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Stem Cell Therapy for Endometrial Regeneration in Asherman Syndrome and Female Infertility

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Abstract

Asherman syndrome is a gynecologic condition characterized by intrauterine adhesions that impair endometrial regeneration and are associated with infertility, menstrual abnormalities, and adverse reproductive outcomes. Current treatments, including hysteroscopic adhesiolysis and hormonal therapy, primarily aim to restore uterine cavity structure but often fail to achieve full functional regeneration of the endometrium, particularly in patients with moderate to severe disease. This paper examines the underlying pathophysiology of Asherman syndrome, emphasizing the role of basal layer damage, impaired vascularization, fibrosis, and disrupted stem cell activity in limiting endometrial repair. Stem cell–based therapies have emerged as a promising regenerative approach to address these limitations. Evidence from preclinical models demonstrates that mesenchymal stem cells and related therapies can promote angiogenesis, reduce fibrosis, enhance cellular proliferation, and improve endometrial thickness and gland formation. Early clinical studies further suggest improvements in menstrual function, endometrial receptivity, and pregnancy outcomes in patients with treatment-resistant disease. However, current findings remain limited by heterogeneity in study design, variability in cell sources and delivery methods, and a lack of standardized protocols and long-term safety and efficacy data. Overall, stem cell–based therapies represent a potential shift toward regenerative treatment strategies for Asherman syndrome. Continued research focused on standardization, optimization of delivery systems, and large-scale clinical trials will be essential to determine their clinical applicability and long-term impact on reproductive outcomes.

Keywords: Asherman syndrome, endometrial regeneration, stem cell therapy, intrauterine adhesions, mesenchymal stem cells.

List of Abbreviations

AS – Asherman syndrome
IUA – Intrauterine adhesions
MSC – Mesenchymal stem cell
eMSC – Endometrial mesenchymal stem/stromal cell
MenSC – Menstrual fluid–derived mesenchymal stromal cell
BMSC – Bone marrow–derived stem cell
UC-MSC – Umbilical cord–derived mesenchymal stem cell
MBMSC – Menstrual blood–derived mesenchymal stem cell
cMSC – Clonal mesenchymal stem cell
hMSC – Heterogeneous mesenchymal stem cell
EV – Extracellular vesicle
MSC-Sec – Mesenchymal stem cell secretome
HA – Hyaluronic acid
IVF – In vitro fertilization
VEGF – Vascular endothelial growth factor
LIF – Leukemia inhibitory factor
TNF-α – Tumor necrosis factor alpha

IL-10 – Interleukin 10
CK18 – Cytokeratin 18
α-SMA – Alpha smooth muscle actin
SUSD2 – Sushi domain containing 2

Introduction

Background on Asherman Syndrome

Asherman syndrome is a gynecologic condition characterized by fibrous adhesions within the uterine cavity that develop following injury to the endometrial lining, most commonly after surgical procedures such as dilation and curettage [1]. Intrauterine adhesionsarebandsofscartissue that form when the normal repair process of the endometrium is disrupted after trauma, often extending into the basal layer and causing opposing uterine surfaces to fuse [2]. Asherman syndrome most frequently results from trauma to the endometrium following uterine instrumentation, particularly dilation and curettage performed after pregnancy loss or childbirth. Additional causes include other uterine surgeries, such as myomectomy or cesarean section, as well as intrauterine infection, all of which can disrupt normal endometrial repair and promote adhesion formation [1].

Intrauterine adhesions impair normal endometrial function by disrupting the basal layer and altering cellular organization, vascularization, and the regenerative capacity of the endometrium [3]. Clinically, Asherman syndrome is associated with menstrual disturbances such as hypomenorrhea or amenorrhea, infertility, recurrent pregnancy loss, and obstetric complications including abnormal placentation and preterm delivery. Although the true prevalence of intrauterine adhesions is difficult to determine due to asymptomatic cases, Asherman syndrome has been reported in up to 45% of women with infertility and occurs most commonly following pregnancy-related curettage, highlighting its clinical relevance in reproductive health [4].

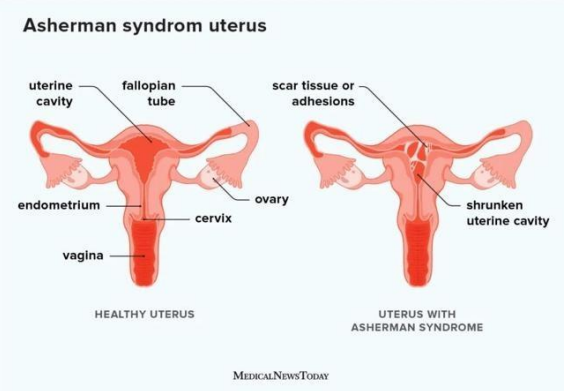

Figure 1: *Comparison of a normal uterine cavity and a uterus affected by Asherman syndrome, illustrating intrauterine adhesion formation and distortion of normal uterine anatomy. Reproduced from* Medical News Today (https://www.medicalnewstoday.com/articles/asherman-syndrome#overview).

Endometrial Structure and Regeneration

The human endometrium consists of a superficial functional layer that undergoes cyclical growth and shedding during the menstrual cycle and a deeper basal layer that remains intact and serves as the source for regeneration of the endometrial lining each cycle. The basal layer (stratum basalis) of the endometrium acts as a permanent regenerative reservoir that drives the repair and rebuilding of the functional layer (stratum functionalis) after it is shed during menstruation [6].

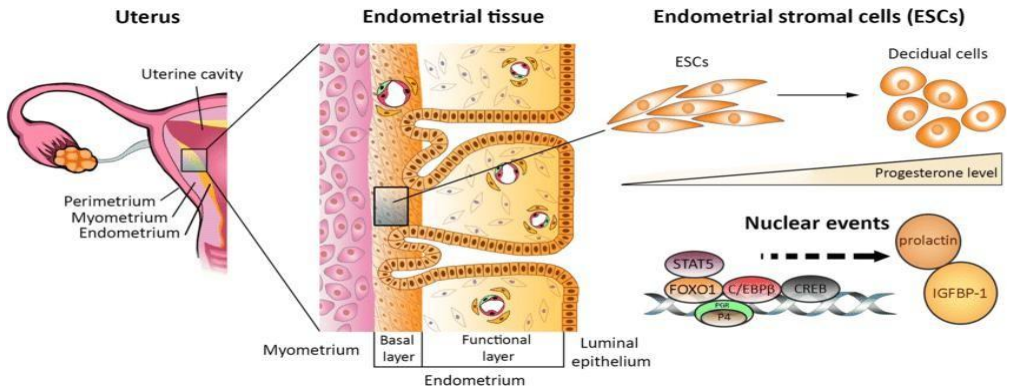

Figure 2: *Structure of the uterus and endometrium, illustrating the basal (stratum basalis) and functional (stratum functionalis) layers and their roles in endometrial regeneration. The basal layer serves as a regenerative source for rebuilding the functional layer following cyclical shedding. Adapted from* [7].

