childbirth or repeated curettage for incomplete abortion during subsequent outpatient hysteroscopy [52]. Moreover, the incidence of intrauterine adhesions from uterine compression sutures for major postpartum hemorrhage at 2–4 weeks postpartum is 19–27 % [53,54].

In a study of complications after hysteroscopic surgery for intracavitary lesions, the incidence rate of intrauterine adhesions is 1.34 % [55]. Taskin et al. [56] examined the prevalence of AS after surgical interventions and revealed varying rates depending on the procedure type: 6.7 % in patients with a septum, 31.3 % in those with a single myoma, and 45.5 % in patients with multiple myomas. These findings underscore that a significant proportion of patients, including potential patients, are at risk of AS development.

3.3. Pathology of AS

AS is considered caused by the partial or complete loss of the functional endometrium due to endometrial basal layer damage and endometrial fibrosis (Fig. 3). This condition can be caused by intrauterine manipulation, childbirth, infection, or blood flow obstruction, such as uterine artery embolization [51,57], and uterine tuberculosis [47]. The adhesion of the uterine cavity and subsequent loss of functional endometrium lead to infertility, pelvic pain, menstrual abnormalities, intrauterine growth retardation, premature delivery, and placental abnormalities, such as abnormal placental positioning and adhesions [7].

Gargett et al. and Santamaria et al. demonstrated that in patients with AS, different factors can cause the destruction of the endometrium through to its basal compartment and loss of endometrial

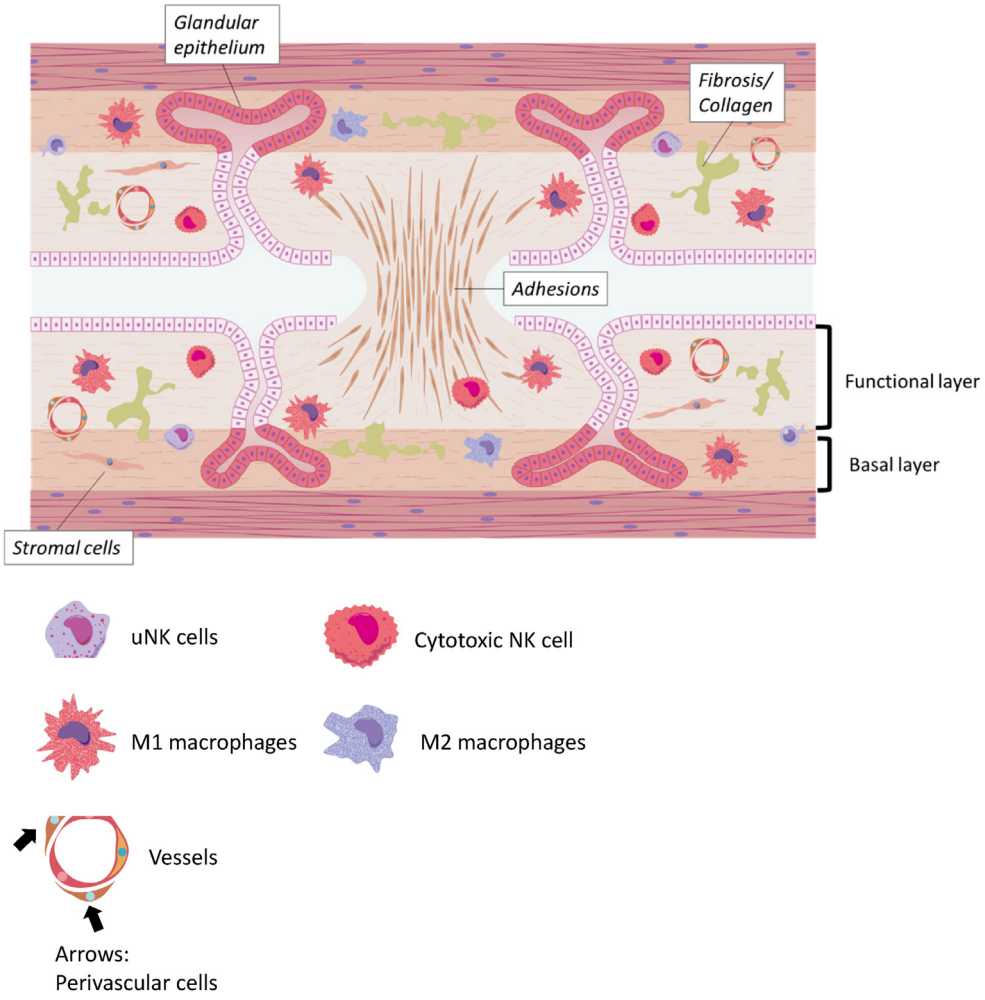

Fig. 3. Schematic diagram of AS endometrium. This is the imaginable schematic of the endometrium in patients with AS, based on pathological and scRNA-seq findings from previous studies. Disruption of the horizontal network within the basal layer impairs the endometrium's repair mechanisms, leading to the formation of avascular endometrial lesions and endometrial thinning. In areas of adhesion, basal layer destruction and the loss of endometrial stem cells result in the depletion of functional endometrial epithelial and stromal cells that normally respond to hormonal stimulation, thereby inhibiting endometrial regeneration. The loss of epithelial cells, along with the presence of fibroblasts and myofibroblasts, promotes adhesion formation between opposing surfaces of the uterine lumen. Additionally, the endometrium exhibits an increased presence of activated cytotoxic natural killer (NK) cells and proinflammatory M1 macrophages, which may suppress the function and proliferation of uNK cells and anti-inflammatory M2 macrophages.

stem cells, and the damaged endometrium then cannot be properly repaired, leading to an increase in avascular endometrial lesions and endometrial thinning, leading to the loss of functional endometrial epithelial and stromal cells responsive to hormonal stimulation and fibrous synechiae forms across the cavity [21,58]. Yu et al. [9] demonstrated that the endometrial stroma is replaced by fibrous tissue; the distinction between the functional and basal layer of the endometrium is lost, which is nonresponsive to hormone stimulation (Fig. 3).

Despite the remarkable regenerative capacity of the endometrium, the precise molecular pathways that result in irreversible endometrial fibrosis in AS remain elusive. Endometrial fibrosis is a common pathological feature in intrauterine adhesions, with fibrin playing a crucial role in the development of fibrotic tissue across the uterine cavity [58]. The ischemia and inflammation induced by endometrial damage are believed to contribute to fibrosis development, and factors such as TGF-β1 and C-X-C chemokine receptor type 4 (CXCR4) are implicated in the activation of fibrosis [59,60]. In addition, the presence of M2 macrophages, which possess anti-inflammatory and antifibrotic properties, was reduced in the endometrium of patients with intrauterine adhesions [61].

3.4. Pathology of AS and thin endometrium based on single-cell RNA sequencing (scRNA-seq)

A study of scRNA-seq of the endometrium of AS revealed a loss of endometrial epithelial cells and an increase in stress-related signaling markers in epithelial cells [62]. Additionally, the stromal cells were found to overexpress anti-angiogenic factors such as *A Disintegrin And Metalloproteinase with Thrombospondin motifs 8* (*ADAMTS8*) and *Decorinand* (*DCN*). Furthermore, it is reported that the intrauterine fibrosis that characterizes AS is a reactive process that develops in response to epithelial damage and inflammation, in which fibroblasts synthesize large amounts of collagen, thereby increasing tissue stiffness [62]. Moreover, an increase in the presence of macrophages and cytotoxic natural killer (NK) cells was observed in comparison with the levels found in a normal endometrium. This finding suggests the occurrence of an inflammatory state within the AS [62]. According to this report, the pathogenesis of AS can be considered as the loss of epithelial cells and the proliferation of collagen, the inhibition of angiogenesis in the extracellular matrix, and the exacerbation of inflammatory conditions (Fig. 3). Based on this result and the pathology of AS described by Gargett et al. [21] and Santamaria et al. [58], the pathogenesis of AS may be considered to involve the exacerbation of inflammatory conditions and the suppression of cell proliferation, as well as the inhibition of angiogenesis due to endometrial basal layer damage.

