Beyond Vaginal Atrophy: A Systematic Review of the Multidimensional Pathophysiology, Phenotypes, and Personalized Management of Genitourinary Syndrome of Menopause

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Abstract

Genitourinary syndrome of menopause (GSM) has traditionally been framed as a consequence of estrogen-deficiency-related vulvovaginal atrophy, yet contemporary evidence indicates a broader disorder spanning epithelial, stromal, microbial, vascular, neural, sexual, and lower urinary tract domains. This systematic literature review synthesized recent evidence to determine how biological and clinical phenotypes relate to treatment response and to assess the basis for phenotype-informed management. Scopus was searched using terms for GSM or vulvovaginal atrophy, menopause, major hormonal, non-hormonal, and energy-based interventions, and clinical outcomes. Of 771 records identified, 420 records published before 2022 were removed. After article-type, language, and scope screening, 43 primary studies were included in the qualitative synthesis. Evidence was organized into four themes: biological architecture and objective phenotypes; clinical phenotypes and multidomain burden; differential therapeutic responses; and patient-specific determinants of management. The synthesis indicates that GSM is not adequately represented by epithelial thinning alone. Vaginal tissue remodeling, collagen architecture, microbiome composition, microvascular and neural characteristics, and emerging molecular markers coexist with heterogeneous genital, sexual, and urinary manifestations. Therapeutic responses were similarly domain-specific: hormonal, non-hormonal, and energy-based approaches differed in the outcomes measured, biological targets, evidence maturity, durability, and relevance to particular patient groups. Local estrogen remains supported by a comparatively mature evidence base, whereas energy-based and regenerative strategies show biological and clinical signals but greater heterogeneity and uncertainty. Breast-cancer survivors and women receiving endocrine therapy exemplify the need to integrate safety constraints with symptom priorities and treatment preferences. Overall, contemporary GSM evidence supports a mechanism-phenotype-intervention-outcome framework rather than a uniform treatment hierarchy. Standardized phenotyping, core outcome sets, longer comparative trials, and explicit incorporation of patient preferences are required before phenotype-guided treatment can be validated as a clinical algorithm.

Keywords: genitourinary syndrome of menopause; vulvovaginal atrophy; vaginal microbiome; personalized management; menopause

1. Introduction

Genitourinary syndrome of menopause (GSM) describes a constellation of genital, sexual, and lower urinary tract changes associated principally with declining sex-steroid stimulation during the menopausal transition and after menopause. The concept is clinically broader than the older terminology of vulvovaginal or urogenital atrophy because women may present with vaginal dryness, burning, irritation, loss of lubrication, dyspareunia, dysuria, urinary urgency, recurrent urinary symptoms, or combinations of these manifestations. GSM is therefore better understood as a chronic pelvic-health disorder than as an isolated visual abnormality of the vaginal epithelium. Contemporary clinical overviews emphasize the breadth of the syndrome, its differential diagnosis, and the need to integrate symptoms with physical examination rather than assume that every postmenopausal vulvovaginal complaint is caused by atrophy (Woods et al., 2024) (Clark & Goetsch, 2024) (Christmas et al., 2024).

The clinical burden is substantial because symptoms can persist after vasomotor symptoms diminish and may progressively affect daily comfort, sexual function, intimate relationships, and quality of life. GSM is also underrecognized: patients may normalize symptoms as an inevitable part of aging, feel reluctant to initiate discussion, or encounter clinicians who do not routinely ask about genitourinary concerns. Population-based studies across different settings have consequently shifted attention from simple prevalence estimates toward predictors, new versus prevalent cases, and treatment utilization (Bevilacqua et al., 2025) (Lambrinoudaki et al., 2024b) (Mahmoudian et al., 2025). The gap between symptom burden and treatment use remains a recurring feature of menopause care (Baquedano et al., 2023) (Trémollieres et al., 2022), indicating that therapeutic availability alone does not resolve underdiagnosis or undertreatment.

Patient experience further complicates the epidemiological picture. In a national sample of 1,500 women, barriers to vaginal estrogen use were sufficiently prominent to warrant dedicated investigation, illustrating how concerns, beliefs, information needs, and treatment preferences can modify real-world uptake (Stair et al., 2025). This implementation dimension is particularly important because contemporary guidelines cover an increasingly broad therapeutic landscape. The AUA/SUFU/AUGS guideline review evaluated effectiveness or harm outcomes across 68 publications and additionally mapped 66 publications describing 46 non-hormonal interventions, underscoring both the breadth of available strategies and the heterogeneity of the evidence base (Kaufman et al., 2025).

A central reason for this heterogeneity is that the biological substrate of GSM extends beyond epithelial thinning. The postmenopausal vaginal environment reflects interactions among endocrine signaling, epithelial maturation, tissue hydration, extracellular-matrix organization, vascular and neural features, local immune activity, pH, and microbial ecology. Reviews of the postmenopausal vaginal microbiome emphasize that hormonal change is accompanied by ecological shifts that may influence mucosal function and symptom expression (Micks et al., 2024). Observational data from the Study of Women's Health Across the Nation directly examined relationships between vaginal microbial communities and GSM symptoms (Waetjen et al., 2023), while more recent studies associated microbial composition with symptom onset, severity, and symptom type (Zeng et al., 2024). Cross-sectional work in Chinese women similarly linked menopausal state, hormone-therapy exposure, and vaginal microbiota (Lan et al., 2024).

Clinical expression is likewise multidimensional. Sexual pain should not be treated as a generic binary symptom, because anatomical localization may identify clinically distinct pain patterns and potential mechanisms (Goetsch et al., 2022). Lower urinary tract manifestations may coexist with genital symptoms, and women may experience one dominant domain rather than a uniform syndrome. This heterogeneity is especially consequential in populations with treatment constraints. Baseline data from the PEONY program demonstrated the importance of distinguishing women with and without a history of breast cancer (Meriggiola et al., 2024), because survivors may experience substantial VVA/GSM burden while simultaneously facing concerns about hormonal exposure or ongoing endocrine therapy.

The appropriate definition of treatment success therefore also requires expansion. Improvement in vaginal appearance, maturation, or tissue structure is clinically relevant, but it is not synonymous with a reduction in pain, urinary symptoms, or quality-of-life impairment. Six-month PEONY data emphasize symptom severity and patient-reported outcomes as meaningful endpoints (Nappi et al., 2025), and the CRETA study examined treatment-associated changes in quality of life using a validated menopause-related scale (Palacios et al., 2023). These studies reinforce a patient-centered principle: a therapy that produces a measurable biological change may still have limited value if it does not improve the symptom domain that matters most to the patient.

The breadth of GSM has implications for clinical organization. Primary-care clinicians, nurse practitioners, gynecologists, urogynecologists, urologists, and sexual-health specialists may encounter different facets of the same syndrome. Practice-oriented literature accordingly emphasizes active symptom inquiry and multidisciplinary recognition rather than waiting for patients to volunteer concerns (Chism et al., 2022) (Brady et al., 2022) (Schmidt, 2023). Comprehensive menopause care similarly argues for

integrating genitourinary symptoms with broader menopausal management instead of treating them as a separate or late-stage problem (Flanagan & Fantasia, 2024).