Endometrial growth and differentiation are tightly regulated by ovarian steroid hormones. Estrogen predominates during the proliferative phase of the menstrual cycle, stimulating cellular proliferation, glandular growth, and angiogenesis within the functional layer of the endometrium. Following ovulation, progesterone promotes differentiation and decidualization of the estrogen-primed endometrium during the secretory phase, preparing the uterus for potential implantation, withdrawal of progesterone triggers endometrial breakdown and menstruation [8].

Endometrial stem/progenitor cells are specialized cell populations with the ability to self-renew and differentiate into multiple endometrial cell types, playing a critical role in the cyclical regeneration of the endometrium. These cells are primarily located within the basal layer of the endometrium, which remains intact during menstruation, as well as in perivascular regions that support tissue repair. Endometrial stem/progenitor cells reside within specialized microenvironments known as stem cell niches that are composed of surrounding stromal cells, immune cells, endothelial cells, and extracellular matrix components that regulate stem cell behavior. Proper interaction between stem/progenitor cells and their niches is essential for maintaining normal endometrial structure and regenerative capacity. Disruption or damage to these stem cell populations or their niches, such as after uterine trauma or inflammation, can impair endometrial repair and contribute to pathological conditions including intrauterine adhesions and Asherman syndrome [9].

The human endometrium undergoes continuous recurrent regeneration throughout the menstrual cycle, characterized by estrogen-driven proliferation of the functional layer, progesterone-mediated differentiation during the secretory phase, and subsequent shedding and repair following progesterone withdrawal [8]. Adequate vascularization and stromal support are essential for normal endometrial regeneration, as stromal cells and endothelial networks regulate tissue remodeling, angiogenesis, and the microenvironment required for epithelial repair and implantation [9].

Current Treatments and Limitations

Hysteroscopic adhesiolysis is considered the standard first-line treatment for intrauterine adhesions and Asherman syndrome, as it allows direct visualization and surgical separation of adhesions with the goal of restoring normal uterine cavity anatomy [4]. Using a hysteroscope inserted trans cervically, fibrous adhesions are incised or removed to reestablish the normal contour of the uterine cavity. This approach is widely used in clinical practice due to its potential to improve menstrual function and reproductive outcomes. However, hysteroscopic adhesiolysis is technically challenging, particularly in cases of severe adhesions, and may be associated with risks such as endometrial injury and adhesion recurrence despite careful surgical technique [10].

Postoperative estrogen therapy is commonly used as an adjunctive treatment following hysteroscopic adhesiolysis to promote endometrial regeneration and reduce the risk of adhesion reformation. Estrogen is thought to stimulate endometrial proliferation and support restoration of the uterine lining after surgical trauma. However, estrogen therapy alone has not been shown to reliably prevent adhesion recurrence. Current evidence suggests that estrogen is most effective when used in combination with mechanical barriers such as intrauterine balloon catheters or intrauterine contraceptive devices, which physically separate opposing uterine walls during healing. The optimal estrogen dosage and treatment regimen remain unclear, and its role is considered supportive rather than definitive in the prevention of recurrent intrauterine adhesions [4].

Mechanical barriers represent a key postoperative strategy aimed at preventing reformation of intrauterine adhesions following hysteroscopic adhesiolysis. By maintaining separation of the uterine walls during the early healing phase, devices such as intrauterine balloon catheters and intrauterine contraceptive devices reduce contact between injured endometrial surfaces and limit scar formation. Despite their widespread use, mechanical barriers do not actively promote endometrial regeneration, and their effectiveness is reduced in patients with extensive basal layer damage. As a result, mechanical approaches are primarily preventative rather than restorative and are often insufficient to fully recover endometrial function in severe cases [4].

Assisted reproductive technologies such as in vitro fertilization are frequently employed in women with Asherman syndrome who desire pregnancy, particularly when spontaneous conception is unsuccessful. While IVF can bypass issues related to ovulation and fertilization, successful implantation and live birth depend heavily on endometrial thickness, receptivity, and structural integrity. In women with moderate to severe intrauterine adhesions, IVF outcomes are compromised, with reduced endometrial thickness, longer time to achieve live birth, and lower pregnancy rates compared with women without Asherman syndrome. These findings highlight the limitations of assisted reproductive technologies in overcoming underlying endometrial dysfunction [11].

Despite advances in hysteroscopic techniques and postoperative management, treatment outcomes for intrauterine adhesions remain highly variable. Success rates following adhesiolysis depend on factors such as adhesion severity, extent of basal layer damage, and postoperative healing. Recurrence of adhesions is common, particularly in patients with moderate to severe disease, often necessitating repeat surgical interventions [4].

In severe cases of Asherman syndrome, extensive damage to the basal layer of the endometrium results in impaired regenerativecapacityandreplacement of normal endometrial tissue with fibrotic scar tissue. Severe intrauterine

adhesions are associated with reduced endometrial stem and progenitor cell populations, persistent inflammation, disrupted vascularization, and excessive extracellular matrix deposition, all of which hinder effective endometrial repair. Consequently, even after surgical adhesiolysis and hormonal therapy, endometrial regeneration may remain inadequate, contributing to poor reproductive outcomes and high rates of adhesion recurrence [12].

Despite hysteroscopic adhesiolysis being the standard treatment approach, a substantial proportion of women with Asherman syndrome continue to experience infertility following intervention. Reported conception rates vary widely and are strongly influenced by disease severity, with significantly lower pregnancy rates observed in moderate and severe cases. Patients requiring repeat adhesiolysis demonstrate particularly poor reproductive outcomes, suggesting that persistent endometrial damage and adhesion reformation limit fertility restoration in severe disease [13].

