

Review

Stem Cell-Based Regenerative Therapy for Genitourinary Syndrome of Menopause (GSM): Current Evidence and Future Perspectives

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Abstract

Genitourinary syndrome of menopause (GSM) is a common hypoestrogenic condition marked by vulvovaginal atrophy and lower urinary tract symptoms that significantly impair quality of life in peri- and postmenopausal women. Although local estrogen therapy remains the standard of care, its use is constrained by contraindications, adherence challenges, and concerns regarding long-term safety, particularly in women with estrogen-sensitive conditions. As a result, interest has grown in regenerative, non-hormonal alternatives. Stem cell-based therapy, particularly using mesenchymal stem cells (MSCs), has emerged as a potential therapeutic strategy for restoring urogenital tissue structure and function. The current body of evidence largely consists of preclinical studies, small clinical case series, and investigations in related but distinct conditions, which provide potential mechanistic insights. Preclinical studies suggest that MSCs from adipose tissue, bone marrow, and umbilical cord promote vaginal epithelial regeneration through paracrine mechanisms, including angiogenesis, immunomodulation, extracellular matrix remodeling, and restoration of local estrogen signaling and vaginal microbiota. To date, current clinical studies have not provided direct evidence on the efficacy of characterized MSC-based therapies specifically in GSM populations. Early clinical evidence, primarily involving adipose-derived tissue products such as micro-fragmented adipose tissue, reports improvements in symptoms overlapping with GSM, including vaginal dryness, dyspareunia, urinary symptoms, and sexual function, with benefits lasting up to two to three years after a single treatment and no serious adverse events reported. However, available data are limited by small cohorts, the absence of randomized trials, and regulatory variability. This review summarizes current evidence and outlines key scientific, ethical, and regulatory challenges that must be addressed to guide future research and clarify the therapeutic potential of MSC-based approaches in GSM, ultimately enabling translation.



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1. Introduction

Genitourinary syndrome of menopause (GSM), formerly referred to as urogenital or vulvovaginal atrophy, encompasses a constellation of symptoms resulting from the decline in estrogen levels during menopause [1]. GSM is characterized by thinning and dryness of the urogenital mucosa, which leads to clinical complaints such as vaginal dryness, dyspareunia, pruritus, irritation, and recurrent vaginal infections, as well as lower urinary tract symptoms, including dysuria, urinary frequency, urgency, and urinary incontinence [2]. While GSM is not life-threatening, it significantly impairs the quality of life in postmenopausal women. GSM impacts 55% of perimenopausal women and 27% to 84% of postmenopausal women worldwide [3]. Physiologically, a decline in estrogen leads to thinning of the vaginal epithelium, reduced elasticity and vascularization, and diminished secretions. The vaginal tissue loses glycogen, which normally supports *Lactobacillus*-dominant flora; consequently, the pH rises, and the risk of infection increases. The vaginal microbiota undergoes alteration, often becoming dominated by non-*Lactobacillus* species in women with GSM. These changes contribute to symptoms such as vaginal dryness, irritation, and recurrent infections of both the vaginal and urinary tracts. Unfortunately, GSM remains frequently underdiagnosed, as many women hesitate to seek medical attention, often perceiving the symptoms as a natural part of aging [4].

Both hormonal and non-hormonal treatments are used in GSM treatment nowadays. With its ability to restore vaginal epithelium and alleviate symptoms, topical estrogen therapy continues to be the gold standard of care [5]. Its widespread use is, however, constrained by issues with possible systemic absorption, contraindications in specific populations, and inconsistent patient acceptance [6]. Non-hormonal substitutes like lubricants, moisturizers, phytoestrogen, and laser treatments alleviate symptoms but do not deal with the underlying tissue deterioration [7,8]. The effectiveness of GSM treatment alone is still uncertain and requires further investigation. Interest in regenerative medicine techniques, especially stem cell-based treatments, has increased because of these restrictions. While GSM is not life-threatening, most patients prefer to avoid invasive treatments. Therefore, when considering stem cell therapy for GSM, it is important to evaluate whether such therapy yields more durable and effective results than existing modalities and whether it can truly rejuvenate or reverse the structural and functional atrophy of the vaginal epithelium.

Recently, stem cell-based treatment has been an emerging treatment for this GSM disorder due to its regenerative capacity and paracrine effects [9]. Direct differentiation into vaginal epithelial cells, growth factor production that promotes angiogenesis and tissue healing, and immunomodulation to lessen local inflammation are some of their modes of action [10]. The paracrine mechanism of stem cells is considered by secreting bioactive molecules such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and transforming growth factor- β (TGF- β) that promote tissue regeneration [11]. Furthermore, they alter the local microenvironment by raising anti-inflammatory mediators and decreasing pro-inflammatory cytokines [12]. In addition to stem cell-based approaches, related regenerative strategies such as adipose tissue-based grafting have also been explored in GSM-related conditions and have shown promising improvements in clinical symptoms [4,13,14]. While these approaches differ from cell-based therapies, their regenerative effects may provide complementary mechanistic insights relevant to the development of stem cell-based interventions.