Therapeutic diversity has expanded in parallel. Established and emerging options include local estrogenic treatments, selective estrogen receptor modulators, intravaginal dehydroepiandrosterone, moisturizers and lubricants, hyaluronic-acid formulations, laser and radiofrequency devices, photobiomodulation, and regenerative approaches. Pharmacological reviews emphasize differences in mechanism, route, safety, and suitability (Salvatore et al., 2023), while focused reviews of hormonal medications highlight the need to distinguish local and systemic exposure and to tailor treatment to clinical priorities (Pinkerton et al., 2024). The broader endocrine context of aging further supports the expectation that tissue responses to hormonal change are organ-specific and heterogeneous (Cappola et al., 2023).

A multidimensional model also changes the clinical question from "Which treatment is most effective for GSM?" to "Which treatment is most appropriate for a particular pattern of disease?" A woman whose principal concern is painful intercourse may value rapid relief of dyspareunia, whereas another with urgency, recurrent urinary symptoms, or marked tissue fragility may prioritize different outcomes. Similarly, a woman receiving aromatase-inhibitor therapy may evaluate even a highly effective local treatment through a different safety lens from a woman without a history of hormone-sensitive cancer. These examples do not establish discrete phenotypes a priori; instead, they motivate a synthesis that evaluates whether reproducible clusters of biological features, symptoms, treatment constraints, and outcome priorities can be identified across the contemporary literature.

Despite this rapidly expanding literature, evidence remains fragmented by symptom, organ system, intervention, biological mechanism, and specialty. Reviews frequently ask whether a particular drug or device improves GSM, whereas fewer syntheses ask whether biological and clinical phenotypes help explain why different women respond differently or prioritize different outcomes. This fragmentation creates five related gaps: limited integration of molecular and tissue mechanisms with symptoms; inadequate synthesis across genital, sexual, and urinary domains; inconsistent treatment-response measures; uncertainty about phenotype-treatment interactions; and incomplete incorporation of preference, adherence, contraindications, and high-risk populations into treatment selection.

This systematic review therefore aimed to synthesize contemporary evidence on the multidimensional pathophysiology, clinical phenotypes, treatment responses, and patient-specific determinants of GSM. Four questions guided the review: what biological mechanisms and clinical manifestations characterize GSM beyond conventional vaginal atrophy; what genital, sexual, urinary, microbial, and tissue phenotypes can be identified; how hormonal, non-hormonal, energy-based, and emerging therapies differ across outcome domains; and what evidence supports phenotype-informed, patient-centered treatment selection. The intended contribution is an integrative mechanism-phenotype-intervention-outcome framework that can organize heterogeneous evidence without prematurely presenting phenotypes as validated disease subtypes or a treatment algorithm.

This framing deliberately distinguishes descriptive phenotype mapping from validated precision medicine: the proposed categories are evidence-organizing constructs that require prospective validation before they can support algorithmic treatment selection.

2. Methods

Search Strategy

This review was designed as a systematic literature review and reported in accordance with the transparency principles of PRISMA 2020 (Page et al., 2021). The review question and eligibility structure were developed prospectively using a PICO framework because clear alignment among the question, eligibility criteria, data extraction, and synthesis reduces arbitrary study selection and supports reproducibility

(Higgins et al., 2024) (Peters et al., 2024). The population comprised menopausal and postmenopausal women with GSM, VVA, or associated genital, sexual, or lower urinary tract manifestations. Interventions or exposures included hormonal, non-hormonal, energy-based, and selected emerging approaches. Comparators included placebo, sham treatment, no treatment, pretreatment baseline, vaginal estrogen or other active hormonal therapy, non-hormonal treatment, and alternative devices. Outcomes encompassed symptoms, sexual function, urinary manifestations, vaginal-health or trophic indices, histological and biological markers, microbiome measures, safety, tolerability, treatment durability, quality of life, satisfaction, and adherence.

Scopus was the principal database. The search used the following expression in the title, abstract, and keyword fields: (“genitourinary syndrome of menopause” OR “vulvovaginal atrophy”) AND (postmenopausal OR menopausal) AND (“vaginal estrogen” OR estrogen OR oestrogen OR moisturizer* OR lubricant* OR ospemifene OR prasterone OR “dehydroepiandrosterone” OR laser OR “energy-based therap*”) AND (outcome* OR efficacy OR effectiveness OR safety OR symptom*). The search strategy deliberately combined condition, population, therapeutic exposure, and outcome blocks. The review focused on contemporary evidence indexed from 2022 through 2026, a period characterized by rapid growth in comparative device studies, microbiome research, objective tissue assessment, and treatment research in complex populations.

Scopus search string: ("genitourinary syndrome of menopause" OR "vulvovaginal atrophy") AND (postmenopausal OR menopausal) AND ("vaginal estrogen" OR estrogen OR oestrogen OR moisturizer* OR lubricant* OR ospemifene OR prasterone OR "dehydroepiandrosterone" OR laser OR "energy-based therap*") AND (outcome* OR efficacy OR effectiveness OR safety OR symptom*)

Eligibility Criteria

Primary human studies were eligible when they evaluated menopausal or postmenopausal women with clinically assessed GSM/VVA or a directly related genital, sexual, or urinary phenotype and reported at least one relevant clinical, biological, functional, safety, or patient-centered outcome. Eligible designs included randomized controlled trials, controlled clinical trials, prospective or retrospective cohorts, cross-sectional studies, and relevant human diagnostic or mechanistic investigations. This breadth was necessary because the review question extended beyond comparative effectiveness to biological architecture and phenotype characterization. Comparator-free observational studies were retained when they contributed epidemiological, diagnostic, mechanistic, safety, or real-world information.

Animal-only experiments, purely preclinical studies, protocols without outcome data, editorials, commentaries, narrative reviews, systematic reviews or meta-analyses as primary evidence, practice guidelines as effectiveness evidence, and studies outside the menopausal GSM/VVA context were excluded from the primary synthesis. Reviews and guidelines were used only to contextualize findings or methodological choices. The distinction was important because the source corpus contained both primary and secondary evidence. Methodological heterogeneity was anticipated: for example, Agrawal et al. used a randomized pilot comparison of vaginal hyaluronic acid and estrogen (Agrawal et al., 2024), whereas Li et al. employed a double-blind sham-controlled design to evaluate vaginal histology after fractional CO2 laser (Li et al., 2023). Multi-arm active comparisons such as radiofrequency versus estrogen and moisturizer further required careful classification of comparator type (Gueldini de Moraes et al., 2024).