Rationale for Stem Cell Therapy

Despite surgical and hormonal interventions, many patients with Asherman syndrome continue to experience inadequate endometrial function. Conventional treatments such as hysteroscopic adhesiolysis and estrogen therapy primarily focus on restoring uterine cavity anatomy but often fail to fully reestablish endometrial thickness, vascularization, and receptivity necessary for implantation. As a result, reproductive outcomes remain inconsistent, particularly in patients with severe disease. Increasing evidence indicates that persistent endometrial dysfunction is driven by irreversible basal layer damage, impaired stem cell activity, and abnormal stromal and vascular remodeling. These limitations highlight the need for novel therapies that not only prevent adhesion recurrence but actively restore functional endometrium capable of supporting normal menstrual cycling and pregnancy [14].

Stem cell–based therapies have therefore gained interest as a regenerative approach aimed at addressing the underlying cellular and structural defects in Asherman syndrome. Endometrial stem and progenitor cells possess the ability to self-renew and differentiate into epithelial, stromal, and endothelial cell types essential for normal endometrial structure and function. In cases of intrauterine adhesions, damage to the basal layer leads to depletion or dysfunction of these stem cell populations, limiting the endometrium's natural regenerative capacity. Preclinical studies have demonstrated that stem cell transplantation can reduce fibrosis, enhance angiogenesis, and increase endometrial thickness by promoting tissue repair through paracrine signaling, immunomodulation, and, to a lesser extent, differentiation into endometrial cell lineages. Early clinical studies using bone marrow-derived, menstrual blood-derived, and umbilical cord-derived stem cells have reported improvements in menstrual function, endometrial thickness, and pregnancy outcomes in women with refractory Asherman syndrome [15].

Beyond their capacity for differentiation, stem cell–based therapies promote endometrial regeneration through paracrine mechanisms that enhance angiogenesis and tissue repair. Experimental studies have demonstrated that stem cell-derived factors, including exosomes, can stimulate neovascularization, reduce fibrosis, and support structural remodeling of damaged endometrial tissue. In preclinical models of intrauterine adhesions, delivery of stem cell-derived exosomes has been shown to induce uterine angiogenesis, promote collagen remodeling, enhance endometrial regeneration, and improve endometrial receptivity, ultimately contributing to recovery of fertility. These findings underscore the importance of angiogenesis and stromal remodeling as key mechanisms underlying stem cell-mediated endometrial repair [16].

Restoration of basal layer integrity represents a particularly critical therapeutic target in severe Asherman syndrome. Endometrial stem and progenitor cells residing within the basal layer play a central role in driving cyclical endometrial regeneration, and their loss or dysfunction has been proposed as a major factor underlying impaired endometrial repair following uterine trauma. Regenerative strategies aimed at replenishing or reactivating these cell populations may therefore offer therapeutic potential for restoring basal layer function and overcoming the limitations of conventional treatments [6].

Among the various stem cell populations investigated, mesenchymal stem cells (MSCs) have emerged as a promising candidate for uterine repair due to their ability to self-renew, differentiate into multiple cell lineages, and modulate tissue repair processes. In the context of endometrial injury, MSCs promote regeneration primarily through paracrine signaling, immunomodulation, and support of angiogenesis rather than direct differentiation alone. Preclinical and early clinical studies suggest that MSC-based therapies may improve endometrial thickness, reduce fibrosis, and enhance endometrial receptivity in cases of intrauterine adhesions and Asherman syndrome, particularly when conventional surgical and hormonal treatments fail. Collectively, these findings from preclinical models and early clinical investigations support the therapeutic potential of MSC-based approaches for endometrial regeneration in Asherman syndrome [17].

Importantly, regenerative therapies may also offer benefits for fertility restoration in refractory cases. In a prospective study evaluating autologous bone marrow-derived stem cell therapy in women with refractory intrauterine adhesions and endometrial atrophy, significant improvements in endometrial thickness and menstrual function were observed following treatment. Notably, a subset one of patients achieved successful pregnancies, including both spontaneous conception and pregnancies following in vitro fertilization, indicating partial restoration of endometrial receptivity. Although overall pregnancy rates remained modest and outcomes were influenced by disease severity, these findings support the potential role of stem cell-based

therapies in improving fertility outcomes in patients with severe or treatment-resistant Asherman syndrome [18].

Discussion

Current Clinical Management of Asherman Syndrome

Current clinical management of Asherman syndrome focuses on restoring uterine cavity anatomy and preventing recurrence of intrauterine adhesions. Hysteroscopic adhesiolysis is considered the standard first-line intervention, allowing direct visualization and surgical separation of adhesions within the uterine cavity. Adjunctive postoperative strategies commonly include estrogen therapy to promote endometrial proliferation and the use of mechanical barriers, such as intrauterine devices or balloon catheters, to reduce adhesion reformation during healing. In patients who continue to experience infertility following surgical management, assisted reproductive technologies, including in vitro fertilization, are often employed to facilitate conception.

Limitations of Conventional Therapies

Despite advances in surgical techniques and postoperative management, clinical outcomes following conventional treatment for Asherman syndrome remain highly variable, particularly in patients with moderate to severe disease. Recurrence of intrauterine adhesions is common after hysteroscopic adhesiolysis, and treatment success is strongly influenced by the severity of disease, extent of basal layer damage, and the endometrium's limited regenerative capacity in severe cases. Importantly, current interventions primarily aim to restore uterine cavity anatomy and prevent adhesion recurrence, but they do not actively regenerate damaged endometrial tissue or repair the basal layer required for sustained endometrial function.

Rationale for Regenerative Therapies

The limitations of conventional surgical and hormonal treatments for Asherman syndrome have driven increasing interest in regenerative strategies aimed at restoring functional endometrium rather than merely preventing adhesion recurrence. Among these approaches, stem cell–based therapies have emerged as a promising strategy due to their regenerative potential, ability to modulate tissue repair processes, and capacity to address the underlying endometrial damage characteristic of severe Asherman syndrome.

Stem Cell–Based Therapies for Endometrial Regeneration

Stem cell–based therapies have been investigated as a regenerative approach for Asherman syndrome with the goal of restoring endometrial structure, enhancing vascularization, and improving functional recovery of the uterine lining.

Evidence from Preclinical Studies

Preclinical studies using animal models of intrauterine adhesions have provided early evidence that stem cell–based therapies can promote endometrial regeneration, reduce fibrosis, and improve structural recovery of the uterine lining.