Whereas Lv et al. [63] reported the result of scRNA-seq concerning thin endometrium without intrauterine adhesions. This report demonstrated that although the cell types present in the thin endometrium are similar to those in the normal endometrium, the overall cell number is significantly reduced, owing to the abnormal activation of the Semaphorins 3 pathway [63]. This reduction was reportedly accompanied by attenuating the epidermal growth factor (EGF), pleiotrophin, and TNF-like weak inducer of apoptosis signaling pathways [63]. Stromal and epithelial cell senescence was also observed, accompanied by excessive perivascular collagen deposition [63]. The deposition of type IV collagen around the blood vessels contributes to impaired angiogenesis, which causes a thin endometrium [64,65]. Furthermore, perivascular cells in the stroma of thin endometrium exhibited the highest levels of senescence-associated genes, and their colony-forming ability was significantly reduced compared with that of the normal endometrium [63]. Considering that perivascular cells in the endometrium, marked by CD146+, CD140b+, and SUSD2+, represent a population of eMSCs with clonogenic, self-renewal, and differentiation capabilities [17,21], a shortage of cellular resources due to the senescence of perivascular cells, or the endometrial stem cells, contributes to the inadequate growth of the endometrium. Furthermore, Lv et al. reported a reduction in macrophages and natural killer (NK) cells in thin endometrium [63]. This decrease in immune cell population may contribute to insufficient endometrial proliferation based on findings that the proliferation of ESCs was significantly promoted by the culture supernatant of human uterine NK (uNK) cells and macrophages [63]. This observation appears to contradict the findings, which reported increasing in the presence of macrophages and cytotoxic natural killer in AS by Santamaria et al. [62], however, the association between the endometrium and immune cells in the pathophysiology of AS need to be elucidated. The quantity of immune cells varies throughout the menstrual cycle, and the functions of macrophages and NK cells are altered or induced in response to cytokine stimulation [66], necessitating further investigations.

A study revealed that uNK cells, as opposed to peripheral blood NK (pNK) cells, are pivotal in establishing pregnancy [67] (Fig. 1). Furthermore, the abundance of M2 macrophages was reduced in the endometrium of patients with AS [61]. These reports hypothesize that in AS, specific inflammatory responses may activate cytotoxic NK cells and proinflammatory M1 macrophages (Fig. 3). This activation could inhibit the function and proliferation of uNK cells and anti-inflammatory M2 macrophages, crucial for maintaining endometrial homeostasis.

Considering these two studies [62,63], the anti-angiogenic effects associated with strong inflammation and the inhibition of cell proliferation, as well as the deposition of collagen fibers and the excessive appearance of inflammatory immune cells suggest that similar treatments could be effective for both conditions. However, since the main pathological feature of AS is intrauterine adhesions, its treatment requires a different approach based on the severity of the condition and its pathological etiology.

3.5. Current treatments of AS

3.5.1. Hysteroscopic adhesiolysis

Surgical treatment of AS is indicated in women with infertility and those with painful hypo- or amenorrhea, surgical. For fertility, the initial goal of treatment is the restoration of a normal calibrated uterine cavity covered with endometrial lining [47]. Hysteroscopic adhesiolysis is a standard surgical treatment for AS, in which adhesions are removed bluntly or with scissors with magnification [68]. Careful dissection with energy instruments is mandatory because the energy may destroy the otherwise healthy endometrium [69] (**Additional file 1: Supplemental video**). Hysteroscopic dissection was reported to improve uterine cavity adhesions and increase pregnancy rates [70]. However, the incidence of complications, such as uterine perforation, rises with advancing adhesions and the procedure becomes more difficult [9]. The pregnancy rates after this treatment also vary with the severity of adhesions; in severe AS, the pregnancy rate reportedly improves by 60 %, although 75 % of these pregnancies result in miscarriages [51]. In addition, postoperative recurrence of adhesions is a significant concern and may occur in 30 %–66 % of women with AS treated with hysteroscopic adhesiolysis [71]. Other treatments, including hormone replacement therapy, have been explored [9,10]; however, their efficacy remains inconsistent across reports, and the experimental results often lack objective validity [14,15]. Although hysteroscopic dissection is commonly used for the treatment for AS, its limitations highlight the need for continued research into more effective and reliable treatment strategies.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.reth.2025.03.019

3.5.2. PRP

Recent reports on endometrial regeneration and tissue repair using intrauterine administration of PRP [14,72]. PRP, collected from peripheral veins, contains growth factors such as vascular endothelial growth factor (VEGF), EGF, platelet-derived growth factor (PDGF), transforming growth factor (TGF), and regulatory cytokines including IL-1β, IL-6, IL-8, IFN-γ, and chemokine ligands (CCL)3, CCL4, and CCL5, which modulate immune responses [14,72,73]. PRP has been used for various medical conditions, including ophthalmic, orthopedic, surgical, and wound-healing applications [74–76]. Pilot studies and case reports on the efficacy of PRP in treating thin endometrium have reported that intrauterine PRP administration increased endometrial thickness and improved pregnancy rates [14,77]. However, in 2023, a randomized clinical trial published reported that intrauterine PRP administration for AS after surgical treatment did not significantly affect intrauterine adhesions, menstrual symptoms, or severity compared with the untreated group [78]. In addition, a meta-analysis of data from 10 clinical studies involving 730 patients reported that PRP administration significantly increased endometrial thickness, menstrual volume and days of menstruation. Additionally, the clinical pregnancy rate also improved [79]. However, there was insufficient evidence to reach a conclusion regarding the effects of PRP on the recurrence rate of moderate to severe IUA, miscarriage rate, and live birth rate. Furthermore, the bias should be noted that this meta-analysis has a limited sample size. Additionally, generally, the method of preparing PRP is also not standardized, which could affect the quality of PRP and treatment outcomes. Therefore, further investigation into the therapeutic effect of PRP on AS is also required.

3.5.3. G-CSF

G-CSF is a cytokine that stimulates neutrophil proliferation and differentiation, commonly used in general clinical practice for treating neutropenia during cancer chemotherapy [80]. Several studies demonstrated the effectiveness of G-CSF in improving endometrial thinning [81–83]. A prospective pilot study without a control group by Gleicher et al. in 2013 reported a notable improvement in endometrial thinning in patients with refractory thinning endometrium [81]. However, a subsequent prospective, double-blind, randomized controlled trial did not find significant differences in endometrial thickness, pregnancy rate, or implantation rate [82]. Zhang et al. [83] reported that G-CSF administration after adhesion resection for AS did not significantly affect adhesion remodeling rates or AFS scores, but significantly increased endometrial thickness in the treatment group. Thus, the results of the intrauterine administrations of G-CSF vary among reports, with no consistent data available. The inconsistency may be derived from the pathophysiology of intrauterine damage; thus, the evidence regarding their efficacy is further investigated.

3.5.4. Cell transplantation

Considering the pathophysiology of AS, in which there is a shortage of endometrial stem cells due to endometrial basal layer damage, cell therapy is considered necessary to develop curative treatment. Oral mucosal epithelial cell sheet transplantation has been demonstrated to effectively prevent intrauterine adhesions following endometrial injury in rat models [84]. Moreover, the transplantation of mouse endometrial epithelial cells into a mouse model of endometrial adhesions has demonstrated successful restoration of the damaged endometrium [85]. Given these findings, it is plausible to consider increasing the number of deficient endometrial epithelial cells *in vitro* to prevent adhesion and subsequently transplanting them back into the uterus as a therapeutic approach. Previous research has explored the long-term culture of endometrial epithelial cells [86,87]. However, it remains challenging to proliferate endometrial epithelial cells sufficiently for use in cell therapy.

The recent focus is on developing novel cell therapies for endometrial regeneration through the paracrine effect of MSCs [88]. Preclinical studies have demonstrated that MSCs derived from bone marrow, adipose tissue, and umbilical cord can increase endometrial thickness and improve fertility through their regenerative properties [89–92]. A pilot study and a prospective case series involving the intrauterine administration of autologous bone marrow-derived MSCs (BMSCs) in patients with AS reported improvements in endometrial thinning without apparent adverse events [93,94]. In addition, a phase I clinical trial that investigated the intrauterine transplantation of allogeneic cells using umbilical cord MSCs following endometrial ablation showed increased endometrial thickness and no significant adverse events over a 30-month follow-up period, and 10 of 26 patients achieved live births without congenital anomalies or placental complications [95]. These studies proposed that intrauterine MSC transplantation may offer a promising treatment for AS. However, further larger-scale clinical trials are needed. Moreover, current MSC sources raise concerns about the invasiveness of collection, complex acquisition, cost-effectiveness, and ethical issues [16]. Therefore, novel MSC resources need to be explored; MenSCs are gathering attention [16,89].

