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Stem Cell-Based Approaches for the Suppression of Inflammation and Fibrosis in Asherman's Syndrome: Biological Mechanisms and Clinical Evidence

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ABSTRACT

Asherman's syndrome is a complex gynecological disorder resulting from endometrial injury and a defective uterine repair mechanism. These complicated manifestations cause irregular menstruation, infertility, and poor reproductive outcomes. Treatment nowadays includes hysteroscopic adhesiolysis and hormonal therapy, and as medicine develops, many innovative and prognostically optimal approaches appear. Recently, stem cell-based therapies have demonstrated highly promising regenerative properties due to their immunomodulatory, antifibrotic, and pro-angiogenic effects. This review evaluates the biological mechanisms by which stem cell-based therapies may reduce inflammation and fibrosis in Asherman's syndrome and summarizes the current clinical evidence. A comprehensive search was conducted across PubMed, Scopus, ClinicalTrials.gov, and Google Scholar for studies published between 2010 and 2026. The sources of stem cells, distribution strategies, and suggested mechanisms of action were systematically analyzed. This review integrates clinical data to demonstrate how stem cell-based interventions modulate the inflammatory and fibrotic pathways in Asherman's syndrome and to identify key limitations that hinder their use in standardized therapies.

Keywords: Asherman's syndrome; endometrial regeneration; fibrosis; infertility; intrauterine adhesions; stem cell therapy.

INTRODUCTION

Asherman's syndrome is a severe gynecological disorder characterized by intrauterine adhesions, recurrent inflammation, and progressive fibrosis.[1-3] It remains one of the main causes of infertility, menstrual disorders, and frequent pregnancy loss worldwide.[1,2] Although the technique of hysteroscopic adhesiolysis improved and hormonal therapy enhanced postoperative patient management, the risk of recurrence remains high.[2,4] In moderate to severe cases, complete endometrial repair is not possible, as current treatments focus primarily on mechanical adjustment of the uterine cavity rather than biological repair.[2,5] Ongoing studies show that healing with mesenchymal stem cells and enzymatic antifibrotic therapy is promising in the treatment of Asherman's syndrome.[6,7] Mesenchymal stem cell therapy is a safe approach and has great potential to increase endometrial thickness, restore menstrual function, and improve pregnancy rates.[6,8,9] They differentiate into endometrial cells and release paracrine factors that reduce inflammation and fibrosis.[7,10] During Antifibrotic therapies, fibrotic tissue breaks down, allowing improved regeneration of the endometrium.[11] However, they are still limited by a lack of standardization.

This literature review focuses on clinical and experimental studies that identify the central biological factors underlying Asherman's syndrome. It is represented by persistent inflammation in the basal layer of the endometrium, scars formed after abortions and curettages, and developed fibrosis.[1-3] According to current findings, inflammation reduces the number of endometrial stem cells and impairs their regenerative capacity.[12,13] It is important to determine the mechanism that disrupts epithelial-stromal interactions and extracellular matrix remodeling.[3,14] Particular emphasis should be placed on how stem cells can paracrinely immunomodulate these pathological pathways, reduce fibrotic signals, and restore endogenous mechanisms.[6,7,11]

Finally, we will discuss innovative treatment options for Asherman's syndrome, including the use of mesenchymal stem cells to dissolve fibrosis and restore endometrial thickness, to plan future pregnancies, and regulate the menstrual cycle.[6,8,9]