Despite promising preclinical results, there are substantial gaps in our comprehension of the optimal cell sources, delivery mechanisms, dosing regimens, and long-term safety profiles [15]. This review assesses available data on the use of stem cells in the management of GSM, drawing on preclinical research, new clinical trial data, and molecular pathways. We evaluate the difficulties in clinical translation critically and suggest future lines of inquiry in this developing area, with emphasis on the translational readiness of stem cell application for GSM patients.

This review was developed through a literature search conducted in PubMed. Search terms included combinations of “genitourinary syndrome of menopause”, “vulvovaginal atrophy”, “mesenchymal stem cells”, “adipose-derived stem cells”, “cell therapy”, “regenerative medicine”, and related keywords. Articles published in English up to January 2026 were considered. Additional relevant studies were identified through manual screening of reference lists from eligible articles. Studies addressing stem cell-based interventions, regenerative therapies, mechanisms of action, safety, and regulatory considerations relevant to GSM were prioritized for inclusion.

2. Conventional Therapy and Its Challenges

The primary treatment for GSM has traditionally focused on estrogen replacement. Topical estrogen therapy remains the gold standard, as it effectively increases epithelial thickness and alleviates GSM symptoms but results in little to no difference in quality of life and no difference in dyspareunia or dysuria [3]. Moreover, the safety of vaginal estrogen in women without any contraindication is established; one systematic review showed the presence of 1 case of endometrial carcinoma among 600 women who received vaginal estrogen (0.17%). However, the trials are of various quality and have a short duration of follow-up; hence, a precise estimate of endometrial safety cannot be determined [16]. Alternatively, systemic estrogen therapy or selective estrogen receptor modulators (SERMs), such as ospemifene, may be appropriate for certain patients. While these hormonal therapies have demonstrated efficacy, they require continuous use, with benefits diminishing upon discontinuation [4]. A major challenge lies in poor long-term adherence and patients’ concerns regarding potential hormonal side effects, such as irregular bleeding, breast pain, abdominal bloating, and weight gain. Fewer than half of women using prescribed therapies report complete satisfaction, and approximately 10–20% continue to experience residual symptoms. Furthermore, certain groups, such as breast cancer survivors with estrogen receptor-positive tumors or women with contraindications to hormone use, are ineligible for estrogen therapy, making optimal management of GSM particularly difficult [17].

As an adjunct or alternative to hormonal therapy, several non-hormonal approaches are available. Over-the-counter vaginal lubricants and moisturizers are often recommended as first-line options. However, these products provide only temporary symptomatic relief and do not reverse the structural atrophic changes associated with GSM. Other options include intravaginal hyaluronic acid injections and energy-based therapies (CO₂ laser, Er:YAG laser, and radiofrequency therapy) [18]. While these emerging interventions show promise in providing short-term improvement, they have not yet delivered sustained long-term outcomes. For example, vaginal laser therapy may stimulate neo-collagenesis, but its effects often diminish within months, and a subset of patients continues to experience persistent symptoms [19]. Moreover, high costs and limited availability further restrict access to these therapies. To date, no conventional therapy has provided lasting relief for GSM. Although local estrogen carries a low risk, concerns about endometrial and breast cancer, application discomfort, and side effects often limit adherence [5,20]. As women now spend a substantial portion of their lives postmenopause, the demand for safe, effective

non-hormonal treatments has grown, driving interest in regenerative approaches such as stem cell-based therapies.

3. Stem Cell Therapy for GSM: Types and Mechanisms

Stem cells are unique cells that have the capacity to differentiate into various cell types (potency) and possess both regenerative and immunomodulatory properties. Based on their potency, stem cells can be classified into five categories: totipotent, pluripotent, multipotent, oligopotent, and unipotent. According to their origin, they are classified as embryonic stem cells (ESCs), adult (somatic) stem cells (ASCs), and induced pluripotent stem cells (iPSCs) (Table 1) [21–23].

Table 1. Summary of stem cell types based on their origins.