4. Novel therapeutic strategies using MenSCs

4.1. MenSCs

In 2007, Cui et al. demonstrated that menstrual blood contains stromal/MSCs. They identified a cell population in menstrual blood with high proliferative potential, displaying a population doubling to senescence of 25–40 [96]. These cells exhibited typical MSC surface markers, adhesive capacity to plastic, and multipotent differentiation potential [96]. Given that the functional endometrial layer is shed during menstruation, eMSCs expressing CD140b+, CD146+, and SUSD2+ are deemed present in the menstrual blood. Menstrual blood is a readily available source of stem cells and do not require invasive and surgical procedures when harvesting stem cells from the bone marrow, adipose tissue, or other sources. MenSCs are also ethically advantageous because they originate from usually discarded samples. Consequently, MenSCs are garnering attention as a viable alternative to conventional adult stem cells (Fig. 4).

4.2. Cell markers of MenSCs

MenSCs fulfill the ISCT criteria, such as adherence to plastic dishes, trilineage differentiation of cultured cells into adipocytes, osteocytes, and chondrocytes, and expression of MSC markers CD73, CD90, and CD105 but not hematopoietic stem cell markers [96–99]. In our previous study, MSCs obtained from the menstrual blood of patients with infertility were positive for CD73, CD90, and CD105. Cells from a patient with AS also fulfilled the ISCT criteria [16]. Regarding other phenotypic markers, Meng et al. [97], Darzi et al. [98], and Khanjani et al. [95] reported positive expression of the pluripotency marker OCT4, whereas Cui et al. reported negative results [96]. To date, ISCT markers have been used as validation markers for MenSCs. However, considering their endometrial origin, evaluation of eMSC markers such as SUSD2, CD146, and CD140b may be essential. Wyatt et al. reported that 4.7 % of the MenSC population was positive for SUSD2 [100], consistent with Masuda's finding that 4.2 % of eMSCs were positive for SUSD2.

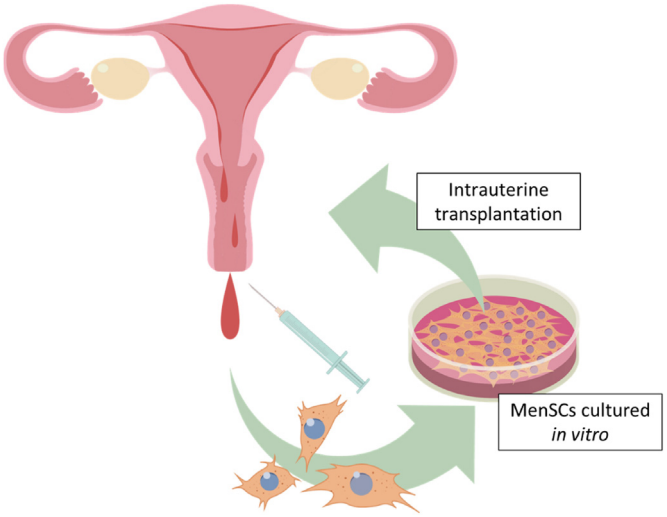

Fig. 4. Schematic diagram of the treatment of AS using autologous MenSCs. Menstrual blood contains cells detached from the functional layer. Menstrual blood from patients with AS is collected. Endometrial mesenchymal stem cells characterized by markers such as CD140b+, CD146+, and SUSD2+ and fulfill the International Society for Cellular Therapy criteria, and have high proliferative potential. These cells cultured *in vitro* are autografted into the uterus of patients with AS.

Influence of menstrual cycle phase, collection methods, and culture conditions on cell surface markers and cell population characteristics have not yet been investigated and should be considered in future research to optimize quality control. Comprehensive investigations of these factors would offer deeper insights into the therapeutic potential of MenSCs.

4.3. Treatment of AS using MenSCs

4.3.1. Angiogenesis and tissue repair effects of MenSCs

Given the loss of endometrial stem cells in AS, augmenting the endometrial stem cell population through intrauterine transplantation of *in vitro* expanded MenSCs may serve to compensate for the loss or reduction of these cells, possibly leading to the recovery of angiogenesis and anti-inflammatory potency. A recent study demonstrated that the regenerative effects of MSCs are primarily due to paracrine mechanisms rather than their differentiation ability [17]. MenSCs, similar to MSCs from other sources, possess regenerative therapeutic effects through angiogenesis and tissue repair [16]. When cocultured with ESCs, MenSCs contribute to tissue repair by attenuating the effect of TGF-β, downregulating the expression of myofibroblast markers alpha-smooth muscle actin (α-SMA) and collagen I, and promoting rapid cell proliferation in ESCs [101].

MenSCs also exhibited superior paracrine response to hypoxic conditions to BMSCs [102]. Alcayaga-Miranda et al. [102] reported that MenSCs demonstrated complete wound closure after 24 h, whereas BMSCs only showed partial wound closure in scratch assay. This finding suggests that the MenSCs may have the higher migratory ability to injured sites after transplantation, where the MenSCs contribute to the surrounding cells in a paracrine manner. In addition, while the conditioned medium from BMSCs did not show a significant difference in tube formation between hypoxic and normoxic conditions, that from MenSCs exhibited significantly enhanced tube formation under hypoxic conditions.

A comparative study with umbilical cord-derived MSCs (UC-MSCs) also revealed that MenSCs exhibited superior clonogenic and migratory abilities to UC-MSCs [103]. This report also revealed that analysis of proliferative rate over time was higher in MenSCs than UC-MSCs. In addition, evaluating the colony-forming unit-fibroblast (CFU–F) assay, MenSCs exhibited a notably higher CFU-F potential compared to UC-MSCs.

Our study demonstrated that MenSCs from patients with AS maintained angiogenic and tissue repair capacities *in vitro* and *in vivo,* mediated by the paracrine effect [16]. This indicates the potential use of MenSCs from patients with AS as cellular therapeutic agents.

4.3.2. Immunomodulatory effect in MenSCs

MenSCs exhibited a higher inhibition rate of T-cell proliferation than UC-MSCs in a T-cell proliferation assay by coculturing at high concentration ratios with PBMCs [103]. However, the suppressive effect was lower at lower concentration ratios [104]. These findings indicate the dose-dependent inhibitory effect of MenSCs on T-cell proliferation. The immunosuppressive effect was maintained when evaluating MSCs pre-stimulated with IL-1β and TNF-α for 24 h under proinflammatory conditions [103]. Nonetheless, the assessment of the activation of the immunosuppressive effect by IFN-γ pretreatment revealed significantly lower suppression of T-cell proliferation in MenSCs than in MSCs [104]. This indicates the need for caution when evaluating the immunosuppressive effect of MenSCs after cytokine pre-stimulation.

Furthermore, MenSCs influence the innate immune system. uNK cells are pivotal in establishing pregnancy [67]. For instance, uNK cells function to prevent rejection reactions and regulate vascular remodeling, thus successfully maintaining pregnancy [105]. The dysregulation of uNK cell function may be implicated in recurrent miscarriages [106]. Compared with BMSCs, unstimulated MenSCs can induce NK cell proliferation; however, in an inflammatory-induced environment, MenSCs significantly inhibit NK cell proliferation and cytotoxicity [107]. These results suggest that MenSCs play a crucial role in maintaining endometrial tissue homeostasis and inducing a pregnancy-compatible phenotype in NK cells. Furthermore, the intravenous injection of MenSCs in a mouse model of colitis promoted M2 macrophage migration and reduced immunoglobulin G deposition in the damaged colon [108]. These results indicate that MenSCs supplementation may improve immunomodulatory effects in AS, with impaired endometrial immunomodulatory mechanisms. However, given the interexperimental variability in the evaluation of immunosuppressive effects *in vitro*, further validations are necessary to assess the immunomodulatory properties of MenSCs comprehensively.

Because MenSCs have potency of angiogenesis, tissue repair and immunomodulation, we considered that MenSCs have therapeutic effect on the AS and thin endometrium, which have conditions such as reduced angiogenic capacity associated with strong inflammation and inhibition of cell proliferation, as well as the excessive appearance of inflammatory immune cells reported by scRNA-seq studies.