Screening, Study Selection, and Synthesis

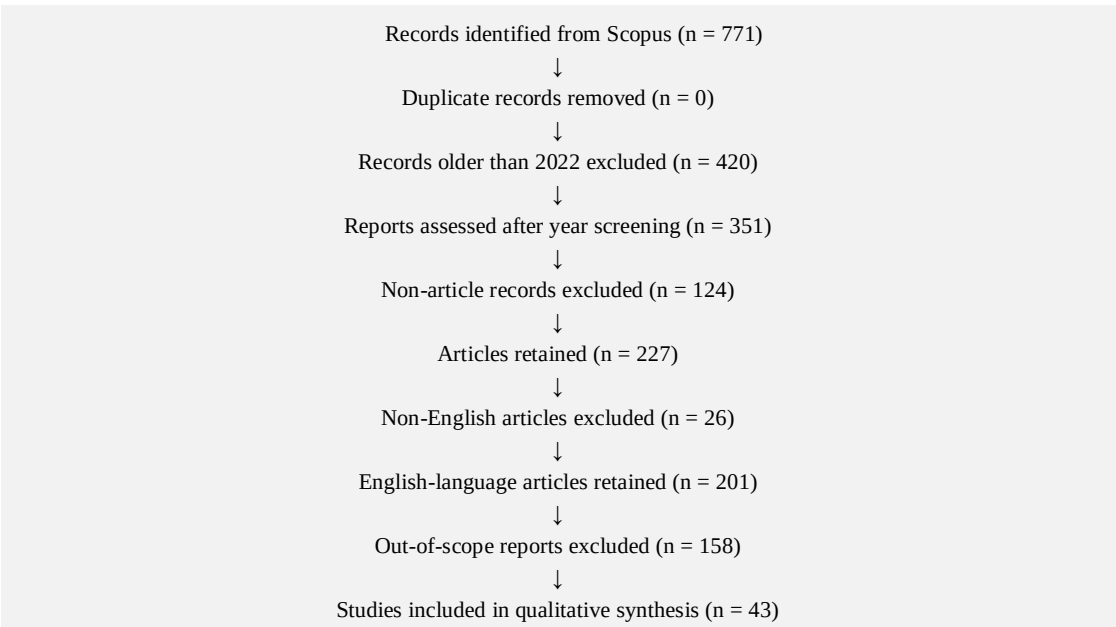
The Scopus search identified 771 records. No duplicate records were identified in the final screening dataset. Applying the publication-year criterion excluded 420 records published before 2022, leaving 351 reports. Document-type screening excluded 124 non-article records, leaving 227 articles; language screening

excluded 26 non-English articles, leaving 201 English-language articles. Title/abstract and eligibility screening then excluded 158 out-of-scope reports, resulting in 43 primary studies for qualitative synthesis.

Data were extracted into a structured framework covering author and year, population, design, intervention or exposure, comparator, biological domain, genital outcomes, sexual outcomes, urinary outcomes, objective or histological measures, safety, patient-reported outcomes, and personalized-management implications. The extraction strategy was intentionally multidomain. A four-arm randomized study of 48 postmenopausal women, for example, assessed symptoms, histology, sexual function, urinary symptoms, satisfaction, and adverse events across four energy-based modalities (Slongo et al., 2025), illustrating why a single composite "GSM improvement" field would obscure clinically meaningful differences.

Risk-of-bias appraisal was prespecified by design: randomized trials were to be assessed with RoB 2, non-randomized intervention studies with ROBINS-I, and observational studies with an appropriate validated design-specific instrument. ROBINS-I is particularly relevant where intervention allocation may be associated with prognostic characteristics and where confounding, selection, exposure classification, missing data, outcome measurement, and selective reporting can influence estimates (Sterne et al., 2016). Protocol literature in breast-cancer populations additionally informed the need to predefine endocrine-treatment status, intervention exposure, symptom criteria, and safety outcomes (Serquiz et al., 2023) (Vergauwen et al., 2023). Because the included studies were clinically and methodologically heterogeneous, no pooled meta-analysis was attempted; evidence was synthesized narratively across four predefined themes: biological architecture, clinical phenotypes, differential treatment response, and personalized management.

Figure 1. PRISMA flow diagram detailing screening and study selection.



3. Theoretical Background

From Estrogen Deficiency to a Multidimensional GSM Model

The classical model of GSM begins with menopause-associated reduction in estrogenic stimulation. Loss of estrogen responsiveness alters epithelial maturation, hydration, lubrication, and tissue elasticity, but contemporary research indicates that these changes occur within a broader stromal and cellular environment. Histological studies increasingly quantify extracellular-matrix components rather than relying only on gross appearance. Bretas et al. evaluated vaginal collagen types I and III after CO2 laser treatment, positioning collagen remodeling as a potentially measurable component of tissue response (Bretas et al., 2022). Miao et al. used optical coherence tomography to quantify vaginal epithelial thickness, demonstrating that structural assessment can move beyond subjective inspection (Miao et al., 2022).

The tissue model is expanding further to include vascular, neural, receptor-level, and molecular processes. Optical coherence tomography angiography has been applied to vaginal-health monitoring and therefore introduces microvascular architecture into objective assessment (Qiu et al., 2023). A pilot study of nerve-fiber and blood-vessel density extended the biological inquiry toward sensory and vascular determinants that may help explain symptom differences among women with apparently similar atrophic changes (Dotson et al., 2025). Studies of steroid receptors after fractional laser treatment (Pinho et al., 2023) and preliminary work on local-estrogen-associated DNA methylation (Szymański et al., 2026) suggest that receptor and epigenetic regulation may also be relevant. Histological investigations of fractional CO2 laser, including studies assessing cellular proliferation and tissue-aging markers, further illustrate the field's shift toward objective biological characterization (Benitez-Roig et al., 2023) (Antono et al., 2026).

The Vaginal Microenvironment as a Biological Interface

The vaginal microenvironment provides a biological interface between endocrine change and clinical phenotype. Estrogen influences epithelial maturation and glycogen availability, which in turn affect pH and the ecological conditions that support Lactobacillus-dominant communities. A randomized study of local estrogen examined vaginal and urinary microbiomes together with pH and maturation, directly linking endocrine exposure with the local ecological environment (Lillemon et al., 2022). Physiological-microbiome models consequently describe GSM as an ecological as well as endocrine disorder (Hamza et al., 2025).

Treatment studies reinforce this interaction. In a study of 64 women allocated to estrogen, CO2 laser, or untreated groups, both active treatments changed vaginal microbial diversity and improved vaginal-health and urinary-distress measures, while longer-term biological trajectories differed between modalities (Qi et al., 2024). Symptom relief after CO2 laser has also been examined alongside changes in vaginal Lactobacillus (Seehanantawong et al., 2025), and a double-blind placebo-controlled trial has tested hormone-therapy effects on the microbiota directly (Panyakhamlerd et al., 2026). These observations support a model in which the microbiome is neither a passive marker nor a proven independent cause, but a treatment-responsive component of the vaginal ecosystem.