Type	Origin & Potency	Key Characteristics	Advantages & Limitations
Embryonic stem cells (ESCs)	Blastocyst inner cell mass, Pluripotent	Differentiate into all three germ layers	(+) High proliferative and differentiation capacity (–) Ethical and safety concerns, tumorigenicity
Adults (somatic) stem cells (ASCs)	Various adult tissues and organs, Mostly multipotent	Immunomodulatory and anti-inflammatory properties	(+) High proliferative and differentiation capacity, easily accessible, low immunogenicity (–) Heterogeneity between sources
Induced pluripotent stem cells (iPSCs)	Reprogrammed somatic cells, Pluripotent	ESC-like properties without embryonic use	(+) Patient-specific therapy potential (–) Genetic instability, tumorigenicity

In the field of gynecology, stem cell-based therapies hold promise for restoring tissues affected by degeneration or atrophy, including those involved in GSM [24]. Among the different types, MSCs are the most extensively studied for clinical applications. MSCs are adult stem cells with fewer ethical concerns compared to embryonic stem cells, a good safety profile, and low immunogenicity, and they can be used for allogeneic (donor) transplantation without triggering significant immune rejection, making them a practical and accessible treatment for GSM [25]. MSCs exert their therapeutic effects through the secretion of growth factors and cytokines that promote tissue repair via paracrine signaling and through direct differentiation into target cell types. The therapeutic goals of MSC application in GSM are to enhance the thickness and hydration of the vaginal mucosa, regenerate collagen and elastin fibers, promote angiogenesis, and improve natural vaginal lubrication [17]. Additionally, MSCs exhibit anti-inflammatory effects that can alleviate chronic irritation or inflammation in atrophic tissues [1]. This combination of regenerative and immunomodulatory functions is expected to restore the vaginal mucosa to a condition that requires confirmation in controlled trials.

MSCs can be derived from a variety of adult tissue sources, such as adipose tissue, bone marrow, menstrual blood, umbilical cord, and others (Figure 1), with each offering distinct advantages and limitations. Adipose-derived MSCs (AD-MSCs) are obtained through minimally invasive liposuction. Given their high yield, low immunogenicity, and autologous use, AD-MSCs exhibit strong regenerative potential and minimal immune rejection [26–28]. However, long-term safety data are still limited due to variability in graft composition and technique. Bone marrow-derived MSCs (BM-MSCs) are considered well-characterized lineages. Although they demonstrate regenerative and angiogenic effects in preclinical studies, their application is limited by the invasive collection and lower cell

yield, making it less practical for large-scale use [1,10]. To date, BM-MSCs have only been evaluated in menopausal animal models for GSM research. Menstrual blood-derived MSCs (MenSCs) can be collected non-invasively and exhibit proliferative capacity, multipotency, and suitability for cryopreservation, making them attractive candidates for personalized therapeutic applications [17]. However, current evidence remains largely limited to preclinical studies, even if the results are promising, due to the lack of standardized collection and differentiation protocols. Their therapeutic potential for GSM has yet to be evaluated in clinical settings. Additionally, allogeneic MSCs, particularly those derived from umbilical cord tissue, offer the advantage of “off-the-shelf” availability and low immunogenicity [29]. Preclinical studies have reported beneficial effects on tissue regeneration, including enhanced collagen, elastin, and vascular density, but concerns regarding regulatory approval, potential immune response, and the absence of clinical validation remain important challenges. In GSM research, having favorable safety and efficacy outcomes, AD-MSCs are the most widely studied and clinically applied MSC source.

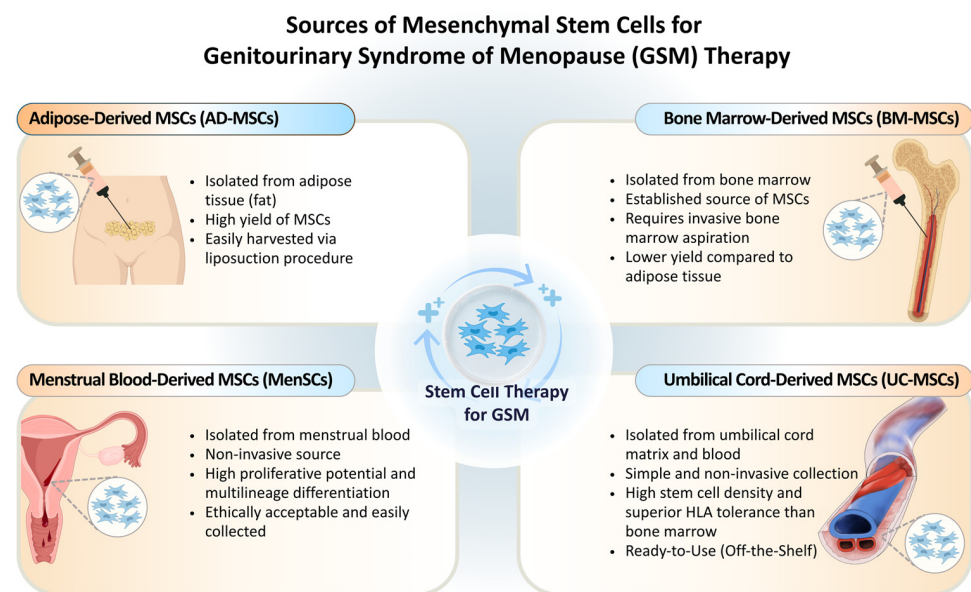


Figure 1. Mesenchymal stem cells for GSM therapy. Different types of MSCs from various sources can be used in the development of regenerative therapies to address GSM symptoms, each with its own advantages and clinical considerations. This illustration was generated using BioRender Basic and Canva Pro.