REVIEW

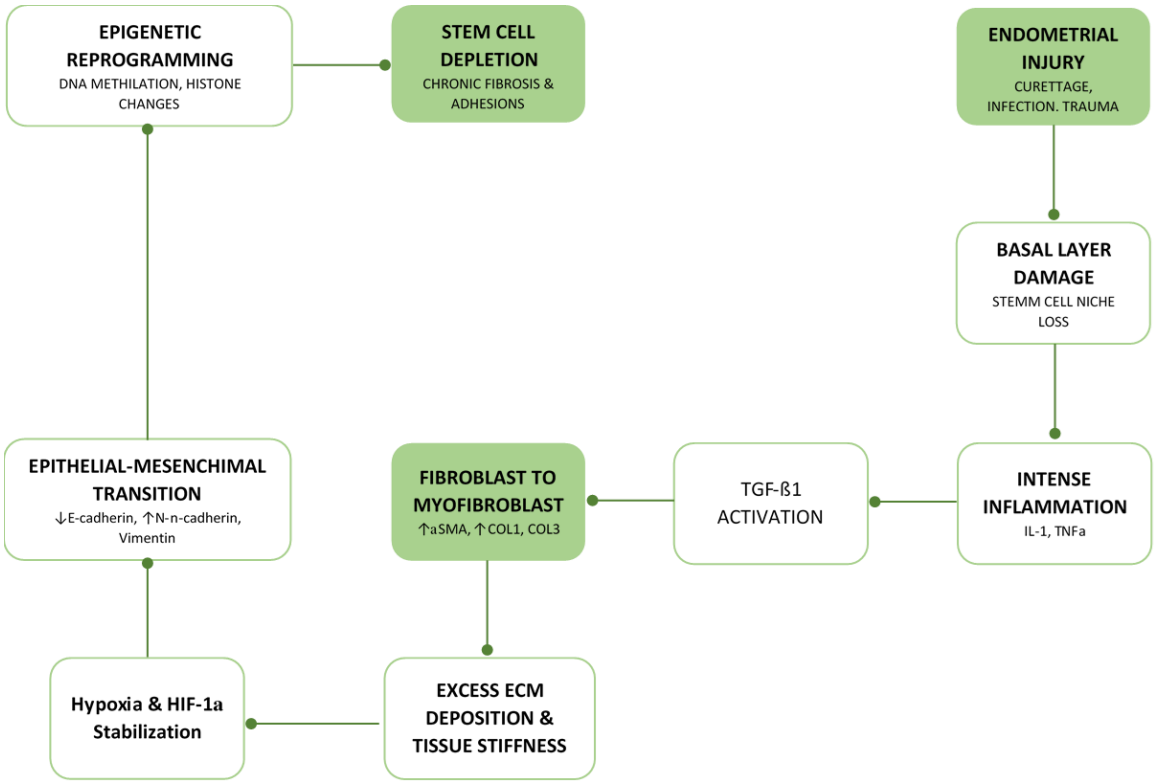
Primary endometrial injury, inflammatory cascade, and central role of TGF-ß1

The main causative mechanism of Asherman's syndrome is severe damage to the basal layer. Upon acute infection, curettage, or postpartum trauma, a pro-inflammatory and profibrotic cascade is rapidly activated.[1-3,15] A tightly regulated inflammatory response is followed by angiogenesis, reepithelialization, and controlled extracellular matrix remodeling.[13,15] However, because the regenerative mechanism is impaired due to the wound inflicted on the endometrium, chronic inflammation and fibrosis develop, leading to irreversible intrauterine adhesions.[1,16] (Fig.1).

After the initial injury to the endometrium, immune cells, particularly macrophages, migrate to the damaged area.[15,17] They primarily adopt a predominantly profibrotic phenotype within the damaged endometrium. Continuous secretion of inflammatory mediators, including interleukins, tumor necrosis factor-α, and chemokines, promotes fibroblast activation and differentiation into α-smooth muscle actin–expressing myofibroblasts.[15,17,18] These cells are the principal

effectors of fibrosis, producing excessive collagen types I and III, as well as other extracellular matrix components, which form avascular fibrous bands characteristic of intrauterine adhesions.[3,18]

FIGURE 1. Molecular mechanisms of Asherman's syndrome



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From a wound-healing perspective, TGF-β1 plays a central role.[14,19,20] At the molecular level, the activation of TGF-ß1 and Smad2/3 signaling was found in the mechanism of intrauterine adhesions.[19,21,22] TGF-β1 promotes myofibroblast differentiation and inhibits matrix metalloproteinases, leading to fibrosis persistence.[16,19,22]

In addition, one of the main pathophysiological mechanisms of Asherman's syndrome is the depletion of endometrial resident stem cells, which are necessary for the cyclic regeneration of the basal layer.[12,13] This raises doubts about the potential positive outcomes of stem cell therapy.