Preclinical work provides mechanistic plausibility while requiring careful separation from human efficacy. Vaginal microbiota transplantation reduced vaginal atrophy in an ovariectomized mouse model (Xu et al., 2025), whereas hydrogel-delivered mesenchymal stem-cell exosomes ameliorated vaginal atrophy in ovariectomized rats (Zhang et al., 2023). Experimental models have also evaluated vaginal collagen and elastin responses to quercetin (Hadi et al., 2024) and modulation of VVA by Gelam honey (Ismail et al., 2023). These studies do not establish clinical effectiveness, but they illustrate the widening mechanistic space in which epithelial, matrix, inflammatory, microbial, and regenerative pathways may interact.

From a Single Syndrome to Overlapping Clinical Phenotypes

A phenotype framework follows logically from this biological heterogeneity. The genital or tissue-dominant phenotype includes dryness, burning, irritation, epithelial fragility, and anatomical changes. A sexual-pain phenotype emphasizes superficial dyspareunia, vestibular discomfort, impaired lubrication, and sexual dysfunction. A urinary-dominant phenotype centers on urgency, frequency, overactive bladder, incontinence, and recurrent urinary symptoms, while mixed presentations combine these domains. The value of such categories is heuristic rather than diagnostic: they organize outcome priorities without implying that GSM consists of mutually exclusive diseases.

Objective assessment technologies may help determine whether clinically meaningful biological phenotypes exist. Diffuse reflectance spectroscopy has been investigated for non-invasive GSM assessment (Dinish et al., 2024), and histological work on vaginal epithelium after CO2 laser provides direct evidence that tissue structure can be measured independently of patient-reported symptoms (Lekskulchai, 2022). Microcirculatory changes after CO2 laser have also been explored experimentally (Latul et al., 2023). The critical theoretical issue is concordance: a measurable change in epithelial thickness, collagen, vascularity, or microbiota should not be assumed to represent a clinically important improvement unless it aligns with symptom and functional outcomes.

The framework also accommodates a complex/high-risk phenotype in which the same symptom cluster has different therapeutic implications because of comorbidity or treatment context. Breast-cancer survivors, women receiving aromatase inhibitors, women who are unable or unwilling to use estrogen, and patients with overlapping pelvic-floor disorders may have similar vaginal findings but markedly different acceptable treatment sets. Thus, phenotype is not defined by symptoms alone. A clinically useful representation must include biological state, dominant symptom domain, treatment constraints, and the patient's priorities. This multidimensional definition avoids the false assumption that a single clinical score can capture all information relevant to treatment selection.

Contemporary Controversies and Evidence Tensions

The principal controversies in GSM arise precisely from this potential discordance. Energy-based interventions can produce plausible tissue effects, yet biological plausibility does not establish superiority over sham treatment or standard therapy. Clinical-histomorphometric comparisons in breast-cancer survivors attempt to bridge these dimensions by linking symptoms and tissue changes across CO2 laser, radiofrequency, and promestriene (Cantarelli et al., 2025). At the same time, experimental investigations of inflammatory signaling, including Mendelian-randomization and transcriptomic approaches, are expanding the candidate mechanisms associated with postmenopausal atrophic vaginitis (Hu et al., 2026). The theoretical challenge is therefore to avoid reducing GSM either to estrogen deficiency alone or to an unbounded collection of biomarkers.

A defensible multidimensional model treats endocrine change as an initiating context, tissue and ecological alterations as interacting biological domains, and genital, sexual, and urinary symptoms as partially overlapping clinical outputs. Treatment then becomes a perturbation of this system rather than a single pathway to “vaginal restoration.” This framework anticipates why different interventions may improve different endpoints, why objective and subjective response may diverge, and why patient constraints can alter the acceptable balance of benefit and risk. It also provides the conceptual basis for the four-theme synthesis that follows.

4. Results

The 43 included primary studies were synthesized across four predefined themes that reflected the review's mechanism-phenotype-intervention-outcome framework. The themes were not mutually exclusive; some studies contributed to more than one conceptual domain, but Tables 1-4 display the principal evidence used to structure each subsection.

Biological Architecture of GSM: Tissue Remodeling, Microbiome, and Objective Phenotypes

The biological evidence supported a conceptual shift from vaginal atrophy as a predominantly visual diagnosis toward a layered tissue and ecological phenotype (Table 1). Studies examining collagen, epithelial structure, vascularity, neural density, microbiota, optical signatures, and epigenetic responses converged on the premise that postmenopausal vaginal health has multiple measurable dimensions. Bretas et al. evaluated collagen I and III after CO2 laser treatment, whereas Miao et al. used optical coherence tomography to quantify epithelial thickness (Bretas et al., 2022) (Miao et al., 2022). Li et al. strengthened this line of inquiry by using a double-blind sham-controlled design to compare vaginal epithelial histology after fractional CO2 laser, an approach that directly tests whether a procedural intervention produces tissue effects beyond nonspecific treatment responses (Li et al., 2023).

The vaginal microenvironment emerged as a second biological axis. Lillemon et al. investigated local estrogen effects on the urogenital microbiome (Lillemon et al., 2022), while Waetjen et al. evaluated associations between vaginal microbial communities and GSM symptoms in a large longitudinal cohort context (Waetjen et al., 2023). Zeng et al. extended this relationship by examining microbiota in relation to symptom onset, severity, and type (Zeng et al., 2024). Qi et al. compared CO2 laser and estrogen and reported treatment-associated differences in vaginal microbiota and mucosal function; in the 64-woman study summarized in the extracted evidence, biological and functional trajectories were not identical across modalities (Qi et al., 2024). Together, these studies suggest that vaginal ecology can both reflect the postmenopausal state and change in response to therapy.

Objective technologies broadened the measurable phenotype beyond histology and microbiome composition. Qiu et al. applied optical coherence tomography angiography to vaginal-health monitoring, introducing microvascular assessment (Qiu et al., 2023), whereas Dinish et al. tested diffuse reflectance spectroscopy and imaging for non-invasive GSM assessment (Dinish et al., 2024). Dotson et al. examined vaginal nerve-fiber and blood-vessel density, explicitly adding neural and vascular elements to GSM biology (Dotson et al., 2025). Preliminary work on DNA methylation following local estrogen therapy further suggests that molecular regulation may accompany tissue-level response (Szymański et al., 2026). These studies are heterogeneous and often exploratory, but their collective significance is conceptual: objective improvement can occur in different biological compartments, and no single tissue marker can yet be considered a validated surrogate for symptom relief.

Table 1. Biological and objective phenotypes of genitourinary syndrome of menopause.