In essence, autologous AD-MSCs represent the primary stem cell type used in clinical studies of regenerative therapies in gynecological conditions, owing to the accessibility and safety of this source. Their therapeutic effects are believed to occur through local tissue regeneration; secretion of paracrine factors such as bioactive molecules, including EGF and TGF- β [27]; stimulation of angiogenesis; immunomodulation within the urogenital area to reduce local inflammation by decreasing pro-inflammatory cytokines (IL-6 and TNF- α) and increasing anti-inflammatory cytokines (IL-10 and TGF- β) [30,31]; restoration of the microbiome and acidic vaginal pH [32–34]; and stimulation of local estrogen production by expressing aromatase, converting androgens to estradiol in vaginal tissue, and upregulating estrogen receptor expression in atrophic tissue [28]. These mechanisms collectively help restore vaginal moisture, elasticity, and mucosal thickness; findings should be interpreted cautiously in the presence of GSM (Figure 2).

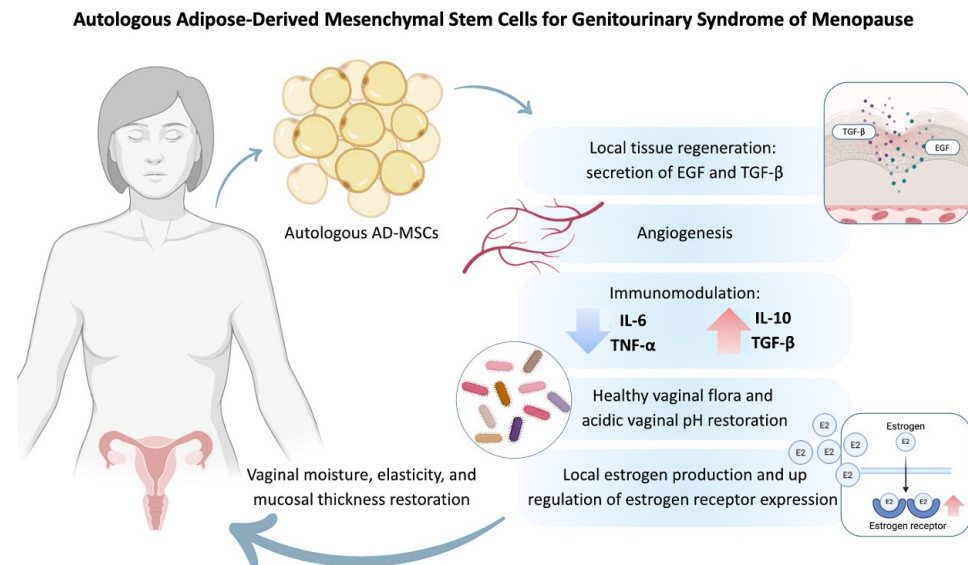


Figure 2. AD-MSCs ameliorate GSM primarily through paracrine mechanisms. Following local administration, AD-MSCs secrete bioactive factors, including EGF and TGF- β , which promote tissue regeneration, angiogenesis, and immunomodulation by suppressing pro-inflammatory cytokines (IL-6 and TNF- α) and enhancing anti-inflammatory mediators (IL-10 and TGF- β). AD-MSCs support restoration of vaginal microbiota and acidic pH and stimulate local estrogen biosynthesis via aromatase activity and estrogen receptor upregulation (in the estrogen image, the black arrow indicates estrogen binding to the estrogen receptor, and its receptor upregulation is indicated by the upward-pointing red arrow), collectively improving vaginal structure, function, and GSM symptoms. This illustration was generated using BioRender Basic and Canva Pro.

4. Current Evidence and Supporting Mechanistic Insights Relevant to GSM

At present, clinical evidence directly evaluating characterized MSC-based therapies for GSM remains scarce. The existing body of literature largely focuses on related conditions or mechanistically relevant outcomes, which may provide indirect insights into their potential application in GSM. Collectively, these studies provide a mechanistic foundation that supports the rationale for further investigation of MSC-based therapies in GSM. Key findings from these studies are summarized in Table 2.