4.3.3. Therapeutic effect of MenSCs on infertility animal models

Previous studies have reported that MSC administration in animal models with damage endometrium established by intrauterine ethanol injection [91,92,109] and electric coagulation [110] leads to increased endometrial thickness, reduced fibrosis, and improved fertility through angiogenesis and tissue repair [91,92,109,110]. Our research team employed a mechanical injury model clinically relevant to the pathophysiology of AS-associated infertility to create a thin endometrium model [16]. We also successfully isolated and cultured MenSCs derived from patients with infertility, including AS. The intrauterine transplantation of MenSCs from a patient with AS into the injury models demonstrated increased endometrial thickness, reduced fibrosis, and improved

fertility through angiogenesis and tissue repair [16]. The results of establishing a method to collect cells from patients undergoing fertility treatment and the therapeutic effect of MenSCs derived from patients with AS in the injury models further underscore their potential as a robust cell source for autologous use in regenerative therapy for damaged endometrium.

4.3.4. Safety of the MenSCs administration

For safety, Chang et al. [111] confirmed the disappearance of MenSCs 4 weeks after administrating into a subserosal layer of the uterus in IUA model mice. As observed, mice maintained average body weight with no mortality, abnormal behavior, transplant-related diseases, or endometriosis up to 6 months after transplantation. In our study, no apparent concerns were noted for local tumorigenicity and distribution to other major organs of intrauterine transplanted MenSCs until 1 month after transplantation [16]. Furthermore, no abnormal findings in blood sample tests were observed in these reports. Despite the need for further preclinical evidence for long-term safety, these preliminary results support the idea that MenSCs transplantation is safe and not toxic or tumorigenic in mid-term evaluations [111]. These findings highlight the potential of intrauterine MenSCs transplantation to offer a proactive therapeutic effect on endometrial damage and impaired reproductive capability.

4.3.5. Clinical trials using MSCs for IUA and thin endometrium

Several clinical studies have used autologous MSCs for treating implantation failure associated with IUA or thin endometrium. Intrauterine transplantation of MenSCs for IUA has been reported by Tan et al. [19] and Ma et al. [20]. Subendometrial administration using in the case of BMSCs for IUA has been performed by both Santamaria et al. [93] and Singh et al. [94]. Adipose-derived MSCs (ADCs) have been administered subendometrially for thin endometrium by Sudoma et al. [112]. Yotsumoto et al. [113] performed intrauterine transplantation of adipose tissue-derived regenerative cells (ADRCs) involving ADCs for suspected implantation failure (Table 1). All these studies observed an improvement in endometrial thickness compared with the pre-transplantation status. MenSCs including IUA grades III-IV [19,20] have reported improvements to an endometrial thickness of >7 mm. Clinical evidence indicates that pregnancy and live birth rates decrease *in vitro* fertilization rates when endometrial thickness falls <8 mm for fresh blastocyst transfer and <7 mm for freeze–thaw embryo transfer cycles [5]. Thus, the endometrium thickness >7 mm is considered one of the surrogate markers of effectiveness.

Several clinical studies have investigated the use of allogeneic transplantation of UC-MSCs. Huang et al. [114] conducted intrauterine transplantation for patients with AS, while Cao et al. [115] performed intrauterine transplantation of UCMSCs loaded onto a collagen scaffold following an adhesion separation procedure for International IUA grade III-IV. Notably, no adverse events were observed in any patients during the study periods [114,115]. Although these studies did not report an improvement in endometrial thickness >7 mm, Cao et al. [115] demonstrated a reduction in intrauterine adhesion scores during second-look hysteroscopic evaluations compared to baseline. These reports suggest that allogeneic cell transplantation can be performed safely and may offer therapeutic efficacy.

Five studies that evaluated pregnancy outcomes [19,20,93,112,115] have demonstrated favorable results regarding pregnancy establishment; however, many cases were still ongoing at the time of reporting, necessitating further follow-up to assess live birth rates. Moreover, all studies did not report significant adverse events. Therefore, clinical trials using autologous and allogeneic MSC transplantation may offer effective and safe treatment for thin endometrium, and late-phase clinical trials are expected.

4.3.6. Challenges in the clinical applications of MenSCs for AS treatment

Several concerns need to be addressed when developing novel cell therapies for AS using MenSCs, particularly in cases utilizing autologous cells. First, whether MenSCs can be isolated from the menstrual blood of patients with AS need to be determined, given that the severity of AS often correlates with reduced menstrual blood volume. In addition, the eMSCs in patients with AS exhibit senescence *in vivo*. Despite these concerns, two clinical studies [19,20] have used autologous MenSCs in severe AS (IUA grades III–IV) cases where conventional treatments failed to achieve pregnancy. These studies (n = 19) successfully isolated MenSCs

Table 1
Clinical trials using MSCs for IUA and thin endometrium.

	Number of patients	Diagnosis	Cell types	Implanting location	Source	Number of cells	Outcomes	
							Major outcomes[b]	Pregnancy rate
Tan J [19]	7	IUA grades III–IV	MenSCs	Intrauterine	Autologous	1.0×10^6	ET > 7 mm in 5 out of 7 participants	42 % (3/7)
Ma H [20]	12	IUA grades III–IV	MenSCs	Intrauterine	Autologous	1.0×10^7	ET: 3.9 ± 0.9 mm to 7.5 ± 0.6 mm[c]	42 % (5/12)
Santamaria X [93]	11	IUA grades I–III + EA	BMSCs	Spiral arterioles	Autologous	4.2×10^7 to 2.0×10^9[a]	ET: 4.3 mm to 6.7 mm[c]	38 % (6/16)
Singh N [94]	6	IUA grades III–IV	BMSCs	Subendometrial zone	Autologous	1.0×10^8	ET: 1.38 ± 0.39 mm to 5.48 ± 1.14 mm[c]	NA
Sudoma I [112]	25	Thin endometrium	ADCs	Subendometrial zone	Autologous	1.0×10^6	ET increased in 20 out of 25 patients	52 % (13/25)
Yotsumoto F [113]	5	Suspected embryo implantation failure	ADRCs	Intrauterine	Autologous	3.8×10^7 to 1.0×10^8[a]	ET: 3.8 ± 1.3 mm to 8.8 ± 2.8 mm[c]	40 % (2/5)
Huang J [114]	6	AS	UC-MSCs	Intrauterine	Allogeneic	2.0×10^7	ET: 3.28 ± 1.20 mm to 3.75 ± 1.08 mm[c]	NA
Cao Y [115]	25	IUA grade III–IV	UC-MSCs	Intrauterine Following an adhesion separation procedure	Allogeneic	1.0×10^7 (loaded onto a collagen scaffold)	ET: 4.46 ± 0.85 mm to 5.74 ± 1.20 mm[c]	40 % (10/25)

Abbreviations: ADCs, Adipose-derived mesenchymal stem cells: ADRCs, Adipose tissue-derived regenerative cells: BMSCs, Bone marrow-derived mesenchymal stem cells, UC-MSCs, Umbilical cord-derived mesenchymal stem cells: EA, Endometrial atrophy: ET, Endometrial thickness: IUA, intrauterine adhesion: MenSCs, Menstrual blood-derived mesenchymal stem cells: NA, Not Available.

[a] Administered cells were those available for collection, with no predetermined cell count.

[b] Outcomes as reported in each manuscript.

[c] Change in ET from pre-administration to post-administration.

from patients and cultured and transplanted them into the uterus [19,20]. In addition, we also confirmed the feasibility of the primary culture of MenSCs from a patient with AS [16]. These results indicate that primary cultures of MenSCs are clinically feasible even in severe AS.

Second, whether MenSCs of patients with AS possess therapeutic efficacy need to be established. Previous studies demonstrated the effectiveness of MenSCs derived from volunteers in infertility treatments; however, no studies have used MenSCs isolated from patients with AS. Consequently, we revealed that the angiogenesis and tissue repair capabilities of MenSCs derived from a patient with AS are comparable with those of MenSCs from a volunteer [16]. In addition, we also demonstrated the potential effects of infertility treatment using a thin endometrium animal model. These findings indicate that MenSCs from a patient with AS can be used as a viable cellular therapeutic agent. Although this is speculative, it is possible that even in a patient with AS, a portion of the endometrium with standard functionality remains. MSCs that detach from this functional endometrium may be collected during menstruation, allowing for the primary culture of MenSCs with therapeutic efficacy. However, given that only a single participant with AS participated in our previous research, further investigation is warranted to determine whether MenSCs derived from multiple AS patients exhibit enough therapeutic potency. Furthermore, it is essential to investigate whether MenSCs can be isolated from menstrual blood even in cases where inflammation has extensively affected the endometrium, and normal endometrial tissue does not remain, such as in chronic endometritis.