One preclinical strategy for intrauterine adhesions combines stem cells with a biomaterial scaffold to support cell retention and tissue repair. In a long-term rat model of intrauterine adhesion, Hu et al. transplanted collagen scaffolds loaded with human menstrual blood derived mesenchymal stem cells (MBMSCs) and assessed uterine healing 90 days later. The authors detected a human nuclear protein (HuNu) in treated uteri, supporting the presence of transplanted human cells in the uterine tissue after implantation. Compared with untreated model animals, MBMSC loaded collagen scaffolds increased the number of endometrial glands and significantly reduced fibrotic area on histology. Treatment also decreased collagen I expression (a fibrosis associated marker) and increased cytokeratin 18 (CK18), which is associated with glandular epithelial cells in the endometrium. Notably, the combined MBMSC plus scaffold condition produced stronger improvements in CK18 and fibrosis than either MBMSCs or scaffold alone, suggesting a synergistic benefit of scaffold assisted stem cell delivery for endometrial repair [19].

In a mechanically induced rat model of Asherman syndrome, it was evaluated whether mesenchymal stem cells (MSCs) or MSC derived extracellular vesicles (EVs) could prevent intrauterine adhesion formation and restore endometrial function. Following uterine mechanical injury, animals were treated immediately with a homogeneous population of human bone marrow derived clonal MSCs (cMSCs), heterogeneous parental MSCs (hMSCs), or EV subpopulations isolated at different centrifugation speeds (EV20K and EV110K). Two weeks after treatment, uterine repair was assessed using hematoxylin eosin staining for endometrial structure, Masson's trichrome staining and α SMA for fibrosis, and Ki67 immunostaining for cell proliferation. Functional recovery was also evaluated using mating trials and fertility outcomes. Compared with vehicle treated injured uteri, MSC and EV treated groups showed improved endometrial morphology, including restoration of gland number and endometrial thickness with reduced fibrotic area, along with increased proliferative activity. Importantly, reproductive function improved after treatment, with higher delivery rates in cMSC treated animals compared with vehicle controls, and the cMSC group also demonstrated the greatest improvement in cumulative number of pups. At the molecular level, treatment was associated with decreased TNF α and increased IL 10, as well as increased VEGF and LIF, supporting a shift toward a less inflammatory and more receptive endometrial environment. Overall, these findings provide preclinical evidence that MSC based interventions, particularly clonal MSCs and selected EV fractions, can promote structural repair and partial functional restoration of the injured endometrium *in vivo* [21].

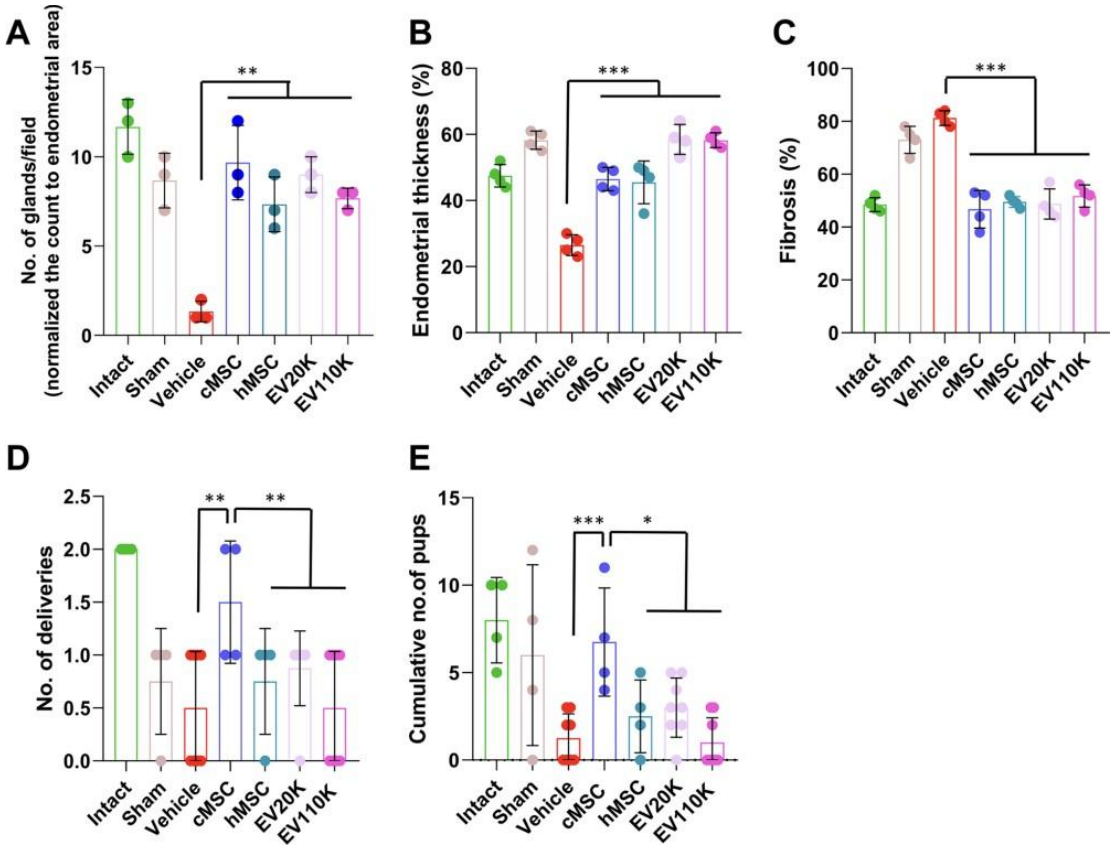

Figure 3: *Quantification of histologic recovery and fertility outcomes in a rat model of intrauterine adhesions following treatment with mesenchymal stem cells (cMSCs, hMSCs) or MSC derived extracellular vesicles (EV20K, EV110K). Outcomes include (A) endometrial glands per field, (B) endometrial thickness, (C) fibrosis percentage, (D) number of deliveries, and (E) cumulative number of pups across experimental groups. Reproduced from [21].*

In a mechanically induced rat model of intrauterine adhesions it was tested whether a collagen scaffold could improve the effectiveness of human umbilical cord mesenchymal stem cells (hUCMSCs) by increasing cell retention at the injury site. Rats received collagen scaffold alone, hUCMSCs alone, or a combined hUCMSC loaded collagen scaffold after injury. The combined scaffold plus hUCMSC group showed significantly greater recovery, with increased endometrial thickness and gland number, increased blood vessel abundance, and reduced endometrial fibrosis compared with either treatment alone. The authors also reported increased expression of markers associated with receptivity and repair, including Vegf, Integrin β3, Lif, and Igf 1, supporting improved endometrial receptivity after treatment. Overall, these findings reinforce the idea that scaffold assisted stem cell delivery can strengthen structural repair and functional recovery in IUA models. Figure 3 visually summarizes this effect, showing that the collagen scaffold + hUCMSC group has a more restored endometrial structure with less collagen deposition (fibrosis) and higher endometrial thickness/ gland number than untreated IUA controls [22].