Reference	Population/design	Biological domain	Assessment/biomarker	Principal finding/focus	Clinical relationship	Implication
Bretas et al., 2022	Postmenopausal women with GSM; pilot study	Extracellular-matrix remodeling	Vaginal collagen I and III	Evaluated collagen changes after CO2 laser treatment	Links structural remodeling with GSM treatment	Collagen remodeling may provide an objective tissue endpoint
Miao et al., 2022	Postmenopausal women; pilot study	Vaginal epithelium	OCT; epithelial thickness	Evaluated epithelial thickness during CO2 laser treatment	Objective structural correlate of vaginal atrophy	OCT may complement symptom assessment
Lillemon et al., 2022	Women with GSM; randomized trial	Urogenital microbiome	Microbiome after local estrogen	Examined estrogen effects on urogenital microbiome	Links estrogen-responsive ecology with GSM	Microbiome change may be part of treatment response
Li et al., 2023	Postmenopausal women; double-blind sham-controlled RCT	Vaginal epithelial histology	Pre/post vaginal histology	Compared histology after fractional CO2 laser with sham	Tests whether procedural effects correspond to tissue change	Separates objective remodeling from nonspecific response
Qiu et al., 2023	Women undergoing vaginal-health evaluation	Microvascular phenotype	OCT angiography	Evaluated OCT angiography for vaginal-health monitoring	Extends assessment beyond epithelial appearance	Microvascular imaging may support objective phenotyping
Waetjen et al., 2023	Postmenopausal women; SWAN cohort	Vaginal microbiome	Vaginal microbial composition	Examined microbiota-GSM symptom relationships	Links microbial ecology with patient-reported symptoms	Supports a microbiome-associated phenotype
Dinish et al., 2024	Women with GSM; pilot study	Optical/tissue phenotype	Diffuse reflectance spectroscopy and imaging	Assessed GSM using non-invasive optical techniques	Explores measurable tissue properties associated with GSM	May reduce dependence on symptom-only assessment
Qi et al., 2024	Women with GSM receiving CO2 laser or estrogen	Microbiome and mucosal function	Vaginal microbiota and functional parameters	Compared biological effects of CO2 laser and estrogen	Treatment modalities may influence different pathways	Biological response may explain differential effects
Zeng et al., 2024	Women with GSM	Microbial phenotype	Vaginal microbiota	Assessed microbiota by onset, severity, and symptom type	Relates microbial patterns to clinical manifestations	Supports biological stratification
Dotson et al., 2025	Postmenopausal women with GSM; pilot study	Neural and vascular biology	Nerve-fiber and blood-vessel density	Investigated neural and vascular density	Extends pathophysiology beyond epithelial atrophy	May help explain pain and sensory heterogeneity
Szymański et al., 2026	Menopausal women; preliminary cross-sectional study	Epigenetic regulation	DNA methylation	Evaluated local-estrogen-associated methylation dynamics	Molecular responses may accompany tissue effects	Introduces epigenetic regulation as an emerging mechanism

Note. *Each row represents one primary reference; interpretation is restricted to the extracted evidence available for this review.*

Clinical Phenotypes and Multidomain Burden: Genital, Sexual, and Urinary Manifestations

Clinical evidence likewise argued against treating GSM as a homogeneous symptom complex (Table 2). Descriptive work in postmenopausal populations documented the broad occurrence of GSM, while population-based studies examined predictors and the transition between newly identified and prevalent cases (Ojha et al., 2022) (Bevilacqua et al., 2025) (Lambrinoudaki et al., 2024b) (Mahmoudian et al., 2025). These studies show that prevalence alone is insufficient to describe disease burden because the syndrome is operationalized through different combinations of symptoms and physical findings. Katayama et al., for example, explicitly assessed GSM prevalence using symptoms and vulval findings in Japanese women, emphasizing the potential divergence between subjective and examination-defined disease (Katayama et al., 2026).

Sexual and urinary domains provided the clearest examples of phenotypic differentiation. Goetsch et al. anatomically localized postmenopausal dyspareunia rather than treating pain as an undifferentiated symptom (Goetsch et al., 2022). In parallel, the LADY lower-urinary-tract study specifically characterized urinary symptoms after menopause, supporting a urinary-dominant dimension that may not be captured by vaginal symptom scales (Lambrinoudaki et al., 2024a). A population-based survey of menopausal symptoms and treatment use demonstrated that symptom burden and healthcare utilization do not necessarily align (Baquedano et al., 2023). These patterns support overlapping genital, sexual, and urinary phenotypes rather than mutually exclusive categories.

Clinical context further modified the meaning of a phenotype. Meriggiola et al. compared VVA characteristics in women with and without a history of breast cancer, highlighting a complex group in whom symptom burden coexists with treatment constraints (Meriggiola et al., 2024). Cucinella et al. investigated VVA signs and symptoms in routine clinical practice and explored a possible association with thyroid autoimmunity, illustrating continuing interest in systemic modifiers of presentation (Cucinella et al., 2025). Finally, Stair et al. demonstrated that patient experience includes barriers to vaginal-estrogen use as well as symptoms (Stair et al., 2025). Thus, the phenotype relevant to management includes not only what a patient feels or what a clinician observes, but also risk context, beliefs, treatment eligibility, and the outcomes that the patient prioritizes.

Table 2. Clinical phenotypes, symptom burden, and patient-centered consequences of GSM.

Reference	Population	GSM phenotype	Genital manifestations	Sexual manifestations	Urinary manifestations	Patient-centered implication
Ojha et al., 2022	Postmenopausal women in a tertiary-care center	General GSM	GSM manifestations assessed	Included within overall burden	Included within syndrome assessment	Describes GSM occurrence in clinical practice
Goetsch et al., 2022	Postmenopausal women with dyspareunia	Sexual-pain phenotype	Pain location evaluated	Dyspareunia was the primary phenotype	Not primary focus	Supports anatomical characterization of sexual pain
Baquedano et al., 2023	Population-based menopausal sample	General menopausal/GSM-related symptoms	Menopausal symptoms assessed	Symptom burden considered	Menopausal symptoms assessed	Links symptom burden with treatment utilization
Lambrinoudaki et al., 2024b	Greek postmenopausal women	Prevalent and incident GSM	GSM case characteristics	Part of multidomain syndrome	Part of GSM assessment	Defines population-level epidemiological characteristics
Lambrinoudaki et al., 2024a	Greek postmenopausal women	Urinary-dominant phenotype	Not principal endpoint	Not principal endpoint	Lower urinary tract symptoms specifically assessed	Supports explicit integration of urinary symptoms
Meriggiola et al., 2024	Women with and without previous breast cancer	Complex/high-risk VVA	Baseline VVA manifestations	Patient-reported burden relevant	Not principal title-level endpoint	Cancer history is an important clinical stratifier
Bevilacqua et al., 2025	Middle-aged Brazilian women; population-based	General GSM	GSM prevalence assessed	Potential multidomain presentation	Potential multidomain presentation	Predictors may support risk-based recognition
Mahmoudian et al., 2025	Postmenopausal women; cross-sectional	General GSM	GSM manifestations	Included within syndrome	Included within syndrome	Predictive factors may identify higher-risk patients
Cucinella et al., 2025	Women in clinical practice	VVA/GSM with possible systemic association	Signs and symptoms of VVA	GSM symptom spectrum	Not principal endpoint	Explores thyroid autoimmunity as a modifier
Stair et al., 2025	National sample of 1,500 women	Patient-experience/treatment-gap phenotype	GSM experiences reported	Patient experience incorporated	GSM-related experiences included	Identifies barriers to vaginal-estrogen use
Katayama et al., 2026	Japanese women	Symptom- and examination-defined GSM	Symptoms and vulval findings	Potential overlap	Potential overlap	Prevalence depends on symptoms and physical findings