Third, the risk of contamination during culture is a concern, as menstrual blood contains bacteria and fungi primarily derived from the vaginal flora, which differs from other primary sources of MSCs such as the bone marrow, adipose tissue, and placenta. This poses a significant challenge for the clinical application of MenSCs. For example, Takagi et al. [116] reported that in their study on oral mucosal sheets, which also faced contamination risks from the oral microbiota, infection was controlled by implementing specific measures. Previous studies have not extensively focused on controlling infections during the primary culture of MenSCs. In our preliminary studies, the culture medium was supplemented with penicillin, streptomycin, and amphotericin B to prevent contamination and ensure the success of primary cultures [16]. However, for future clinical applications, antibiotic allergies should be considered, and further investigations into suitable antibiotics are warranted.

Furthermore, the detail protocols of MSC therapy, including the administration timing during the menstrual cycle, dosage, and frequency of MSC administration, need to be considered to achieve the desired therapeutic effect. Specifically, considering intrauterine transplantation of MSCs, the expulsion of transplanted cells during menstruation is concerned. However, several clinical studies [93,94,112] reported that the therapeutic effect had persisted even after repeated menstrual cycles following MSC administration. Interestingly, these three studies adopted the administration to the subendometrial lesion or spiral arterioles. These results may suggest that transplanted MSCs can persist after menstruation and the administration method may be important for the therapeutic permanency. Moreover, intrauterine administration following an adhesion separation procedure, with cells loaded onto a collagen scaffold, as demonstrated by Cao et al. [115] showed a reduction in intrauterine adhesion scores during second-look hysteroscopic evaluations compared to baseline. Therefore, further studies are warranted to identify the most effective therapeutic strategies based on these findings.

In the two preliminary clinical studies, Tan et al. [19] administered 1.0×10^6 cells 2 weeks after menstruation, whereas Ma et al. [20] administered 1.0×10^7 cells on the second day of menstruation. Both studies have reported that the endometrial thickness exceeded 7 mm during the ovulation phase in patients with severe AS, with some cases resulting in successful pregnancies. Nevertheless, the most optimal treatment protocol remains uncertain. This is pertinent for the endometrium, which undergoes dynamic histological changes such as shedding, proliferation, and secretion every month, necessitating careful consideration of the timing of MSC administration. Based on these findings, an optimal treatment protocol that balances safety and efficacy needs to be developed.

Moreover, a common issue with MSC-derived products is the variability in “quality” due to the heterogeneity of MSC, which needs to be thoroughly investigated in future studies. MSCs exhibit biological characteristics and function differences depending on the source tissue and microenvironment. This means variations in MSC cell properties between different tissues and donors within the same tissue source. Miura et al. [117] identified a biomarker using scRNA-seq that enables the identification of cell subpopulations contributing to the angiogenic properties of BMSCs. Similarly, for MenSCs, it is crucial to identify the active components and related cell subpopulations that are effective against intrauterine adhesions in AS, and to determine the biomarkers specific to these cell populations.

Finally, the potential cost of cell culture needs to be addressed for clinical applications of MenSCs. In our recent research using a nationwide database in Japan, the price using MSCs for infertility treatment is approximately eight times more expensive that of those involving PRP [118]. From a cost perspective, allogeneic transplantation of MenSCs may present a viable alternative. Menstrual blood can be non-invasively collected multiple times, which presents a significant advantage compared to other cell sources, even though MenSCs can only be harvested from women. Notably, MenSCs exhibit low expression levels of histocompatibility antigens HLA-B and HLA-C and do not express HLA-DR [104]. This characteristic suggests that clinical application of the allogeneic MenSCs transplantation would be expected for other fibrotic or inflammatory diseases than AS, even in male patients. Thus, further clinical investigations of allogeneic MenSCs would be warranted.

5. Future perspectives

Given MenSCs have the angiogenesis, tissue regeneration, and immunomodulatory properties, MenSCs may also prevent fibrosis formation after surgery. For instance, intrauterine administration after adhesion removal surgery could enhance the therapeutic outcomes of the surgery. From a similar perspective, preventive treatments to avert adhesions after hysteroscopic surgeries—such as those performed for submucosal fibroids or endometrial polyps—could be a viable strategy to prevent the progression to AS.

MenSCs are widely utilized in preclinical research, demonstrating practical therapeutic functions not only for AS but also for other diseases, including liver diseases, diabetes, stroke, Duchenne muscular dystrophy, ovarian-related disorders, myocardial infarction, Alzheimer's disease, acute lung injury, skin wounds, and endometriosis [17]. A search for MenSCs on ClinicalTrials.gov revealed clinical trials for ARDS and type 1 diabetes conducted in various countries (https://clinicaltrials.gov/, accessed on Sep 23rd, 2024).

For clinical application, exploring the precise signaling pathways of MenSCs and improving the microenvironment to maintain stem cell functions are essential. Because MenSCs are derived from donors with varying age and environmental conditions (e.g., epidemiological background, age, and hormonal status), establishing standard criteria for MenSCs collection, identifying optimal molecular markers, and further verifying active components are essential. These investigations are expected to significantly

contribute to the development and clinical application of treatments using MenSCs in regenerative medicine.

6. Conclusions

The current treatment approaches for AS and their limitations are discussed, focusing on the therapeutic strategies in employing MSCs, particularly MenSCs. MSCs, which can be isolated from various tissues, have attracted significant attention as a cell source for regenerative medicine. However, the clinical application of MSCs is often hampered by the invasiveness of tissue-harvesting procedures and the scarcity of tissues such as the placenta and umbilical cord. Conversely, products such as PRP and G-CSF have emerged. Although they are being studied extensively, they are used mainly in private practice in Japan and have yet to become standard treatments [118]. MenSCs address these limitations related to MSC tissue harvesting. With a focus on the high regenerative capacity of the endometrium, MenSCs offer a noninvasive, monthly renewable, and attractive source of MSCs. Future research should standardize the collection and isolation methods for MenSCs and deepen the understanding of their biological and functional characteristics, including proliferative capacity, angiogenic potential, differentiation ability, and immunomodulatory effects. Further investigations are desired to maintain or enhance these functions by optimizing the microenvironment. In addition, functional differences due to donor backgrounds and environmental conditions should be explored, and practical components should be identified. This will help identify critical cellular subpopulations involved in the various functions of MSCs and establish indicators for functional assessment.

Informed consent for participation and publication

Written informed consent was obtained from the patient the images and video.

Ethical statement

We did not require any research ethics approval for this review.

Author contributions

Conceptualization: SAK, SH, and RY; Collection of related reports: SAK and SH; Patient recruitment: HK; Project administration: SAK, SH, RY, HK, and AO; Supervision: AO; Writing—original draft: SAK; Writing—review and editing: SH, RY, HK, and AO. All the authors approved the final version of the manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, SAK used DeepL, Grammarly, and ChatGPT for English writing. After using DeepL, Grammarly, and ChatGPT, SAK reviewed and edited the content as needed and take full responsibility for the content of the publication.