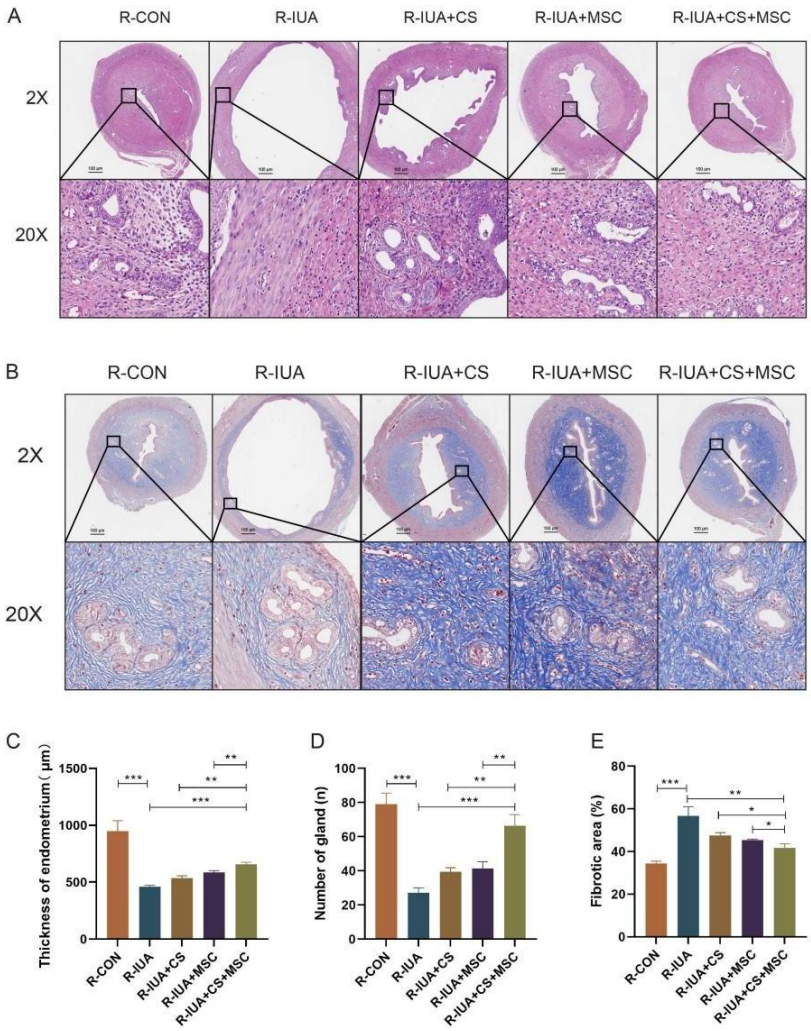

Figure 4: *Collagen scaffold combined with human umbilical cord mesenchymal stem cells improves endometrial repair in a rat intrauterine adhesion model. (A) H and E-stained uterine sections demonstrate restoration of endometrial morphology in the collagen scaffold plus hUCMSC group compared with untreated IUA controls. (B) Masson's trichrome staining shows reduced collagen deposition (fibrosis) with treatment. Quantification shows increased endometrial thickness (C), increased gland number (D), and decreased fibrotic area (E) in the collagen scaffold plus hUCMSC group relative to IUA controls. Reproduced from [22].*

In addition to stem cell and extracellular vesicle approaches, some preclinical work has focused on cell free regenerative therapies to avoid limitations of live cell delivery. In a rat model of endometrial injury intended to mimic Asherman syndrome, Liu et al. reported a sustained release system using mesenchymal stem cell secretome (MSC Sec) loaded into a crosslinked hyaluronic acid (HA) gel for intrauterine delivery. The authors note that while stem cell-based therapies are promising, they can be limited by low engraftment and practical issues related to storage and transportation, and that MSC Sec may offer a safer and more convenient alternative that can be stored without losing regenerative activity. After inducing uterine injury by electrocoagulation, rats were assigned to receive MSC Sec loaded HA gel, HA gel alone, or MSC Sec alone, with the contralateral uterine horn receiving PBS as an internal control. The crosslinked HA carrier was designed to prolong uterine retention and spread MSC Sec release over a 7-day period. Functionally, fertility was assessed by mating, and the MSC Sec plus HA gel condition produced a significantly higher number of fetuses on the treated side, whereas HA alone or MSC Sec alone did not produce a significant difference compared with PBS, suggesting that sustained delivery was important for efficacy. Consistent with these functional findings, the authors also report improved uterine repair with thicker endometrium, increased gland formation, and higher pregnancy success in the treatment group compared with controls [23].

Preclinical studies collectively suggest that stem cell-based strategies can promote meaningful structural and functional recovery after endometrial injury by addressing both tissue regeneration and the fibrotic, inflammatory environment that drives adhesion formation. Across models, three recurring approaches emerge: scaffold assisted delivery to improve cell retention and local repair, MSC and EV based therapies to reduce fibrosis and enhance proliferation and

receptivity signals, and cell free secretome delivery systems designed to provide sustained regenerative cues without the practical limitations of live cell transplantation. Although these studies differ in cell source and delivery method, they converge on similar outcomes including increased endometrial thickness and gland formation, decreased collagen deposition and fibrosis, and in some cases improved fertility endpoints. Together, these findings provide a strong rationale for continued translational work and help justify why regenerative therapies are being pursued as a potential option for treatment resistant Asherman syndrome.