Note. *Each row represents one primary reference; interpretation is restricted to the extracted evidence available for this review.*

Differential Therapeutic Response Across Hormonal, Non-Hormonal, and Energy-Based Interventions

Comparative treatment evidence was characterized less by a single hierarchy than by variation in mechanism, comparator, and outcome domain (Table 3). Hormonal approaches included local estrogenic preparations and systemic or receptor-modulating strategies. Palacios et al. directly compared low-dose vaginal 17β-estradiol with vaginal promestriene (Palacios et al., 2022), while Gaspard et al. evaluated estetrol in a multicenter randomized placebo-controlled study that included vaginal cytology, GSM outcomes, and health-related quality of life (Gaspard et al., 2023). Two phase III randomized trials of oral lasofoxifene evaluated moderate-to-severe vaginal atrophy, showing that receptor-modulating systemic strategies remain an active area of development (Kagan et al., 2024). These studies differ substantially in route and biological target, making class-wide generalizations inappropriate.

Non-hormonal comparisons were clinically important because many women prefer to avoid estrogen or have treatment-related concerns. Agrawal et al. randomized women in a pilot trial comparing vaginal hyaluronic acid with vaginal estrogen (Agrawal et al., 2024), and Azari et al. compared vaginal vitamin E with conjugated-estrogen cream while also evaluating overactive-bladder outcomes (Azari et al., 2023). These designs illustrate why treatment effectiveness should be evaluated across the dominant phenotype: a non-hormonal therapy may be acceptable for vaginal dryness yet have a different evidence base for urinary or sexual outcomes. Short-term comparisons of laser alone or combined with estriol or moisturizers similarly demonstrate how multimodal regimens complicate attribution of benefit to a single component (Alvisi et al., 2022).

Energy-based modalities produced the greatest methodological diversity. Gueldini de Moraes et al. compared non-invasive radiofrequency with vaginal estrogen and moisturizer in a randomized clinical trial, directly juxtaposing device-based, hormonal, and non-hormonal options (Gueldini de Moraes et al., 2024). Seganfredo et al. compared promestriene, fractional CO2 laser, and radiofrequency (Seganfredo et al., 2024), while Dedonatto et al. examined laser, radiofrequency, and promestriene specifically in breast-cancer survivors (Dedonatto et al., 2026). Such head-to-head designs are especially valuable because they address clinical alternatives rather than simple pre-post change.

Within energy-based therapy, modality itself should not be assumed to be interchangeable. Slongo et al. randomized 48 postmenopausal women across non-ablative Er:YAG laser, microablative CO2 laser, non-ablative radiofrequency, and fractional microablative radiofrequency and assessed symptoms, histology, sexual function, urinary symptoms, satisfaction, and adverse events (Slongo et al., 2025). The breadth of endpoints shows that a device can plausibly have different effects across tissue, symptom, and patient-reported domains. Photobiomodulation has also advanced from protocol work toward placebo-controlled clinical evaluation; Pereira et al. reported a double-blind placebo-controlled trial in postmenopausal women with GSM (Pereira et al., 2026). Collectively, these studies support therapeutic pluralism but also underscore unequal evidence maturity. Apparent effectiveness should therefore be interpreted in relation to comparator rigor, follow-up duration, objective versus subjective outcomes, adverse-event reporting, and whether the study population represents women likely to receive the intervention in practice.

Table 3. Differential therapeutic effects across GSM interventions and outcome domains.

Reference	Intervention	Comparator	Design/follow-up	Genital/trophic	Sexual	Urinary	Objective/biological	Safety	Evidence signal
Alvisi et al., 2022	Non-ablative laser alone or with estriol/moisturizers	Active strategies	Short-term comparative	VVA response assessed	GSM symptoms assessed	Not central	Treatment-associated vaginal effects	Explicitly evaluated	Compares device and adjunctive topical strategies
Palacios et al., 2022	Low-dose vaginal 17β-estradiol	Vaginal promestriene	Comparative clinical study	VVA efficacy assessed	Not primary	Not primary	Clinical vaginal response	Comparative acceptability	Direct comparison of local hormonal approaches
Azari et al., 2023	Vaginal vitamin E cream	Conjugated-estrogen vaginal cream	RCT	VVA outcomes compared	Not primary	Overactive bladder assessed	-	Comparative evaluation	Non-hormonal versus estrogen across domains
Gaspard et al., 2023	Estetrol	Placebo	Multicenter randomized placebo-controlled	Vaginal cytology and GSM	HRQoL assessed	GSM-related outcomes	Vaginal cytology	Trial tolerability	Links hormonal treatment with objective and patient outcomes
Agrawal et al., 2024	Vaginal hyaluronic acid	Vaginal estrogen	Randomized pilot trial	GSM response compared	Symptomatic response	Not primary	-	Comparative tolerability	Direct evidence for a non-hormonal alternative
Gueldini De Moraes et al., 2024	Non-invasive radiofrequency	Vaginal estrogen and moisturizer	RCT	VVA response compared	Related GSM outcomes	Not primary	Clinical/tissue assessment	Comparative safety	Contrasts energy, hormonal, and non-hormonal approaches
Kagan et al., 2024	Oral lasofoxifene	Control arms	Two phase III RCTs	Moderate-severe vaginal atrophy	Relevant symptom improvement	Not primary	Vaginal atrophy endpoints	Phase III safety	Advanced-stage evidence for receptor modulation
Seganfredo et al., 2024	Promestriene	Fractional CO2 laser and radiofrequency	Comparative study	GSM response	Relevant symptoms	Relevant GSM spectrum	-	Comparative	Head-to-head pharmacologic and energy-based comparison
Dedonatto et al., 2026	Laser and radiofrequency	Promestriene	RCT in breast-cancer survivors	GSM outcomes	Clinical symptoms	Multidomain effects	Clinical/histomorphometric context	High-risk population	Head-to-head evidence under treatment constraints
Slongo et al., 2025	Four laser/radiofrequency modalities	Other energy modalities	Four-arm RCT	GSM response	Sexual outcomes	Urinary outcomes	Histology	Adverse events	Tests whether energy technologies are equivalent
Pereira et al., 2026	Photobiomodulation	Placebo	Double-blind placebo-controlled trial	GSM outcomes	Symptomatic outcomes	Syndrome outcomes	Light-based mechanism	Placebo-controlled	Controlled evidence for an emerging modality

Note. *Each row represents one primary reference; interpretation is restricted to the extracted evidence available for this review.*

Toward Personalized GSM Management: Patient Selection, Treatment Constraints, and Preference-Sensitive Care

The strongest rationale for personalized management came from populations in whom treatment choice is constrained by cancer history, endocrine therapy, or patient preference (Table 4). A Danish observational cohort assessed systemic or vaginal hormone therapy after early breast cancer, providing real-world evidence for a clinically sensitive decision context (Cold et al., 2022). Research on priorities after cancer further demonstrates that women may value relief of menopausal symptoms while balancing oncologic concerns and competing health priorities (Lan et al., 2023). In breast-cancer patients receiving aromatase inhibitors, prospective measurement of serum estradiol during vaginal-estrogen therapy directly addressed systemic-exposure concerns that are not equally relevant to the general postmenopausal population (Faltinová et al., 2025).