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References

[1] Kliman HJ, Frankfurter D. Clinical approach to recurrent implantation failure: evidence-based evaluation of the endometrium. Fertil Steril 2019;111:618–28.
[2] Jabbour HN, Kelly RW, Fraser HM, Critchley HO. Endocrine regulation of menstruation. Endocr Rev 2006;27:17–46.
[3] Gargett CE. Uterine stem cells: what is the evidence? Hum Reprod Update 2007;13:87–101.
[4] Cervello I, Gil-Sanchis C, Santamaria X, Cabanillas S, Diaz A, Faus A, et al. Human CD133(+) bone marrow-derived stem cells promote endometrial proliferation in a murine model of Asherman syndrome. Fertil Steril 2015;104. 1552-60 e1-3.
[5] Liu KE, Hartman M, Hartman A, Luo ZC, Mahutte N. The impact of a thin endometrial lining on fresh and frozen-thaw IVF outcomes: an analysis of over 40 000 embryo transfers. Hum Reprod 2018;33:1883–8.
[6] Gargett CE, Ye L. Endometrial reconstruction from stem cells. Fertil Steril 2012;98:11–20.
[7] Benor A, Gay S, DeCherney A. An update on stem cell therapy for Asherman syndrome. J Assist Reprod Genet 2020;37:1511–29.
[8] Therapy. Japan society of gynecologic and obstetric endoscopy and minimally invasive therapy. In: JSGOE guidelines for endoscopic surgery in obstetrics and gynecology; 2019.
[9] Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome–one century later. Fertil Steril 2008;89:759–79.
[10] Zhang SS, Xia WT, Xu J, Xu HL, Lu CT, Zhao YZ, et al. Three-dimensional structure micelles of heparin-poloxamer improve the therapeutic effect of 17beta-estradiol on endometrial regeneration for intrauterine adhesions in a rat model. Int J Nanomed 2017;12:5643–57.
[11] Kim H, Shin JE, Koo HS, Kwon H, Choi DH, Kim JH. Effect of autologous platelet-rich plasma treatment on refractory thin endometrium during the frozen embryo transfer cycle: a pilot study. Front Endocrinol 2019;10:61.
[12] Ranisavljevic N, Raad J, Anahory T, Grynberg M, Sonigo C. Embryo transfer strategy and therapeutic options in infertile patients with thin endometrium: a systematic review. J Assist Reprod Genet 2019;36:2217–31.
[13] Jensen JR, Witz CA, Schenken RS, Tekmal RR. A potential role for colony-stimulating factor 1 in the genesis of the early endometriotic lesion. Fertil Steril 2010;93:251–6.
[14] Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: a pilot study. JBRA Assist Reprod 2017;21:54–6.
[15] Gharibeh N, Aghebati-Maleki L, Madani J, Pourakbari R, Yousefi M, Ahmadian Heris J. Cell-based therapy in thin endometrium and Asherman syndrome. Stem Cell Res Ther 2022;13:33.
[16] Hosoya S, Yokomizo R, Kishigami H, Fujiki Y, Kaneko E, Amita M, et al. Novel therapeutic strategies for injured endometrium: intrauterine transplantation of menstrual blood-derived cells from infertile patients. Stem Cell Res Ther 2023;14:297.
[17] Sanchez-Mata A, Gonzalez-Munoz E. Understanding menstrual blood-derived stromal/stem cells: definition and properties. Are we rushing into their therapeutic applications? iScience 2021;24:103501.
[18] Khoury M, Alcayaga-Miranda F, Illanes SE, Figueroa FE. The promising potential of menstrual stem cells for antenatal diagnosis and cell therapy. Front Immunol 2014;5:205.
[19] Tan J, Li P, Wang Q, Li Y, Li X, Zhao D, et al. Autologous menstrual blood-derived stromal cells transplantation for severe Asherman's syndrome. Hum Reprod 2016;31:2723–9.
[20] Ma H, Liu M, Li Y, Wang W, Yang K, Lu L, et al. Intrauterine transplantation of autologous menstrual blood stem cells increases endometrial thickness and pregnancy potential in patients with refractory intrauterine adhesion. J Obstet Gynaecol Res 2020;46:2347–55.
[21] Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 10 years. Hum Reprod Update 2016;22:137–63.
[22] Murakami K, Lee YH, Lucas ES, Chan YW, Durairaj RP, Takeda S, et al. Decidualization induces a secretome switch in perivascular niche cells of the human endometrium. Endocrinology 2014;155:4542–53.
[23] Tempest N, Hill CJ, Maclean A, Marston K, Powell SG, Al-Lamee H, et al. Novel microarchitecture of human endometrial glands: implications in endometrial regeneration and pathologies. Hum Reprod Update 2022;28:153–71.
[24] Gray CA, Bartol FF, Tarleton BJ, Wiley AA, Johnson GA, Bazer FW, et al. Developmental biology of uterine glands. Biol Reprod 2001;65:1311–23.