Human Clinical Studies

One of the earliest human studies exploring regenerative cell therapy for refractory intrauterine adhesions evaluated autologous CD133+ bone marrow-derived stem cells delivered directly to the uterine vasculature. In this prospective, non-controlled pilot cohort, 18 patients with refractory Asherman syndrome or endometrial atrophy were enrolled and 16 completed follow-up. CD133+ cells were mobilized with granulocyte colony-stimulating factor, collected via peripheral blood apheresis, and infused into the uterine spiral arterioles by catheterization. Outcomes included menstrual changes, ultrasound-measured endometrial thickness, hysteroscopic assessment of the uterine cavity, and markers of neovascularization. Two months after therapy, patients with Asherman syndrome demonstrated improvement in uterine cavity appearance, and mean endometrial thickness increased from 4.3 mm to 6.7 mm ($P = 0.004$). Patients with endometrial atrophy also showed an increase in thickness (4.2 mm to 5.7 mm, $P = 0.03$). The authors reported increased mature vessel density and improved menstrual flow early after treatment, although these benefits tended to diminish toward baseline by 6 months. Pregnancies occurred both spontaneously and after embryo transfer, indicating potential improvement in endometrial receptivity in a subset of patients. However, interpretation is limited by the small sample size and lack of a control group, so the findings primarily support feasibility and a signal of benefit rather than definitive efficacy [20]. Although early CD133 plus studies suggested feasibility, subsequent human work has tested other cell sources and delivery strategies to improve endometrial thickness, uterine cavity architecture, and pregnancy outcomes.

A prospective, open-label randomized controlled trial evaluated the efficacy of autologous bone marrow stem cells (BMSCs) delivered on a collagen scaffold in women with moderate to severe intrauterine adhesions following hysteroscopic adhesiolysis. A total of 152 patients were randomized to receive either BMSCs-scaffold transplantation with a Foley balloon catheter or a Foley balloon catheter alone, with 140 participants included in the per-protocol analysis. The primary outcome was ongoing pregnancy, defined as the presence of fetal cardiac activity beyond 12 gestational weeks, assessed over a 24-month follow-up period. Ongoing pregnancy occurred in 62.5% of patients in the BMSCs-scaffold group compared with 41.2% in the control group (RR = 1.52, 95% CI 1.08–2.12), with a corresponding increase in live birth rate (56.9% vs. 38.2%). Secondary outcomes demonstrated greater improvements in menstrual volume and maximal endometrial thickness at six months post-procedure in the intervention group. No severe treatment-related adverse events were reported; however, a higher incidence of mild placenta accreta requiring manual placental removal was observed among patients receiving BMSCs-scaffold therapy. While this study provides the strongest clinical evidence to date supporting stem cell–based endometrial regeneration in Asherman syndrome, limitations include its open-label design, restriction to two centers, and limited representation of patients with the most severe adhesions, underscoring the need for further multicenter trials with longer obstetric follow-up [24].

A single-center before-and-after clinical study evaluated the therapeutic potential of autologous endometrial stem cells in 15 women with recurrent moderate to severe intrauterine adhesions. Endometrial stem cells were isolated from patient endometrial tissue obtained during hysteroscopic adhesiolysis, expanded in vitro, and subsequently infused into the uterine cavity in combination with sodium hyaluronate gel, estrogen, and low-dose acetylsalicylic acid. Within two years of treatment, all patients demonstrated reductions in American Fertility Society adhesion scores and hysteroscopic improvement of the uterine cavity. The overall pregnancy rate was 60.0%, with a live birth rate of 53.3%. Improvements in maximal endometrial thickness were observed in the majority of patients with thin endometrium, enabling embryo transfer in most cases. No serious adverse events related to stem cell infusion were reported. However, interpretation of these findings is limited by the small sample size, absence of a parallel control group, and concurrent use of adjunctive therapies, which precludes isolation of the independent effect of endometrial stem cell transplantation [25].

A prospective before-and-after pilot study evaluated the use of allogeneic umbilical cord–derived mesenchymal stem cells (UC-MSCs) seeded onto collagen scaffolds in women with unresponsive thin endometrium secondary to Asherman syndrome. Eighteen infertile women with persistent endometrial thickness ≤ 5.5 mm despite repeated hysteroscopic adhesiolysis and hormone therapy were enrolled, with sixteen completing the protocol. Participants underwent hysteroscopic transplantation of collagen scaffolds loaded with 20 million UC-MSCs over two consecutive menstrual cycles, followed by frozen–thawed embryo transfer where feasible. Three months after treatment, mean endometrial thickness increased significantly from 4.08 ± 0.26 mm to 5.87 ± 0.77 mm ($P < 0.001$). Of the fifteen patients who proceeded to embryo transfer, three achieved pregnancies, resulting in two live births and one second-trimester miscarriage; an additional spontaneous pregnancy occurred in a patient who did not undergo embryo transfer. No treatment-related serious adverse events were reported. Histological and immunohistochemical analyses demonstrated increased micro vessel density, gland number, and expression of Ki67,

estrogen receptor-α, and progesterone receptor, suggesting enhanced angiogenesis, cellular proliferation, and hormonal responsiveness following treatment. However, interpretation of clinical efficacy is limited by the small sample size, absence of a control group, and heterogeneity in reproductive outcomes, underscoring the need for larger randomized trials to clarify the therapeutic role and long-term safety of UC-MSC–based therapies in this population [26].

Advantages and Limitations of Stem Cell–Based Therapies for Asherman Syndrome

Stem cell–based therapies offer several potential advantages over conventional surgical and hormonal treatments for Asherman syndrome, particularly in patients with moderate to severe disease characterized by extensive endometrial damage and limited regenerative capacity. Current standard interventions, including hysteroscopic adhesiolysis and estrogen therapy, often yield inconsistent improvements in endometrial thickness and fertility outcomes, especially in refractory cases. In contrast, cell-based approaches aim to promote active tissue repair and regeneration rather than solely stimulating residual endometrium or preventing adhesion recurrence, making them particularly relevant for treatment-resistant Asherman syndrome [27, 28].

A major advantage of stem cell–based therapies is their ability to support endometrial regeneration primarily through paracrine mechanisms rather than direct cellular replacement. Mesenchymal stem cells secrete a broad array of cytokines, growth factors, and extracellular vesicles that promote angiogenesis, enhance cellular proliferation, and facilitate tissue remodeling within the damaged endometrium. These paracrine effects have been associated with increased endometrial thickness, improved glandular development, and enhanced vascularization in both preclinical models and early clinical studies, even when long-term engraftment of transplanted cells is limited [29-31]. This mechanism is particularly advantageous in fibrotic uterine environments, where structural damage may impede direct cell integration.

Stem cell–based therapies also demonstrate anti-fibrotic and immunomodulatory properties that directly target key pathological features of Asherman syndrome. Intrauterine adhesions are associated with excessive collagen deposition, chronic inflammation, and dysregulated immune signaling, all of which contribute to adhesion recurrence and impaired endometrial receptivity. Reviews of cell-based therapies report reductions in fibrotic markers alongside shifts toward a more favorable immune milieu, characterized by decreased pro-inflammatory Th1 and Th17 responses and increased regulatory T-cell and Th2 activity. These changes may help create a uterine microenvironment that supports sustained endometrial repair and implantation [27, 31].