Mesenchymal stem cells exert potent immunomodulatory and antifibrotic effects primarily through paracrine mechanisms. Notably, preclinical studies in Asherman's syndrome demonstrated reduced fibrosis and partial reconstruction of endometrial architecture following MSC-based treatments.[6,7,21]

Stem cell dysfunction and impaired endometrial regeneration

Physiological recovery of the endometrium depends on stem cells located in the basal layer.[12,13] In Asherman's syndrome, not only is the structural integrity of the endometrium damaged, but also the endogenous regenerative system. Recent studies clearly show that the central determining factor of Asherman's syndrome is precisely the reduction in the number of stem cells in the basal layer.[1-3] Disruption of the stem cell niche by chronic inflammation and hypoxia leads to the replacement of tissue regeneration mechanisms with scar formation.[13,15,17]

Experimental and clinical observations demonstrate that Wnt–β-catenin signaling is an essential pathway for endometrial stem cell activation and epithelial proliferation.[23,24] In Asherman's syndrome, suppression of the syndrome has been observed to reduce tissue regeneration. Eliminated Wnt activity limits β-catenin nuclear translocation and transcription of regeneration-associated genes, thereby locking the tissue in a non-proliferative state.[23] In parallel, TGF-ß1 signaling antagonizes Wnt signaling and reinforces fibrotic

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differentiation by promoting the phosphorylation and degradation of β-catenin, which is essential for repairing the endometrial lining.[19,23,24]

These changes are accompanied by a decrease in the expression of HOXA10 and leukemia inhibitory factor (LIF), which are critical for endometrial receptivity.[25-27] HOXA10 is required for glandular maturation. At the same time, LIF is responsible for epithelial differentiation. Downregulation of these factors causes regenerative failure and reproductive impairment.[25,26]

Together, these changes create a pathological feedback loop in which stem cell loss, niche disruption, and signaling imbalance prolong fibrosis and prevent the restoration of a functional endometrium.[3,7,10] This framework highlights that endometrial restoration in regenerative therapies should not only consider cellular replacement but also reprogramming of the molecular microenvironment.

Epigenetic alterations, epithelial-mesenchymal transition, and hypoxia-driven fibrosis

The main cause of Asherman's syndrome is not only inflammation or stem cell damage.[1-3] One factor to consider here is epigenetic changes.[28,29] After severe endometrial damage, when the intensity of inflammatory and profibrotic factor release increases, epigenetic modifications also occur.[15,19,28] The DNA methylation and histone remodeling that develop at this time fix the stromal and epithelial cells in a fibrogenic phenotype.[28-30] Accordingly, fibrosis occurs, which is the leading problem in this disease.[28-30] The tissue's regenerative function is suppressed, and recovery of the damaged tissue is limited.[13,15,28]

The result of this reprogramming is the pathological activation of the epithelial-mesenchymal transition (EMT) in the endometrium.[14,31,32] EMT results in loss of epithelial polarity and adhesion, leading to downregulation of E-cadherin and increased expression of N-cadherin and vimentin.[31-33] Experimental models of intrauterine adhesions demonstrate that TGF-β1 signaling is a major inducer of EMT.[14,19,31] This is achieved through Smad-dependent and non-canonical pathways to inhibit epithelial gene expression and promote mesenchymal differentiation.[14,19,31] Clinically, reduced E-cadherin expression can correlate with certain hysteroscopic findings, such as thinning or complete absence of the endometrial lining.[9] On ultrasound, such alterations might present as irregular endometrial surfaces or the formation of scars, giving practitioners a visual cue to the molecular changes occurring during EMT.[14,31,32]