[25] Cooke PS, Spencer TE, Bartol FF, Hayashi K. Uterine glands: development, function and experimental model systems. Mol Hum Reprod 2013;19:547–58.
[26] Maruyama T, Yoshimura Y. Stem cell theory for the pathogenesis of endometriosis. Front Biosci (Elite Ed) 2012;4:2754–63.
[27] Padykula HA. Regeneration in the primate uterus: the role of stem cells. Ann N Y Acad Sci 1991;622:47–56.
[28] Nguyen HP, Sprung CN, Gargett CE. Differential expression of Wnt signaling molecules between pre- and postmenopausal endometrial epithelial cells suggests a population of putative epithelial stem/progenitor cells reside in the basalis layer. Endocrinology 2012;153:2870–83.
[29] Valentijn AJ, Palial K, Al-Lamee H, Tempest N, Drury J, Von Zglinicki T, et al. SSEA-1 isolates human endometrial basal glandular epithelial cells: phenotypic and functional characterization and implications in the pathogenesis of endometriosis. Hum Reprod 2013;28:2695–708.
[30] Nguyen HPT, Xiao L, Deane JA, Tan KS, Cousins FL, Masuda H, et al. N-cadherin identifies human endometrial epithelial progenitor cells by in vitro stem cell assays. Hum Reprod 2017;32:2254–68.
[31] Yamaguchi M, Yoshihara K, Suda K, Nakaoka H, Yachida N, Ueda H, et al. Three-dimensional understanding of the morphological complexity of the human uterine endometrium. iScience 2021;24:102258.
[32] Gargett CE, Masuda H. Adult stem cells in the endometrium. Mol Hum Reprod 2010;16:818–34.
[33] Evans J, Salamonsen LA. Inflammation, leukocytes and menstruation. Rev Endocr Metab Disord 2012;13:277–88.
[34] Evans J, Salamonsen LA, Winship A, Menkhorst E, Nie G, Gargett CE, et al. Fertile ground: human endometrial programming and lessons in health and disease. Nat Rev Endocrinol 2016;12:654–67.
[35] Gaide Chevronnay HP, Galant C, Lemoine P, Courtoy PJ, Marbaix E, Henriet P. Spatiotemporal coupling of focal extracellular matrix degradation and reconstruction in the menstrual human endometrium. Endocrinology 2009;150:5094–105.
[36] Gargett CE. Review article: stem cells in human reproduction. Reprod Sci 2007;14:405–24.
[37] Schwab KE, Chan RW, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. Fertil Steril 2005;84(Suppl 2):1124–30.
[38] Spitzer TL, Rojas A, Zelenko Z, Aghajanova L, Erikson DW, Barragan F, et al. Perivascular human endometrial mesenchymal stem cells express pathways relevant to self-renewal, lineage specification, and functional phenotype. Biol Reprod 2012;86:58.
[39] Masuda H, Anwar SS, Buhring HJ, Rao JR, Gargett CE. A novel marker of human endometrial mesenchymal stem-like cells. Cell Transplant 2012;21:2201–14.
[40] Gurung S, Williams S, Deane JA, Werkmeister JA, Gargett CE. The transcriptome of human endometrial mesenchymal stem cells under TGFbetaR inhibition reveals improved potential for cell-based therapies. Front Cell Dev Biol 2018;6:164.
[41] Ulrich D, Edwards SL, Su K, Tan KS, White JF, Ramshaw JA, et al. Human endometrial mesenchymal stem cells modulate the tissue response and mechanical behavior of polyamide mesh implants for pelvic organ prolapse repair. Tissue Eng 2014;20:785–98.
[42] Bozorgmehr M, Gurung S, Darzi S, Nikoo S, Kazemnejad S, Zarnani AH, et al. Endometrial and menstrual blood mesenchymal stem/stromal cells: biological properties and clinical application. Front Cell Dev Biol 2020;8:497.
[43] Darzi S, Werkmeister JA, Deane JA, Gargett CE. Identification and characterization of human endometrial mesenchymal stem/stromal cells and their potential for cellular therapy. Stem Cells Transl Med 2016;5:1127–32.
[44] Asherman JG. Amenorrhoea traumatica (atretica). J Obstet Gynaecol Br Emp 1948;55:23–30.
[45] Hanstede MMF, van der Meij E, Veersema S, Emanuel MH. Live births after Asherman syndrome treatment. Fertil Steril 2021;116:1181–7.
[46] Ad A. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, mullerian anomalies and intrauterine adhesions. Fertil Steril 1988;49:944–55.
[47] Dreisler E, Kjer JJ. Asherman's syndrome: current perspectives on diagnosis and management. Int J Womens Health 2019;11:191–8.
[48] World Health Organization. Infertility prevalence estimates, 1990–2021. 2023.
[49] National Institute of Population and Social Security Research. 16th basic survey of birth trends. 2024.
[50] Hooker A, Fraenk D, Brolmann H, Huirne J. Prevalence of intrauterine adhesions after termination of pregnancy: a systematic review. Eur J Contracept Reprod Health Care 2016;21:329–35.
[51] Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update 2014;20:262–78.
[52] Westendorp IC, Ankum WM, Mol BW, Vonk J. Prevalence of Asherman's syndrome after secondary removal of placental remnants or a repeat curettage for incomplete abortion. Hum Reprod 1998;13:3347–50.
[53] Poujade O, Grossetti A, Mougel L, Ceccaldi PF, Ducarme G, Luton D. Risk of synechiae following uterine compression sutures in the management of major postpartum haemorrhage. BJOG 2011;118:433–9.
[54] Rasheed SM, Amin MM, Abd Ellah AH, Abo Elhassan AM, El Zahry MA, Wahab HA. Reproductive performance after conservative surgical treatment of postpartum hemorrhage. Int J Gynaecol Obstet 2014;124:248–52.
[55] Awano-Kim S, Kasahara Y, Hosoya S, Yokomizo R, Kishi H, Okamoto A. A retrospective analysis for acute and non-acute postoperative complications following transcervical resection, vol. 76; 2024. S-357.
[56] Taskin O, Sadik S, Onoglu A, Gokdeniz R, Erturan E, Burak F, et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. J Am Assoc Gynecol Laparoscopists 2000;7:351–4.
[57] Khan Z. Etiology, risk factors, and management of asherman syndrome. Obstet Gynecol 2023;142:543–54.
[58] Santamaria X, Isaacson K, Simon C. Asherman's Syndrome: it may not be all our fault. Hum Reprod 2018;33:1374–80.
[59] Ning J, Zhang H, Yang H. MicroRNA-326 inhibits endometrial fibrosis by regulating TGF-beta1/Smad3 pathway in intrauterine adhesions. Mol Med Rep 2018;18:2286–92.
[60] Zhou Q, Wu X, Hu J, Yuan R. Abnormal expression of fibrosis markers, estrogen receptor alpha and stromal derived factor-1/chemokine (C-X-C motif) receptor-4 axis in intrauterine adhesions. Int J Mol Med 2018;42:81–90.
[61] Feng D, Li Y, Zheng H, Wang Y, Deng J, Liu T, et al. IL-4-induced M2 macrophages inhibit fibrosis of endometrial stromal cells. Reprod Biol 2024;24:100852.
[62] Santamaria X, Roson B, Perez-Moraga R, Venkatesan N, Pardo-Figuerez M, Gonzalez-Fernandez J, et al. Decoding the endometrial niche of Asherman's Syndrome at single-cell resolution. Nat Commun 2023;14:5890.
[63] Lv H, Zhao G, Jiang P, Wang H, Wang Z, Yao S, et al. Deciphering the endometrial niche of human thin endometrium at single-cell resolution. Proc Natl Acad Sci U S A 2022;119.
[64] Lei L, Lv Q, Jin Y, An H, Shi Z, Hu G, et al. Angiogenic microspheres for the treatment of a thin endometrium. ACS Biomater Sci Eng 2021;7:4914–20.
[65] Zong L, Zheng S, Meng Y, Tang W, Li D, Wang Z, et al. Integrated transcriptomic analysis of the miRNA-mRNA interaction network in thin endometrium. Front Genet 2021;12:589408.
[66] Chen K, Yu Q, Sha Q, Wang J, Fang J, Li X, et al. Single-cell transcriptomic analysis of immune cell dynamics in the healthy human endometrium. Biochem Biophys Rep 2024;39:101802.
[67] Von Woon E, Greer O, Shah N, Nikolaou D, Johnson M, Male V. Number and function of uterine natural killer cells in recurrent miscarriage and implantation failure: a systematic review and meta-analysis. Hum Reprod Update 2022;28:548–82.
[68] Sugimoto O. Diagnostic and therapeutic hysteroscopy for traumatic intrauterine adhesions. Am J Obstet Gynecol 1978;131:539–47.
[69] Cararach M, Penella J, Ubeda A, Labastida R. Hysteroscopic incision of the septate uterus: scissors versus resectoscope. Hum Reprod 1994;9:87–9.
[70] Rein DT, Schmidt T, Hess AP, Volkmer A, Schondorf T, Breidenbach M. Hysteroscopic management of residual trophoblastic tissue is superior to ultrasound-guided curettage. J Minim Invasive Gynecol 2011;18:774–8.
[71] Aagl Elevating Gynecologic Surgery. AAGL practice report: practice guidelines on intrauterine adhesions developed in collaboration with the European Society of Gynaecological Endoscopy (ESGE). Gynecol Surg 2017;14:6.
[72] Farimani M, Poorolajal J, Rabiee S, Bahmanzadeh M. Successful pregnancy and live birth after intrauterine administration of autologous platelet-rich plasma in a woman with recurrent implantation failure: a case report. Int J Reprod Biomed 2017;15:803–6.
[73] Srivastava A, Sengupta J, Kriplani A, Roy KK, Ghosh D. Profiles of cytokines secreted by isolated human endometrial cells under the influence of chorionic gonadotropin during the window of embryo implantation. Reprod Biol Endocrinol 2013;11:116.
[74] Fotouhi A, Maleki A, Dolati S, Aghebati-Maleki A, Aghebati-Maleki L. Platelet rich plasma, stromal vascular fraction and autologous conditioned serum in treatment of knee osteoarthritis. Biomed Pharmacother 2018;104:652–60.
[75] Meftahpour V, Malekghasemi S, Baghbanzadeh A, Aghebati-Maleki A, Pourakbari R, Fotouhi A, et al. Platelet lysate: a promising candidate in regenerative medicine. Regen Med 2021;16:71–85.
[76] Tian J, Lei XX, Xuan L, Tang JB, Cheng B. The effects of aging, diabetes mellitus, and antiplatelet drugs on growth factors and anti-aging proteins in platelet-rich plasma. Platelets 2019;30:773–92.
[77] Chang Y, Li J, Chen Y, Wei L, Yang X, Shi Y, et al. Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. Int J Clin Exp Med 2015;8:1286–90.
[78] Naghshineh E, Rouholamin S, Derakhshandeh Z. Hormone therapy with or without platelet-rich plasma (PRP) for treatment asherman syndrome; A randomized clinical trial. Adv Biomed Res 2023;12:17.
[79] Tang R, Xiao X, He Y, Qiu D, Zhang W, Wang X. Clinical evaluation of autologous platelet-rich plasma therapy for intrauterine adhesions: a systematic review and meta-analysis. Front Endocrinol 2023;14:1183209.
[80] Gomez Raposo C, Pinto Marin A, Gonzalez Baron M. Colony-stimulating factors: clinical evidence for treatment and prophylaxis of chemotherapy-induced febrile neutropenia. Clin Transl Oncol 2006;8:729–34.
[81] Gleicher N, Kim A, Michaeli T, Lee HJ, Shohat-Tal A, Lazzaroni E, et al. A pilot cohort study of granulocyte colony-stimulating factor in the treatment of unresponsive thin endometrium resistant to standard therapies. Hum Reprod 2013;28:172–7.