Another important advantage of stem cell–based approaches is their potential to compensate for the loss or dysfunction of resident endometrial stem and progenitor cell populations following severe uterine injury. The endometrium is a highly regenerative tissue under normal conditions, with cyclical remodeling driven in part by basal layer stem cells. In Asherman syndrome, damage to this basal compartment disrupts normal regenerative processes, contributing to persistent thin endometrium and infertility. Stem cell therapies, including mesenchymal stem cells and endometrial-derived stem cells, may help restore regenerative signaling pathways and partially reestablish structural and functional integrity of the endometrium [28, 32].

Collectively, these advantages suggest that stem cell–based therapies address multiple dimensions of Asherman syndrome pathophysiology, including impaired regeneration, fibrosis, inflammation, and vascular insufficiency. By targeting underlying biological mechanisms rather than solely managing anatomical consequences, stem cell–based strategies represent a promising adjunct or alternative for patients with treatment-resistant disease. However, the clinical relevance of these advantages must be interpreted cautiously considering current limitations in human evidence, which are discussed in the following section [28, 30].

Limitations and Challenges of Stem Cell–Based Therapies in Asherman Syndrome

Despite the promising regenerative potential of stem cell–based therapies for Asherman syndrome, several limitations and challenges currently restrict their clinical translation. Reviews focused specifically on Asherman syndrome emphasize that existing human studies are highly heterogeneous, with substantial variation in stem cell source, delivery method, dosage, scaffold use, and adjunctive therapies, which complicates comparison across studies and limits reproducibility of outcomes [34,36]. Most available clinical investigations remain small, exploratory, or nonrandomized, with short follow-up periods and inconsistent outcome measures, including endometrial thickness, menstrual recovery, pregnancy, or live birth rates, making interpretation of long-term efficacy and functional endometrial regeneration challenging [34]. In addition, mechanistic reviews of endometrial repair highlight that severe intrauterine adhesions are characterized by extensive extracellular matrix remodeling and fibrosis, which disrupt the biomechanical and signaling environment required for effective regeneration [35]. As a result, stem cell transplantation alone may be insufficient to restore normal endometrial architecture if the underlying fibrotic matrix persists, contributing to the variable and often incomplete clinical responses observed in current studies [35].

In addition to limitations related to study design and efficacy, safety, ethical, and translational concerns remain important considerations. While serious adverse events have been uncommon in reported studies, long-term safety data are limited, particularly with respect to potential risks such as aberrant differentiation, ectopic

tissue formation, immunologic effects, and theoretical tumorigenicity associated with stem cell therapies [33,36]. Ethical and regulatory challenges further complicate clinical implementation, including variability in manufacturing standards, quality control, and regulatory oversight, as well as concerns surrounding unregulated or premature clinical use of stem cell–based interventions [33,36]. These issues are especially relevant in reproductive medicine, where therapeutic interventions may influence not only maternal health but also pregnancy outcomes and fetal development. Collectively, current evidence supports cautious optimism while underscoring the need for standardized protocols, rigorously designed randomized trials, and long-term follow-up before stem cell–based therapies can be widely adopted for the treatment of Asherman syndrome [34–36].

While stem cell–based therapies have emerged as a potential regenerative strategy for Asherman syndrome, several limitations and challenges currently restrict their clinical translation. Reviews focused specifically on Asherman syndrome emphasize that existing human studies are highly heterogeneous, with substantial variation in stem cell source, delivery method, dosage, scaffold use, and adjunctive therapies, which complicates comparison across studies and limits reproducibility of outcomes [34,36]. Most available clinical investigations remain small, exploratory, or nonrandomized, with short follow-up periods and inconsistent outcome measures, including endometrial thickness, menstrual recovery, pregnancy, or live birth rates, making interpretation of long-term efficacy and durable functional regeneration difficult [34]. Mechanistic reviews further indicate that severe intrauterine adhesions are characterized by extensive extracellular matrix remodeling, fibrosis, and disruption of the endometrial stem cell niche, which collectively create a hostile microenvironment that may limit cell engraftment, decidualization, and sustained tissue repair despite short-term structural improvement [35,37,38]. In addition to efficacy-related limitations, safety and ethical concerns remain important considerations. Although serious adverse events have been uncommon in reported studies, long-term safety data are limited, particularly regarding potential risks such as aberrant differentiation, ectopic tissue formation, immunologic effects, and theoretical tumorigenicity associated with stem cell therapies [33,36]. Ethical and regulatory challenges further complicate clinical implementation, including variability in manufacturing standards, quality control, and regulatory oversight, as well as concerns surrounding premature or unregulated clinical use [33,36]. Collectively, current evidence supports cautious optimism while underscoring the need for standardized protocols, rigorously designed randomized trials, and long-term follow-up before stem cell–based therapies can be widely adopted for the treatment of Asherman syndrome [34–38].

Future Research Directions

A key area of focus in future research for Asherman syndrome is the optimization and standardization of homologous endometrial-derived cell sources, particularly endometrial mesenchymal stem/stromal cells (eMSCs) and menstrual fluid–derived mesenchymal stromal cells (MenSCs). Reviews of endometrial-derived MSCs highlight their accessibility through minimally invasive biopsy or menstrual fluid collection and their relevance as tissue-specific regenerative agents for gynecological disorders, including intrauterine adhesions. Both eMSCs and MenSCs have been shown to exert therapeutic effects primarily through paracrine mechanisms, including immunomodulation, angiogenesis, and attenuation of fibrosis, rather than long-term engraftment, suggesting that optimization of cell quality and secretory function may be more critical than cell persistence. However, significant heterogeneity in MenSC populations and variability in isolation and expansion protocols currently limit reproducibility and clinical translation. Future studies in Asherman syndrome should therefore focus on establishing standardized isolation and characterization strategies, such as SUSD2-based cell sorting, alongside optimization of production, storage, and delivery methods to improve therapeutic consistency and scalability. Addressing these factors will be essential for the development of reliable, reproducible stem cell–based interventions tailored to the fibrotic and regenerative challenges of the Asherman syndrome uterus [39].