Expanding on diagnostic implications, these molecular changes can also serve as biomarkers to improve the diagnosis and prognosis of Asherman's syndrome.[9,33] For instance, levels of E-cadherin and expression of N-cadherin and vimentin in tissue samples could serve as indicators of disease progression or treatment efficacy.[9,34] Monitoring these changes could help tailor individualized treatment plans, enhancing the connection between molecular mechanisms and clinical practice.[33]

It is noteworthy that hypoxia amplifies these processes. Endometrial ischemia resulting from vascular disruption stabilizes hypoxia-inducible factor-1α (HIF-1α), which synergizes with TGF-β signaling to promote EMT and fibrogenesis.[35,36] HIF-1α release induces the transcription of profibrotic mediators. This, in turn, improves the expression of mesenchymal genes and changes endometrial cellular architecture.[35-37] It is important to highlight those epigenetic changes induced by hypoxia may persist even after revascularization.[28,29]

However, there is growing evidence suggesting that both epigenetic and hypoxia-induced changes can be partially reversible. These therapeutic approaches are still being explored and have the potential to find new ways to reduce the progression of Asherman's syndrome.[28,29,35] Collaborative efforts highlight why regenerative therapies should be established so that they not only restore cells but also prevent future pathological epigenetic programming.

Myofibroblast activation and extracellular matrix remodeling failure in Asherman's syndrome

From a pathomorphological perspective, one of the central mechanisms of Asherman's syndrome is the pathological transition of stromal fibroblasts into matrix-producing myofibroblasts.[15,17,18] TGF-ß1 induces myofibroblast differentiation, which can occur through the Smad2/3-dependent pathway or non-canonical signaling cascades, such as MAPK, Rho/ROCK, and PI3K/AKT.[19,30] It should be highlighted that TGF-ß1 strongly upregulates collagen and fibronectin synthesis while suppressing matrix degradation.[15,16,19] When the receptors are activated, phosphorylated Smad complexes enter the nucleus and lead to transcription of fibrogenic genes: encoding α-smooth muscle actin, α-SMA, COL1A1, and COL3A1.[18,19]

The reciprocal regulation of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) is critical in suppressing matrix degradation.[15,16] Myofibroblasts form strong integrin-mediated attachments to the extracellular matrix, stimulating the transmission of cytoskeletal tension to the extracellular matrix.[14] This induces the contraction of the tissues, as it is the hallmark of dense intrauterine adhesions.[3] A progressively dense extracellular matrix enhances myofibroblast activation via integrins, focal adhesion kinase (FAK), and YAP/TAZ signaling in Asherman's syndrome.[15,19] Matrix stiffness functions not only as a consequence of fibrosis but also as an active driver of sustained myofibroblast persistence.

In the endometrium, this remodeling failure has additional consequences beyond structural scarring. Extracellular matrix deposition damages glandular architecture and impairs oxygen diffusion.[5,35] As mentioned, hypoxia activates profibrotic signaling, which can also result from compressed microvasculature.[35,36] This creates a self-reinforcing circuit in which TGF-β1 signaling, myofibroblast contractility, and

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extracellular matrix stiffening mutually support one another.[15,19,35]

Importantly, a key feature of antifibrotic interventions in Asherman's syndrome is targeting the fibroblast-myofibroblast transition and extracellular matrix remodeling.[15,16,19]

Paracrine anti-inflammatory and antifibrotic mechanisms of stem cells in Asherman's syndrome

The therapeutic effects of mesenchymal stem cells in Asherman's syndrome are mostly guided by paracrine signaling rather than direct tissue replacement.[8,9,20] As experimental evidence increases, it becomes more obvious that transplanted stem cells show long-term persistence within the endometrium. Stem cell therapies provide better antifibrotic and pro-regenerative effects.[7,20] Growth factors, chemokines, and lipid mediators collectively modulate inflammation and lead to epithelial regeneration.[7,38]