4.1. Preclinical and Mechanistic Context

Currently, no widely established animal model comprehensively captures GSM as a multi-symptom syndrome. However, ovariectomized (OVX) and hypoestrogenic animal models remain valuable for understanding the specific tissue-level changes associated with estrogen deficiency and the regenerative mechanisms of stem cells. In an ovariectomized rat model combining hypoestrogenism with metabolic syndrome, human amniotic fluid stem cells improved bladder storage function, reduced postvoid residual urine volume, and downregulated the overexpression of purinergic and muscarinic receptors. Additionally, the intervention mitigated oxidative stress, inflammation, and apoptosis by modulating mitochondrial pathways. Collectively, these results suggest that amniotic fluid-derived stem cells may restore urogenital structure and function in complex hypoestrogenic states, including postmenopausal metabolic syndrome. The study of human umbilical cord mesenchymal stem cells (HUMSCs) in an animal model evaluated collagen expression in the anterior vaginal wall of menopausal rats. Using an ovariectomized rat model, researchers found that HUMSC administration significantly increased collagen expression compared with the control group. Approximately 72% of treated rats showed

strong collagen expression, while all control rats demonstrated only weak-to-moderate expression. The regenerative effect of HUMSCs is thought to occur through extracellular matrix remodeling [35], stimulation of smooth muscle regeneration [36,37], reduction in collagen degradation [37,38], and secretion of anti-inflammatory cytokines [39] and growth factors [40]. These mechanisms may improve vaginal tissue integrity and pelvic floor strength.

Another type of stem cell, bone marrow-derived mesenchymal stem cells (BM-MSCs), showed a significant effect on the animal model. The researchers compared estrogen therapy, intravenous BM-MSC administration, and intravaginal BM-MSC injection to evaluate their effects on vaginal tissue regeneration. The results showed that ovariectomy caused thinning of the vaginal epithelium, inflammation, collagen loss, reduced estrogen receptor expression, and elevated inflammatory markers such as TGF- β , iNOS, and GAPDH. Treatment with BM-MSCs improved epithelial healing, increased collagen deposition, enhanced vascularization, and restored estrogen receptor expression. Among all treatment groups, intravaginal BM-MSC administration demonstrated the strongest regenerative effects and produced better structural restoration than estrogen therapy alone [41].

Together, these findings demonstrate the regenerative capability of various MSCs in improving urogenital dysfunction associated with menopause through several shared mechanisms. Across different stem cell sources, including amniotic fluid-derived stem cells, HUMSCs, and BM-MSCs, treatment consistently improved tissue structure and functional outcomes in animal models, which appear to be mediated mainly through extracellular matrix remodeling, increased collagen deposition, and epithelial and smooth muscle regeneration. The overall evidence supports stem cells' potential to restore tissue integrity and functional capacity in hypoestrogenic conditions.

4.2. Supportive Clinical Evidence in GSM-Related Conditions

While direct evidence for GSM is lacking, clinical studies using characterized stem cells in related urogenital or hypoestrogenic conditions provide supportive mechanistic context. One early human study evaluated ADSC therapy in eight patients with vulvar dystrophy [42]. In this investigation, ADSCs were isolated, expanded in culture, and injected directly into vulvar tissue. Follow-up assessments showed significant increases in epithelial thickness and marked improvement in the histological quality of vulvar and vaginal tissues across all participants. These objective findings were accompanied by substantial relief of symptoms, including burning, pruritus, pain, and dyspareunia, as well as improvements in sexual function. Histopathological evaluation confirmed enhanced trophism and tissue regeneration, indicating potential regenerative effects. Notably, the therapeutic benefits were sustained for up to two years, with no evidence of tissue degeneration or symptom recurrence, and no significant adverse events were reported. Although vulvar dystrophy is a distinct clinical entity and does not fully capture the multifactorial nature of GSM, these findings provide indirect, hypothesis-generating evidence for the regenerative potential of ADSCs in vulvovaginal tissues. This may be mechanistically relevant, as tissue atrophy and compromised epithelial integrity are key features of GSM.

Another clinical study investigated the use of autologous menstrual blood-derived stem cells (MenSCs) in women with menopausal syndrome and ovarian dysfunction. Fifteen patients aged 30–60 years received intravenous MenSC administration at doses of either 3×10^7 or 1×10^8 cells, with follow-up assessments of menopausal symptoms and hormonal profiles. The results demonstrated significant improvement in menopausal symptoms, including vasomotor symptoms, psychological disturbances, and musculoskeletal complaints, as early as one month after treatment. Symptom reduction persisted for up to six months, and the higher dose of MenSCs showed greater therapeutic efficacy. Hormonal

evaluation revealed an increasing trend in serum estradiol (E2) levels and a reduction in follicle-stimulating hormone (FSH) levels following MenSC therapy, particularly in postmenopausal patients. These findings suggest that MenSC administration may partially restore endogenous ovarian function and improve hormonal balance without conventional hormone replacement therapy [43].