Comparative studies in cancer survivors illustrate how treatment context changes the interpretation of efficacy. Cantarelli et al. compared clinical and histomorphometric outcomes across CO2 laser, radiofrequency, and promestriene in survivors receiving adjuvant therapy (Cantarelli et al., 2025). The VEMORA randomized trial compared vaginal estrogen with a non-hormonal moisturizer in women receiving aromatase inhibitors (Niravath et al., 2026). Vaginal tamoxifen has also been investigated as a potential option for postmenopausal women unable to use estrogen (Nyback et al., 2026), with related research extending outcomes to anxiety, depression, and health-related quality of life in women with and without breast cancer (Yazici Sarikaya et al., 2026). These studies demonstrate that the “best” intervention cannot be separated from eligibility, safety perception, and the broader consequences of treatment.

Preference and adherence also emerged as determinants of real-world effectiveness. Dell'Utri et al. explicitly designed a patient-preference comparison between local hormone therapy and radiofrequency (Dell'Utri et al., 2024). CRETA data evaluated satisfaction and medication adherence among women treated for VVA, emphasizing that persistence with therapy is part of effectiveness rather than merely a behavioral afterthought (Sánchez-Borrego et al., 2023). In the PEONY program, quality of life and satisfaction with ospemifene were examined among breast-cancer survivors (Villa et al., 2025). Stair et al. similarly documented barriers to vaginal-estrogen use in a national sample (Stair et al., 2025).

Taken together, Table 4 supports a management model in which treatment selection is conditional on four elements: the dominant symptom phenotype, the biological or objective features considered clinically relevant, treatment constraints or comorbidities, and patient preference. The evidence does not yet validate a formal phenotype-treatment algorithm, but it consistently shows why a universal sequence based only on average symptom efficacy is insufficient. Personalization in GSM is therefore best viewed at present as structured shared decision-making informed by phenotype and evidence maturity rather than precision medicine in the strict biomarker-guided sense.

Table 4. Patient-specific determinants and evidence for personalized management of GSM.

Reference	Patient subgroup/phenotype	Treatment constraint	Intervention	Clinical focus	Safety/tolerability	Preference/adherence	Personalized-management implication
Cold et al., 2022	Early breast-cancer survivors	Concern about hormonal exposure	Systemic or vaginal hormone therapy	Post-cancer hormone outcomes	Safety central	-	Requires individualized oncologic benefit-risk assessment
Lan et al., 2023	Women with menopausal symptoms after cancer	Cancer-related therapeutic constraints	Symptom-management approaches	Patient priorities	Safety affects management	Patient priorities central	Care should reflect survivor-valued outcomes
Dell'Utri et al., 2024	Women with VVA	Choice between local hormones and device treatment	Local hormone therapy vs radiofrequency	VVA management	Comparative acceptability	Patient preference central	Efficacy alone does not determine treatment choice
Faltinová et al., 2025	Breast-cancer patients on aromatase inhibitors	Potential systemic estrogen exposure	Vaginal estrogen	VVA treatment during AI therapy	Serum estradiol measured	-	Systemic-exposure data matter in AI users
Cantarelli et al., 2025	Breast-cancer survivors on adjuvant therapy	Hormonal-treatment concerns	CO2 laser, radiofrequency, promestriene	Clinical GSM outcomes	Histomorphometric/clinical safety	-	Provides alternatives for constrained populations
Stair et al., 2025	National sample of 1,500 women	Barriers to vaginal-estrogen use	Vaginal estrogen context	Experiences with GSM/treatment	Perceived safety concerns relevant	Barriers explicitly assessed	Care must address beliefs, access, and willingness
Sánchez-Borrego et al., 2023	Women with VVA receiving therapy	Long-term engagement	VVA therapies	Symptom treatment	-	Satisfaction and adherence assessed	Adherence is part of therapeutic effectiveness
Villa et al., 2025	Breast-cancer survivors with VVA	History of hormone-sensitive disease	Ospemifene	Six-month VVA outcomes	Cancer-survivor context	Satisfaction assessed	Supports alternative receptor-modulating therapy
Niravath et al., 2026	Women receiving aromatase inhibitors	Restricted/controversial estrogen use	Vaginal estrogen vs moisturizer	Randomized GSM comparison	Safety highly relevant	Acceptability implicit	Directly informs hormonal vs non-hormonal choice
Nyback et al., 2026	Postmenopausal women unable to use estrogen	Inability to use conventional estrogen	Vaginal tamoxifen	Vaginal atrophy symptoms	Alternative receptor approach	Designed for constrained subgroup	Therapy developed around contraindication profile
Yazici Sarikaya et al., 2026	Postmenopausal women with/without breast cancer	Cancer history and treatment constraints	Vaginal tamoxifen	Psychological and HRQoL outcomes	Population-specific context	Patient-reported QoL central	Personalized care extends beyond vaginal symptoms

Note. *Each row represents one primary reference; interpretation is restricted to the extracted evidence available for this review.*

5. Discussion

The principal finding of this review is that GSM is biologically and clinically broader than vaginal atrophy. Across the included literature, tissue remodeling, microbiome composition, vascular and neural characteristics, genital symptoms, sexual pain, urinary dysfunction, and patient-reported burden were measured as partially distinct domains. This breadth matters because a treatment can improve one component without establishing restoration of the entire syndrome. The implication is not that every woman requires molecular or imaging assessment, but that research should stop treating a single vaginal score as a complete representation of a multidimensional disorder.

This distinction is particularly important when interpreting biological endpoints. Histological, collagen, microbial, or optical changes can support mechanistic plausibility, yet they are not validated surrogates for clinically meaningful benefit. Energy-based therapy illustrates this tension. Earlier systematic synthesis of CO2 laser studies identified substantial interest and encouraging pre-post signals while also revealing heterogeneity (Filippini et al., 2022). More recent systematic review of randomized and prospective energy-based studies continued to emphasize uneven evidentiary maturity (Zerzan et al., 2025). Professional assessments have consequently urged caution in translating device innovation into routine care (Giarenis et al., 2024) (Phillips et al., 2022). The correct interpretation is therefore neither dismissal of biological findings nor assumption of established clinical equivalence.