A central antifibrotic mechanism involves suppression of TGF-β1–dominant signaling. This is the main cause of myofibroblast activation in Asherman's syndrome.[6,21,22] MSC-derived factors downregulate TGF-β/Smad signaling and reduce collagen deposition in intrauterine adhesions.[38,39] This effect is achieved by the secretion of hepatocyte growth factor, prostaglandin E2, and antifibrotic microRNAs. Altogether, they inhibit profibrotic transcriptional programs.[39,40]

Mesenchymal stem cells also have strong immunomodulatory effects that recover endometrial injury.[7,20] Through secretion of interleukin-10 and prostaglandin E2, MSCs suppress pro-inflammatory cytokine production. In addition, MSC paracrine signaling supports angiogenic and epithelial repair pathways.[6,8,9] Experimental models of Asherman's syndrome demonstrate increased vascular density and glandular restoration following stem cell therapy.[6,8,9]

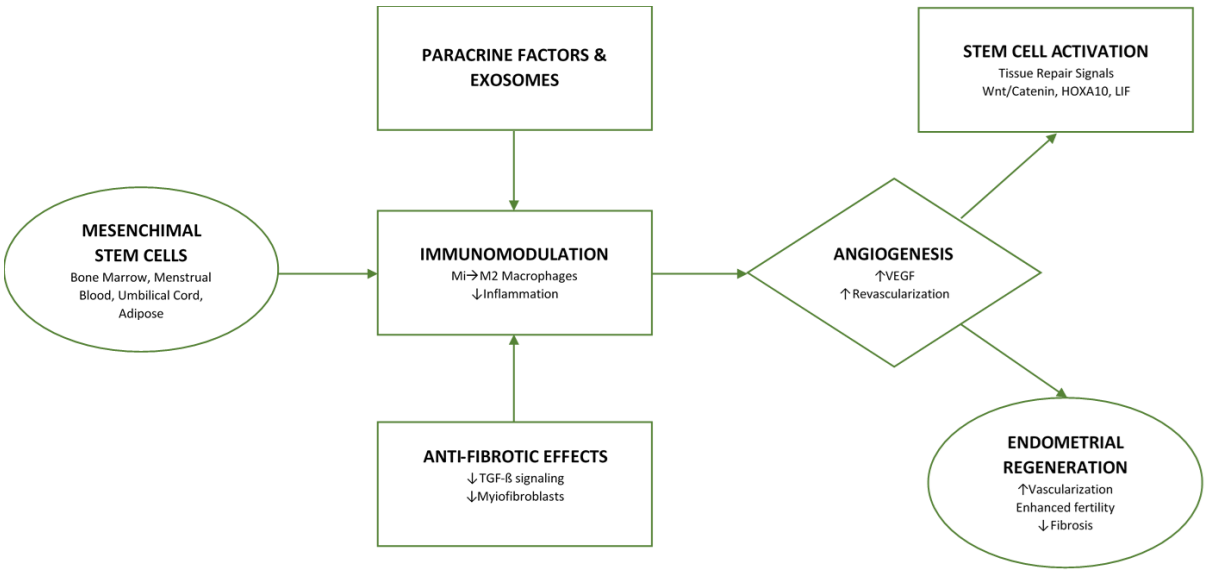
Extracellular vesicles and exosomes represent a concentrated and biologically active component of the mesenchymal stem cell secretome.[39,40] These vesicles suppress myofibroblast differentiation with microRNAs and proteins.[21,39,40] It also activates collagen synthesis and increases epithelial proliferation. Because exosomes demonstrate antifibrotic and anti-inflammatory effects, they are promising therapeutic methods for endometrial fibrosis.[39]

Regenerative functional profiles of stem cell–based therapies in endometrial repair