The available clinical evidence cumulatively suggests that MSC-based therapies may represent a promising regenerative strategy for GSM. The improvements observed across multiple studies, coupled with sustained therapeutic benefits and a favorable safety profile, indicate the potential of MSCs to address underlying tissue dysfunction rather than solely providing symptomatic relief. Nevertheless, larger controlled clinical trials are still required to establish long-term efficacy and safety.

4.3. Adipose Tissue Grafting: Micro-Fragmented Adipose Tissue (MFAT)

It is critical to distinguish characterized MSC therapy from adipose tissue grafting procedures. While micro-fragmented adipose tissue (MFAT) contains a stromal vascular fraction rich in stem cells, it is a tissue-based therapy rather than a characterized MSC preparation [44]. Nevertheless, MFAT has shown promising results in improving symptoms overlapping with GSM.

An observational case series further demonstrated the safety and feasibility of using MFAT for genitourinary disorders [4]. Ten patients received local injections of autologous MFAT (Lipogems, Lipogems International S.p.A., Milan, Italy) into the vaginal wall, labia, and periurethral region. Clinical outcomes were evaluated using validated tools, including the FSFI, the ICIQ-UI SF, and the VSQ. All participants reported symptomatic improvement within 6–16 months following treatment, with noted benefits such as enhanced vaginal lubrication, reduced dyspareunia, alleviation of irritation and dysuria, and partial improvement in mild urinary incontinence. Significant increases were observed in FSFI scores and overall quality-of-life measures (SF-12). Importantly, no procedure-related adverse events or complications were identified during treatment or follow-up, including the absence of infection, hematoma, or abnormal findings at injection sites. These preliminary findings suggest potential clinical benefit in patients with genitourinary symptoms, some of which overlap with GSM.

A larger case series evaluated the effects of autologous MFAT therapy in 35 postmenopausal women with severe GSM who had not previously received hormonal treatment [14]. All participants underwent a single injection of MFAT (Lipogems) into the vaginal and vulvar tissues. At six months post-treatment, 46% of patients reported complete resolution of symptoms, while the remaining individuals experienced only mild residual complaints. These clinical improvements were largely sustained during long-term follow-up of 2–3 years, with most patients remaining asymptomatic and free of relapse; only three women reported mild symptom recurrence after two years. Both clinical examination and histological assessment demonstrated restoration of a healthy vaginal mucosa, with biopsy findings showing epithelial thickening and normalization of vaginal flora. No serious adverse events or procedure-related complications were observed.

The observed efficacy of MFAT in alleviating GSM-related symptoms provides an important mechanistic foundation. Given that the regenerative effects of MFAT are driven, at least in part, by resident progenitor cells, including pericyte populations within its stromal vascular fraction [14], this supports the hypothesis that cell-mediated mechanisms may contribute to tissue restoration. Building on this, it is plausible that more targeted approaches using isolated and characterized MSCs may offer more controlled and reproducible regenerative effects. However, further well-designed studies are required to clarify the role of MSC-based therapies in GSM.

Table 2. Clinical and preclinical evidence of stem cell- and MFAT-based therapies in GSM research context.