In addition to cell source optimization, advancing regenerative therapies for Asherman syndrome will require a shift from short-term anatomical repair toward strategies that support sustained endometrial function and healthy pregnancy outcomes. Although hysteroscopic adhesiolysis can restore uterine cavity patency, systematic analyses demonstrate that reproductive success after surgery alone remains inconsistent, with ongoing risks of implantation failure, abnormal placentation, and adverse obstetric outcomes [40]. These limitations underscore the need for adjunctive regenerative approaches capable of restoring endometrial receptivity and supporting long-term uterine function. At the same time, preclinical meta-analyses of mesenchymal stem cell–based therapies show consistent improvements in endometrial thickness, angiogenesis, fibrosis attenuation, and pregnancy rates following endometrial injury; however, these findings are derived almost entirely from animal models and display substantial heterogeneity in cell source, dose, delivery method, and study design [41]. Translating these promising results into clinical benefit for patients with Asherman syndrome will require well-powered, disease-specific trials that incorporate standardized protocols, clinically meaningful fertility endpoints, and extended obstetric follow-up. Future investigations should evaluate biomaterial- and scaffold-assisted delivery platforms that enhance local cell retention and modulate the fibrotic uterine microenvironment, which may be critical for achieving durable regeneration in severe intrauterine adhesions.

Further progress in this field will also depend on improving delivery strategies to enhance therapeutic efficacy within the damaged uterine environment. Emerging evidence suggests that scaffold-assisted stem cell delivery may play a critical role in enhancing treatment outcomes by

improving cell retention, survival, and localized regenerative signaling. A recent systematic review and meta-analysis demonstrated that stem cell–loaded scaffolds significantly improve endometrial thickness, gland formation, and fertility outcomes in models of endometrial injury; however, findings remain variable and are largely derived from preclinical or early-stage clinical data, emphasizing the need for standardized protocols and larger trials [42]. In parallel, recent developments in bio-scaffold materials highlight their potential to modulate the fibrotic and inflammatory microenvironment characteristic of severe intrauterine adhesions, thereby creating conditions more conducive to tissue repair and functional regeneration [43]. Future studies should therefore focus on integrating biomaterial-based delivery systems with stem cell therapies in well-designed, Asherman-specific clinical trials to determine whether these approaches can achieve durable restoration of endometrial function and improve long-term reproductive outcomes.

Another important direction involves optimizing delivery methods while also exploring cell-free regenerative approaches. Emerging evidence suggests that mesenchymal stem cell–derived extracellular vesicles may play a critical role in endometrial repair through paracrine signaling mechanisms that promote angiogenesis, reduce fibrosis, and enhance cellular regeneration [44]. Unlike whole-cell therapies, extracellular vesicles offer advantages such as lower immunogenicity and improved safety profiles, making them a promising alternative for clinical application. In preclinical models of intrauterine adhesion, extracellular vesicle–based therapies have demonstrated improved endometrial regeneration while avoiding key limitations associated with direct stem cell transplantation, such as poor cell survival and safety concerns [47]. In parallel, advances in biomaterials, including scaffold-based and hydrogel delivery systems, may further improve stem cell retention and function within the damaged endometrium [42,43]. However, translating these approaches into effective treatments for Asherman syndrome will require well-designed clinical trials that evaluate long-term reproductive outcomes and establish standardized therapeutic protocols.

At the same time, the successful clinical translation of stem cell–based therapies for Asherman syndrome will depend on addressing key challenges related to standardization, safety, and long-term efficacy. Current approaches remain highly variable in terms of cell source, dosing, delivery route, and adjunctive treatments, highlighting the need for standardized protocols to ensure reproducibility across studies. The clinical application of mesenchymal stem cells is further complicated by their inherent heterogeneity, as variations in cell source, donor characteristics, culture conditions, and expansion methods can significantly influence therapeutic outcomes [50]. Although early clinical findings suggest favorable safety profiles, long-term risks, including abnormal tissue remodeling, immunologic responses, and potential effects on pregnancy outcomes, remain insufficiently characterized. Future research should therefore prioritize large-scale, multicenter clinical trials with extended follow-up periods to evaluate both therapeutic durability and reproductive safety [49]. Stem cell therapy has been shown to improve key reproductive outcomes in patients with intrauterine adhesions, including pregnancy rates, live birth rates, menstrual recovery, and endometrial thickness; however, variability in treatment protocols and limited long-term data underscore the need for further rigorous investigation [51]. Establishing regulatory frameworks and consensus guidelines will also be critical for translating regenerative therapies into routine clinical practice for patients with Asherman syndrome. Broader evidence from reproductive medicine highlights the expanding role of regenerative therapies in addressing infertility and uterine disorders. Advances in induced pluripotent stem cells and mesenchymal stem cell–based approaches suggest potential for more personalized and scalable treatment strategies, although challenges related to safety, differentiation control, and clinical translation remain significant [45,46]. In addition, mesenchymal stem cell–derived secretomes and extracellular vesicles are emerging as promising cell-free therapeutic alternatives with potentially reduced safety risks; however, these approaches similarly require standardization and long-term evaluation before widespread clinical adoption [48]. Collectively, these findings emphasize the need for continued innovation alongside rigorous clinical validation to ensure the safe and effective integration of stem cell–based therapies into the management of Asherman syndrome.

Conclusion

Asherman syndrome remains a complex condition that significantly affects endometrial function and fertility, particularly in patients with moderate to severe disease. This paper highlights that while current treatments such as hysteroscopic adhesiolysis and hormonal therapy can restore uterine cavity structure; they often fail to achieve full functional regeneration of the endometrium. As a result, reproductive outcomes remain inconsistent, largely due to persistent basal layer damage, impaired vascularization, and reduced regenerative capacity.

Advances in stem cell–based therapies have demonstrated meaningful progress toward addressing these limitations. Preclinical and early clinical studies show that these therapies can reduce fibrosis, promote angiogenesis, and improve endometrial thickness and receptivity, with some evidence of improved fertility outcomes. These findings suggest that regenerative approaches can target the underlying pathophysiology of Asherman syndrome rather than solely managing its structural consequences. However, despite these promising developments, significant gaps remain. Current evidence is limited by small sample sizes, variability in cell sources and delivery methods, and a lack of standardized protocols and long-term safety data. Moving forward, future research should focus on large-scale, well-designed clinical trials, optimization of stem cell delivery systems, and evaluation of long-term reproductive and

obstetric outcomes to determine the true clinical potential of these therapies.

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