Stem cell therapy is being investigated for the treatment of Asherman's syndrome. One of the most studied methods remains the bone marrow-derived mesenchymal stem cells.[6,7,11] It demonstrates immunomodulatory and antifibrotic effects by suppressing TGF-ß1 signaling.[10,11,20,38] Studies have shown that in laboratory rats with intrauterine adhesions, bone marrow stem cells improved endometrial thickness and vascular density.[6,21,22] A main regenerative feature of stem cell-based therapies is microenvironmental immunoregulation.[7,34] Active stem cells secrete soluble mediators that suppress pro-inflammatory cytokines.[11,20,38] In parallel, its antifibrotic signaling is mediated by inhibition of α-SMA expression and downregulation of collagen synthesis.[18,19]

Secondly, stem cells express pro-angiogenic and perfusion-restorative activity. Effective regenerative cell therapies produce vascular endothelial growth factor and angiopoietins, thereby stabilizing microvessels in the endometrium.[8,9] Menstrual blood-derived stem cells demonstrated strong proliferative and angiogenic capacity as they originate from endometrial tissue.[12,41] Preclinical studies show that menstrual blood-derived stem cells reduce fibrosis in injury models.[12,41] (Fig.2).

FIGURE 2. Mesenchymal stem cell therapy for Asherman's syndrome



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Thirdly, Adipose-derived mesenchymal stem cells are easily accessible and provide core immunomodulatory properties.[7,9] Regenerative profiles also include epithelial and stromal proliferative support. Hepatocyte growth factors, IGF-1, and epidermal growth factors mediate it.[10,13] In particular, regenerative stem cell activity increases the expression of genes associated with receptivity and hormonal responsiveness.

Systematic reviews have shown that stem cell therapy is important for its immunoregulatory properties, rather than for the tissue from which it is derived.[11,38] Taken together, stem cell–based therapies for Asherman's syndrome should be evaluated and optimized based on their functional signatures, such as anti-inflammatory, antifibrotic, and angiogenic effects. Standardized studies are important for optimizing cell source selection.[11,38]

CONCLUSIONS

Asherman's syndrome is a symptom complex of endometrial disease that includes severe inflammation, fibrosis, and regenerative failure. Studies conducted over many years have shown that Asherman's syndrome is characterized by destruction of the basal layer, with activation of the TGF-β1 pathway playing a key role, because it leads to fibroblast-to-myofibroblast transition and extracellular matrix accumulation. These processes are enhanced by hypoxia-dependent signaling, epigenetic reprogramming, and inhibition of developmental pathways, such as the Wnt-β-catenin pathway. Altogether, causes depletion and dysfunction of endometrial stem cell populations. The development of fibrosis and reproductive dysfunction is also well explained by the downregulation of HOXA10 and leukemia inhibitory factor. Collectively, these mechanisms define why traditional treatment often fails to achieve sustained functional recovery in moderate to severe disease.

As it turns out, damage to stem cells in the endometrial layer is behind all pathophysiological mechanisms. The resulting infertility and cycle disruption are sometimes irreversible with inappropriate treatment. In the 21st century, bioengineering plays a major role in the discovery of new treatment methods; identifying the molecular mechanisms of the causative agent and defeating it with biologically active agents is a strategy that promises positive results. Experimental models, mainly using albino rats, show that the beneficial effects on the endometrium, which can lead to long-term resolution, are mediated by paracrine mechanisms. Mesenchymal stem cells, derived autologously from bone marrow, adipose tissue, or even menstrual blood, increase the thickness of the endometrium, which is necessary for the restoration of future fertility. In addition, stem cells also exhibit fibrosis-reducing properties.

Therefore, before stem cell treatment is established in clinical practice, several important factors should be considered. These include optimizing dosage, delivery routes, and long-term safety. More clinical trials are needed to compare the effectiveness of different stem cell sources. Future research should prioritize understanding the cellular function of the endometrium in both normal and fibrotic states to allow for more targeted regenerative interventions.

In summary, stem cell-based approaches show promise for suppressing inflammation and fibrosis in Asherman's syndrome. Although preclinical data from clinical trials are strong and early clinical results are promising, standardized clinical trials will be needed. Regenerative medicine, which provides antifibrotic and anti-inflammatory treatments, will make significant progress in the coming years.

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