	Therapy Source	Study Design & Sample	Intervention & Follow-Up	Main Findings & Safety
MSC	ADSCs + Hyaluronic acid (HA)—Human [42]	Clinical trial. Eight women with vulvar dystrophy with an average age of 56.5 years.	Two injections of ADSCs + HA (5×10^5 cells for each mL hyaluronic acid) over 3 months. Follow-up for 2 years.	Improved tissue trophism and elasticity, with increased FSFI scores and histologic evidence of regeneration. No reported adverse effects.
	Menstrual blood-derived stem cells—Human [43]	Clinical trial. Fifteen patients with menopausal syndrome.	Injection of 3×10^7 to 1×10^8 cells intravenously 1–5 times, with an interval of more than 1 month. Follow-up at 1, 3, 6, and 12 months.	The Simplified Menopausal Index score was significantly reduced; the increased estradiol level. No serious adverse events.
	Human Amniotic fluid stem cells—Animal [45]	Experimental animal study. In vivo study in 48 ovariectomized rats.	Intravenous 3×10^6 human amniotic fluid stem cells (hAFSCs). Follow-up of 1–3 months.	Bladder function improved alongside reduced fibrosis and apoptosis, with normalization of receptor expression. No immune or hormonal effects were detected.
	Human umbilical cord stem cells (HUMSC)—Animal [46]	Experimental animal study. Forty female ovariectomized rats.	Injecting 3×10^6 HUMSC into subepithelial–vaginal wall rats. Follow-up at 12 weeks.	Increased collagen expression. No complications reported.
	Bone Marrow-Derived Mesenchymal Stem Cells—Animal [41]	Experimental animal study. Fifty-five ovariectomized female albino rats.	Injection of 5×10^6 MSCs intravenously and another group intravaginally. Follow-up at 15 days and 30 days.	Increased estrogen levels are superior in intravaginal MSCs in rats compared to intravenous injection. Increased regeneration of vaginal epithelium is better with intravaginal MSCs than with intravenous. Both decreased the production of pro-inflammatory inhibitors. No adverse effect reported
MFAT	Autologous MFAT (Lipogems®)—Human [13]	Clinical trial. Three postmenopausal women with urogenital atrophy (average age 58.7 years).	Single 15 mL Lipogems® injection. Follow-up of 3 to 36 months.	Vaginal dryness, burning, and itching were resolved, accompanied by the restoration of normal pH, microbiota, and regeneration of epithelium and subcutaneous tissue (histology results). No complications or adverse effects.
	Autologous MFAT (Lipogems®)—Human [4]	Clinical trial. Ten women with vaginal atrophy, vulvovaginal dystrophy, and/or stress urinary incontinence (SUI).	20 mL Lipogems® vulvovaginal injection. Follow-up of 6 to 16 months.	Dryness, dyspareunia, and stress urinary incontinence improved, accompanied by higher FSFI and VHI scores. No complications.
	Autologous MFAT (Lipogems®)—Human [14]	Clinical trial. Thirty-five postmenopausal women.	Single 15 mL submucosal injection. Follow-up of 6 to 36 months.	At 12 months, 85% of patients were asymptomatic, with restored vaginal sensitivity and Lactobacillus-dominant flora. No adverse events were reported.
	Autologous MFAT (SEFFIGYN™)—Human [47]	Clinical trial. Eleven postmenopausal women.	10 mL micro-fragmented fat injected at the vaginal introitus. Follow-up at 15 days and 5 months.	Dryness, burning, and pain were reduced, with improved vaginal color, turgor, and elasticity. No complications reported.

5. Safety Profile of Stem Cell Therapy in GSM

Safety remains a critical consideration in innovative therapies such as stem cell-based treatments. Because direct clinical trials evaluating MSC transplantation specifically for GSM are currently lacking, the anticipated safety profile must be inferred from related regenerative procedures and broader MSC applications related to GSM. It is essential to distinguish the safety profiles of tissue-based grafts from isolated cell therapies. In tissue-grafting procedures, such as autologous MFAT injections, no adverse effects have been observed [4,13,14,47]. Mechanically processed adipose tissue (e.g., Lipogems) is classified as minimally manipulated, preserving native cellular niches and structural integrity that support regeneration while minimizing abnormal growth potential [48]. To date, no neoplastic transformation or tissue overgrowth has been reported following these tissue-based injections in the urogenital area.

Fortunately, current evidence regarding characterized autologous MSCs is highly reassuring. The use of autologous cells offers key advantages, notably the minimal risk of immune reaction or rejection. As the cells originate from the patient, there is no risk of graft-versus-host disease or allergy. Furthermore, theoretical concerns about tumorigenicity have not been substantiated; in fact, a meta-analysis of 36 MSC clinical trials across various non-GSM indications found no increase in cancer incidence or mortality [49]. These findings provide indirect reassurance regarding the safety profile of MSC-based approaches; however, their applicability to GSM-specific applications remains to be established.

In preclinical animal models, intravaginal or local injection appears to be one of the most effective approaches for ameliorating markers of vaginal atrophy and pelvic floor regeneration because stem cells are delivered directly into the affected tissue. Studies using BM-MSCs and HUMSCs in ovariectomized models demonstrated greater improvement in vaginal epithelial thickness, collagen deposition, vascularization, and estrogen receptor expression after local intravaginal administration compared with systemic administration or estrogen therapy alone. Local delivery also enhances tissue targeting and reduces cell loss during circulation [41,46]. These mechanistic results suggest that localized delivery may offer a safe and targeted route for future human GSM therapies.

Intravenous administration is considered relatively safe and suitable for systemic menopausal symptoms because it provides broader immunomodulatory and endocrine effects. In the MenSC study involving patients with menopausal syndrome, intravenous infusion improved vasomotor symptoms, mood disturbances, musculoskeletal complaints, and hormonal balance without serious adverse events such as thrombosis or infection. This route may be particularly beneficial for patients requiring systemic anti-inflammatory, endocrine, and regenerative effects rather than localized tissue repair alone [43].