[82] Barad DH, Yu Y, Kushnir VA, Shohat-Tal A, Lazzaroni E, Lee HJ, et al. A randomized clinical trial of endometrial perfusion with granulocyte colony-stimulating factor in in vitro fertilization cycles: impact on endometrial thickness and clinical pregnancy rates. Fertil Steril 2014;101:710–5.
[83] Zhang Y, Chen X, Chen S, Wei C, Li B, Wang Z, et al. Intrauterine administration of G-CSF for promoting endometrial growth after hysteroscopic adhesiolysis: a randomized controlled trial. Hum Reprod 2022;37:725–33.
[84] Kuramoto G, Takagi S, Ishitani K, Shimizu T, Okano T, Matsui H. Preventive effect of oral mucosal epithelial cell sheets on intrauterine adhesions. Hum Reprod 2015;30:406–16.
[85] Xia S, Wu M, Zhou X, Zhang X, Ye L, Zhang K, et al. Treating intrauterine adhesion using conditionally reprogrammed physiological endometrial epithelial cells. Stem Cell Res Ther 2022;13:178.
[86] Riaz MA, Kary FL, Jensen A, Zeppernick F, Meinhold-Heerlein I, Konrad L. Long-term maintenance of viable human endometrial epithelial cells to analyze estrogen and progestin effects. Cells 2024;13.
[87] Yokomizo R, Fujiki Y, Kishigami H, Kishi H, Kiyono T, Nakayama S, et al. Endometrial regeneration with endometrial epithelium: homologous orchestration with endometrial stroma as a feeder. Stem Cell Res Ther 2021;12:130.
[88] Wang F, Gao L, Fu X, Yan Q, Hu L, Mao J. Comparison of two representative methods for differentiation of human induced pluripotent stem cells into mesenchymal stromal cells. J Vis Exp 2023. https://doi.org/10.3791/65729.
[89] Zhang L, Li Y, Dong YC, Guan CY, Tian S, Lv XD, et al. Transplantation of umbilical cord-derived mesenchymal stem cells promotes the recovery of thin endometrium in rats. Sci Rep 2022;12:412.
[90] Song YT, Liu PC, Tan J, Zou CY, Li QJ, Li-Ling J, et al. Stem cell-based therapy for ameliorating intrauterine adhesion and endometrium injury. Stem Cell Res Ther 2021;12:556.
[91] Alawadhi F, Du H, Cakmak H, Taylor HS. Bone Marrow-Derived Stem Cell (BMDSC) transplantation improves fertility in a murine model of Asherman's syndrome. PLoS One 2014;9:e96662.
[92] Yotsumoto F, Iwaguro H, Harada Y, Sobajima S, Suwabe T, Miyamoto S. Adipose tissue-derived regenerative cells improve implantation of fertilized eggs in thin endometrium. Regen Med 2020;15:1891–904.
[93] Santamaria X, Cabanillas S, Cervello I, Arbona C, Raga F, Ferro J, et al. Autologous cell therapy with CD133+ bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: a pilot cohort study. Hum Reprod 2016;31:1087–96.
[94] Singh N, Mohanty S, Seth T, Shankar M, Bhaskaran S, Dharmendra S. Autologous stem cell transplantation in refractory Asherman's syndrome: a novel cell based therapy. J Hum Reprod Sci 2014;7:93–8.
[95] Kaczynski JB, Rzepka JK. Endometrial regeneration in Asherman's syndrome and endometrial atrophy using Wharton's jelly-derived mesenchymal stem cells. Ginekol Pol 2022;93:904–9.
[96] Cui CH, Uyama T, Miyado K, Terai M, Kyo S, Kiyono T, et al. Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation. Mol Biol Cell 2007;18:1586–94.
[97] Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, et al. Endometrial regenerative cells: a novel stem cell population. J Transl Med 2007;5:57.
[98] Darzi S, Zarnani AH, Jeddi-Tehrani M, Entezami K, Mirzadegan E, Akhondi MM, et al. Osteogenic differentiation of stem cells derived from menstrual blood versus bone marrow in the presence of human platelet releasate. Tissue Eng 2012;18:1720–8.
[99] Khanjani S, Khanmohammadi M, Zarnani AH, Akhondi MM, Ahani A, Ghaempanah Z, et al. Comparative evaluation of differentiation potential of menstrual blood- versus bone marrow-derived stem cells into hepatocyte-like cells. PLoS One 2014;9:e86075.
[100] Wyatt KA, Filby CE, Davies-Tuck ML, Suke SG, Evans J, Gargett CE. Menstrual fluid endometrial stem/progenitor cell and supernatant protein content: cyclical variation and indicative range. Hum Reprod 2021;36:2215–29.
[101] Zhu H, Pan Y, Jiang Y, Li J, Zhang Y, Zhang S. Activation of the Hippo/TAZ pathway is required for menstrual stem cells to suppress myofibroblast and inhibit transforming growth factor beta signaling in human endometrial stromal cells. Hum Reprod 2019;34:635–45.
[102] Alcayaga-Miranda F, Cuenca J, Luz-Crawford P, Aguila-Diaz C, Fernandez A, Figueroa FE, et al. Characterization of menstrual stem cells: angiogenic effect, migration and hematopoietic stem cell support in comparison with bone marrow mesenchymal stem cells. Stem Cell Res Ther 2015;6:32.
[103] Cuenca J, Le-Gatt A, Castillo V, Belletti J, Diaz M, Kurte GM, et al. The reparative abilities of menstrual stem cells modulate the wound matrix signals and improve cutaneous regeneration. Front Physiol 2018;9:464.
[104] Luz-Crawford P, Torres MJ, Noel D, Fernandez A, Toupet K, Alcayaga-Miranda F, et al. The immunosuppressive signature of menstrual blood mesenchymal stem cells entails opposite effects on experimental arthritis and graft versus host diseases. Stem Cell 2016;34:456–69.
[105] Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med 2006;12:1065–74.
[106] Dosiou C, Giudice LC. Natural killer cells in pregnancy and recurrent pregnancy loss: endocrine and immunologic perspectives. Endocr Rev 2005;26:44–62.
[107] Shokri MR, Bozorgmehr M, Ghanavatinejad A, Falak R, Aleahmad M, Kazemnejad S, et al. Human menstrual blood-derived stromal/stem cells modulate functional features of natural killer cells. Sci Rep 2019;9:10007.
[108] Xu X, Wang Y, Zhang B, Lan X, Lu S, Sun P, et al. Treatment of experimental colitis by endometrial regenerative cells through regulation of B lymphocytes in mice. Stem Cell Res Ther 2018;9:146.
[109] Shao X, Ai G, Wang L, Qin J, Li Y, Jiang H, et al. Adipose-derived stem cells transplantation improves endometrial injury repair. Zygote 2019;27:367–74.
[110] Zhang Y, Lin X, Dai Y, Hu X, Zhu H, Jiang Y, et al. Endometrial stem cells repair injured endometrium and induce angiogenesis via AKT and ERK pathways. Reproduction 2016;152:389–402.
[111] Chang QY, Zhang SW, Li PP, Yuan ZW, Tan JC. Safety of menstrual blood-derived stromal cell transplantation in treatment of intrauterine adhesion. World J Stem Cell 2020;12:368–80.
[112] Sudoma IGY, Pylyp L, Kremenska Y. Application of autologous adipose-derived stem cells for thin endometrium treatment in patients with failed ART programs. J Stem Cell Ther Transplant 2019;3:1–8.
[113] Yotsumoto F, Yoshikawa K, Hirakawa T, Urushiyama D, Kiyoshima C, Arima H, et al. Safety and potential effect of intrauterine infusion of autologous adipose tissue-derived regenerative cells in patients with implantation failure: a pilot study. Cureus 2024;16:e57220.
[114] Huang J, Li Q, Yuan X, Liu Q, Zhang W, Li P. Intrauterine infusion of clinically graded human umbilical cord-derived mesenchymal stem cells for the treatment of poor healing after uterine injury: a phase I clinical trial. Stem Cell Res Ther 2022;13:85.
[115] Cao Y, Sun H, Zhu H, Zhu X, Tang X, Yan G, et al. Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial. Stem Cell Res Ther 2018;9:192.
[116] Takagi R, Yamato M, Murakami D, Kondo M, Ohki T, Sasaki R, et al. Fabrication and validation of autologous human oral mucosal epithelial cell sheets to prevent stenosis after esophageal endoscopic submucosal dissection. Pathobiology 2011;78:311–9.
[117] Miura T, Kouno T, Takano M, Kuroda T, Yamamoto Y, Kusakawa S, et al. Single-cell RNA-seq reveals LRRC75A-expressing cell population involved in VEGF secretion of multipotent mesenchymal stromal/stem cells under ischemia. Stem Cells Transl Med 2023;12:379–90.
[118] Hosoya S, Awano-Kim S, Yokomizo R, Ukon Y, Morita K, Kasahara Y, et al. Regenerative medicine in Obstetrics & Gynecology: current status under the act on the safety of regenerative medicine in Japan. Regen Ther 2024;26:564–70.