Therapeutic efficacy was also domain-specific. Local hormonal and receptor-modulating therapies, non-hormonal moisturizers, and devices were evaluated using different combinations of vaginal symptoms, sexual function, urinary outcomes, histology, microbiota, quality of life, and safety. A network meta-analysis of ospemifene and other VVA therapies illustrates the usefulness of comparative synthesis but also shows why efficacy, tolerability, endometrial safety, route, and treatment suitability must be considered together (Simon et al., 2023). Phase III lasofoxifene trials further demonstrate continued development of systemic receptor-modulating approaches (Kagan et al., 2024), while direct comparison of low-dose vaginal estradiol with promestriene illustrates clinically relevant variation even within local hormonal treatment (Palacios et al., 2022).

Non-hormonal strategies remain important because preference and treatment context vary. Randomized evidence for hyaluronate-based vaginal gel supports moisturization as a therapeutic option (Nappi et al., 2022), and a randomized comparison of polycarbophil and hyaluronic-acid gels demonstrates that non-hormonal formulations should not automatically be regarded as equivalent (Cagnacci et al., 2022). Vaginal vitamin E compared with conjugated estrogen also incorporated overactive-bladder outcomes, making clear that comparative treatment studies can cross the conventional boundary between vaginal and urinary symptoms (Azari et al., 2023). Short-term laser studies combined with estriol or moisturizers further illustrate how multimodal care can resemble real-world management while complicating causal attribution (Alvisi et al., 2022).

Sexual and urinary outcomes provide perhaps the strongest argument for phenotype-oriented trials. A multi-arm randomized study of non-invasive radiofrequency assessed sexual function explicitly (Gueldini de Moraes et al., 2025), whereas a randomized comparison of vaginal dehydroepiandrosterone and estradiol focused on dyspareunia (Strandberg et al., 2026). Prasterone has also been evaluated using urodynamic outcomes in women with urge incontinence (Collà Ruvolo et al., 2025), and vaginal DHEA has been studied in stress urinary incontinence (Misasi et al., 2025). Ospemifene research likewise extended into overactive-bladder outcomes (Russo et al., 2023). These studies imply that a therapy's value may depend on which symptom domain dominates, not merely whether a composite GSM score changes.

Special populations expose the limitations of one-size-fits-all management most clearly. Observational evidence on systemic or vaginal hormone therapy after early breast cancer provides valuable real-world safety context, but treatment selection and residual confounding must temper causal interpretation (Cold et al.,

2022). In women receiving aromatase inhibitors, serum estradiol measurement during vaginal-estrogen therapy addresses a safety concern that is specific to the oncologic context (Faltinová et al., 2025). The VEMORA randomized comparison of vaginal estrogen and non-hormonal moisturizer is therefore especially informative because it evaluates clinically realistic alternatives within a treatment-constrained population (Niravath et al., 2026). Personalized management in this setting is fundamentally a benefit-risk decision rather than a simple efficacy ranking.

Patient preference, satisfaction, and adherence should accordingly be considered components of treatment effectiveness. A patient-preference trial contrasting local hormone therapy with radiofrequency explicitly recognized choice as part of the therapeutic process (Dell'Utri et al., 2024). CRETA data show that satisfaction and medication adherence are measurable outcomes that can influence persistence (Sánchez-Borrego et al., 2023), while PEONY findings in breast-cancer survivors extend evaluation of ospemifene to quality of life and satisfaction (Villa et al., 2025). These data caution against assuming that the intervention with the strongest average biological effect will necessarily produce the greatest real-world value for every patient.

The synthesis therefore supports a mechanism-phenotype-intervention-outcome framework. Menopausal endocrine change creates a biological context in which epithelial, stromal, vascular, neural, immune, and microbial alterations may occur. These alterations contribute to overlapping genital, sexual, urinary, and mixed clinical phenotypes. Treatment selection is then filtered through comorbidity, cancer history, contraindications, previous response, patient preference, and treatment burden. Interventions act on different biological targets and are assessed through different outcome domains. Comparative studies of promestriene, CO2 laser, and radiofrequency illustrate the practical need to interpret treatments across mechanisms rather than assume a common pathway (Seganfredo et al., 2024). This framework is an evidence-derived organizing model, not a validated clinical decision rule.

For this framework to become clinically actionable, future studies should pre-specify phenotype strata, use common outcome sets, and test treatment-by-phenotype interactions rather than infer personalization from post hoc subgroup effects. Objective tissue, microbial, vascular, or neural markers should be treated as candidate effect modifiers until their incremental predictive value over symptoms and clinical context is demonstrated.

Several limitations constrain the conclusions. The search relied principally on Scopus and deliberately emphasized contemporary literature from 2022 onward, which may omit earlier foundational trials. The search terms were intervention-heavy and therefore may preferentially retrieve therapeutic studies over purely observational phenotyping research. Terminology remains inconsistent between GSM and VVA, outcome instruments vary, follow-up is often short, and emerging device or regenerative studies commonly have small samples. Direct head-to-head evidence remains limited, especially for phenotype-specific treatment questions. These limitations argue for standardized GSM phenotype definitions, a core outcome set spanning genital, sexual, urinary, objective, safety, and patient-reported domains, adequately powered comparative trials, longer follow-up, and prospective stratification by clinically relevant phenotype and treatment constraint.

6. Conclusion

Contemporary evidence supports a transition from viewing genitourinary syndrome of menopause as a synonym for estrogen-deficiency-driven vaginal atrophy toward understanding it as a heterogeneous, multidimensional disorder. The reviewed studies identify interacting epithelial, stromal, microbial, vascular, neural, genital, sexual, and urinary domains, while also showing that these domains are not consistently interchangeable as measures of disease severity or treatment response. Hormonal, non-hormonal, and energy-based interventions target different biological processes and have been evaluated against different clinical endpoints, producing an evidence landscape in which efficacy depends on what is measured, in whom, and over what period.

The synthesis also demonstrates why personalized management cannot be reduced to selecting the intervention with the largest average symptom improvement. Dominant phenotype, breast-cancer history, endocrine therapy, contraindications or concerns regarding estrogen, treatment burden, adherence, and patient preference can materially change the acceptable benefit-risk balance. Local estrogen is supported by a comparatively mature evidence base, whereas energy-based and emerging regenerative strategies require stronger sham-controlled, head-to-head, and long-term evidence.

The main theoretical contribution of this review is a mechanism-phenotype-intervention-outcome framework that organizes these interacting dimensions without treating provisional phenotypes as validated disease subtypes. Future research should standardize phenotype definitions and core outcome sets, incorporate genital, sexual, urinary, objective, safety, and patient-reported outcomes, and prospectively evaluate whether phenotype-stratified treatment improves clinically meaningful outcomes. Such work is required before personalized GSM management can progress from structured shared decision-making to a validated precision-care model.

The next evidentiary step is prospective validation of treatment-by-phenotype interactions, rather than further expansion of uncontrolled modality-specific evidence alone.

Declarations

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