Nevertheless, strict procedural standards must be upheld. Cell harvesting and preparation should follow Good Manufacturing Practice (GMP) protocols to prevent contamination, and aseptic technique is essential to avoid infection, with prophylactic antibiotics occasionally considered [50]. Procedures are typically performed under local anesthesia or mild sedation, ensuring comfort and safety, even in older patients with comorbidities [51]. In conclusion, while currently extrapolated data from related regenerative procedures and general MSC literature suggest a highly favorable safety profile, these findings primarily serve to offer theoretical hope and scientific rationale rather than definitive proof. It remains entirely premature to draw definitive conclusions regarding the absolute safety of pure MSC transplantation for GSM. Therefore, rigorous, well-designed clinical trials are fundamentally required to definitively establish the safety and efficacy of direct MSC transplantation in this patient population before widespread clinical adoption.

6. Regulatory and Ethical Aspects

Stem cell-based therapies occupy a regulatory grey zone between medical procedures and biological products. To date, no stem cell treatment has received official approval from major regulatory agencies such as the FDA or EMA for the indication of GSM. Thus, their use remains experimental, restricted to clinical trials or research-based services.

In the United States, the FDA classifies human cell and tissue-based products as Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). Minimally manipulated autologous adipose tissue, when used for homologous purposes such as in Lipogems-based procedures, may be exempt from formal premarket approval, provided it fulfills key criteria, including minimal manipulation, homologous use, same-patient and same-session application, and the absence of added substances [52]. Therefore, the use of adipose-derived stem cells for vaginal rejuvenation in the U.S. generally requires Investigational New Drug (IND) authorization, and clinicians typically perform such procedures under research protocols or registries.

In Europe, products involving more-than-minimally manipulated autologous cells are regulated as Advanced Therapy Medicinal Products (ATMPs), requiring formal authorization and clinical trial oversight [53]. Japan has introduced conditional early approval pathways for certain regenerative treatments, but none yet cover GSM [54].

Given the absence of formal regulatory approval, stem cell therapy for GSM is considered “off-label experimental use”. Ethical obligations require clear patient disclosure about its investigational nature, uncertain long-term efficacy, and potential risks [55]. High costs and lack of insurance coverage raise additional concerns regarding commercialization and equitable access. Therefore, rigorous informed consent and transparent patient communication are essential.

From an ethical standpoint, key issues include ensuring fairness in access, maintaining scientific accountability by publishing both positive and negative outcomes, and safeguarding donor screening in the case of future allogeneic or banked-cell applications (Figure 3). Embryonic stem cells are not involved in GSM research, thereby avoiding related bioethical controversies. Future policies may accelerate approvals once safety and efficacy data mature. At present, professional societies still classify stem cell therapy for GSM as investigational but recognize its strong potential, emphasizing the need for multidisciplinary collaboration to establish safe clinical standards.



Figure 3. The ethical and regulatory framework surrounding stem cell therapy for GSM. The therapy is presented as investigational, encompassed by four core pillars: patient protection through

informed consent and transparency, scientific accountability through balanced and reproducible reporting, considerations of access and equity, and governance with prospects for future regulatory approval. The lower elements emphasize the non-use of embryonic stem cells and the essential role of multidisciplinary collaboration in developing safe and ethical clinical standards. This illustration was generated using BioRender Basic and Canva Pro.

7. Conclusions

GSM is common among peri- and postmenopausal women and substantially reduces quality of life through vulvovaginal atrophy and lower urinary tract symptoms. While local estrogen therapy is generally effective and safe, careful monitoring is required in high-risk populations. Systemic hormone therapy can alleviate symptoms but is constrained by contraindications, adherence challenges, and limited durability, prompting interest in alternative regenerative strategies.

Stem cell-based approaches, including both adipose-derived tissue products and MSCs, have emerged as a potential option for urogenital tissue restoration in GSM. Early clinical studies, primarily from adipose-derived tissue-based interventions, suggest meaningful and sustained symptom improvement, including reduced vaginal dryness, dyspareunia, and urinary urgency, with benefits lasting up to two to three years after a single local treatment. AD-MSCT therapy appears to enhance vaginal epithelial thickness, lubrication, sexual function, and continence, offering potentially longer-lasting effects than hormone therapy.

Available safety data are reassuring, with no serious adverse events reported. The use of minimally manipulated autologous cells limits immunologic risk, and current evidence does not indicate increased malignancy or systemic complications, although long-term follow-up remains necessary. Nevertheless, existing studies are small and largely uncontrolled. Well-designed randomized controlled trials and clearer regulatory frameworks are required before routine clinical adoption. With robust evidence and appropriate oversight, stem cell therapy may become an important regenerative option for GSM, particularly for women who cannot use estrogen.

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