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Conventional Hormonal Therapy versus Emerging Regenerative Interventions for Genitourinary Syndrome of Menopause: A Technical Comparative Matrix and Evidence-Tiered Feasibility Analysis of 2024–2026 Systematic Reviews and Meta-Analyses

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Abstract

Background: Genitourinary syndrome of menopause (GSM) affects between 13% and 87% of postmenopausal women depending on ascertainment method, with vaginal dryness reported by 47–100% and dyspareunia by 20–77.6% of symptomatic cohorts [1,10]. Low-dose vaginal estrogen and vaginal dehydroepiandrosterone (DHEA, prasterone) are the established pharmacological standards, while energy-based devices (fractional microablative CO2 laser, non-ablative Er:YAG laser, radiofrequency) and platelet-rich plasma (PRP) are marketed as regenerative alternatives. Clinicians therefore face a decision problem in which biological plausibility, surrogate-endpoint responsiveness and controlled clinical benefit diverge.

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Objective: To construct a technical comparative matrix of conventional hormonal therapy versus emerging regenerative interventions for GSM, anchored on systematic reviews, meta-analyses, network meta-analyses and guidelines published in 2024–2026, and to translate that matrix into an evidence-tiered clinical feasibility analysis that distinguishes normatively endorsed from experimental interventions.

Methods: We performed a structured umbrella-type synthesis of secondary evidence, extracting quantitative estimates for the vaginal maturation index/value (VMI/VMV) and cytological fractions, vaginal pH, Vaginal Health Index (VHI/VHIS), dyspareunia severity, Female Sexual Function Index (FSFI), urinary outcomes, histological endpoints and adverse events. Interventions were then mapped onto a three-tier feasibility model (Tier 1, guideline-endorsed; Tier 2, signal-positive but not endorsed; Tier 3, experimental) using the strength of recommendation and evidence grade assigned by the issuing bodies, GRADE certainty where reported, comparator rigour, and minimal clinically important difference (MCID) attainment.

Results: Vaginal estrogen produced the largest and most reproducible objective effects: superficial cells increased by 19.28 percentage points (95% CI 13.40 to 25.16; $p < 0.00001$), parabasal cells decreased by 24.85 points (95% CI –32.96 to –16.73), and pH fell by 0.94 units (95% CI –1.05 to –0.84; $p < 0.00001$) across 18 trials and 4,723 participants, although heterogeneity reached $I^2 = 90\text{--}99\%$ [11]. Pooled dyspareunia benefit was statistically significant but small (mean difference –0.52; 95% CI –0.63 to –0.41) [11], and the Agency-grade systematic review concluded 'little to no difference' versus placebo for patient-reported symptoms with low certainty [41]. Vaginal DHEA reduced dyspareunia by 0.40 units (95% CI –0.66 to –0.15) across five trials and 1,611 participants [14]. Energy-based devices improved VHI (SMD 0.40; 95% CI 0.16 to 0.64; low certainty) and dyspareunia (SMD –0.85; 95% CI –1.59 to –0.10; low certainty) but did not change pH (SMD –1.14; 95% CI –2.60 to 0.32; very low certainty) [20]; restriction to double-blind sham-controlled trials abolished the FSFI and dyspareunia signals [21,25]. PRP evidence for GSM rests on a single 60-participant double-blind randomised trial reporting an FSFI of 19.0 ± 4.5 versus 9.7 ± 4.3 for saline ($p < 0.001$) [32] and on uncontrolled series; the 2026 systematic review of PRP in vulvovaginal conditions included only 87 patients with vulvovaginal atrophy among 480 across 18 studies [33]. No intervention attained Level A / Grade A evidence; the highest grade in the 2025 AUA/SUFU/AUGS guideline is Grade B, for vaginal estrogen in recurrent urinary tract infection, and that guideline classifies CO₂ laser as experimental outside clinical trials [1].

Conclusion: The comparative matrix supports a hierarchical, non-equivalent decision structure: vaginal estrogen and vaginal DHEA are Tier 1 first-line options with the only guideline-endorsed risk–benefit profiles; energy-based devices are Tier 2 second-line options for patients with contraindication, intolerance or failure of hormonal therapy, to be offered with explicit disclosure that major societies do not support routine use and that effects last roughly 12–18 months; and PRP remains Tier 3, appropriate only within registered clinical trials. The most consequential research priority is an adequately powered, sham-controlled PRP trial using co-primary objective (VMI, pH) and patient-reported (dyspareunia, FSFI) endpoints, since placebo response accounts for an estimated 55.2% of quality-of-life improvement in procedural GSM trials and approximately 1,384 participants are required for adequate power in this setting [25].

Keywords

Genitourinary syndrome of menopause; Vulvovaginal atrophy; Vaginal estrogen; Prasterone; Platelet-rich plasma; Fractional CO₂ laser; Radiofrequency; Regenerative medicine; Evidence-based medicine; Vaginal maturation index.

Abbreviations

AE, adverse event; AUA, American Urological Association; AUGS, American Urogynecologic Society; CEE, conjugated equine estrogens; CI, confidence interval; CrI, credible interval; DHEA, dehydroepiandrosterone; E₂, 17 β -estradiol; FDA, US Food and Drug Administration; FEBRASGO, Brazilian Federation of Gynecology and Obstetrics Associations; FSFI, Female Sexual Function Index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GSM, genitourinary syndrome of menopause; HA, hyaluronic acid; MBS, most bothersome symptom; MCID, minimal clinically important difference; MD, mean difference; NMA, network meta-analysis; PRP, platelet-rich plasma; RCT, randomised controlled trial; RF, radiofrequency; RR, risk ratio; SERM, selective estrogen receptor

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modulator; SMD, standardised mean difference; VHI/VHIS, Vaginal Health Index/Score; VMI/VMV, vaginal maturation index/value; VVA, vulvovaginal atrophy.

Introduction

Genitourinary syndrome of menopause is the currently preferred nomenclature for the constellation of vulvovaginal and lower urinary tract signs and symptoms attributable to estrogen and androgen deprivation, encompassing dryness, burning, irritation, loss of lubrication, dyspareunia, dysuria, urinary urgency and recurrent urinary tract infection. Prevalence estimates span 13% to 87% for at least one symptom, with vaginal dryness reported in 47–100% and dyspareunia in 20–77.6% of affected cohorts, the wide ranges reflecting heterogeneous case definitions and ascertainment rather than genuine population variance [1,10]. Unlike vasomotor symptoms, GSM is progressive and does not remit spontaneously, so therapeutic decisions made in the perimenopausal window commit patients to years of management.

The pharmacological standard of care is well delimited. Low-dose vaginal estrogen formulations (estradiol tablets and softgel inserts, estradiol and conjugated estrogen creams, estradiol rings, estriol and promestriene preparations in Europe and Latin America) restore epithelial maturation, glycogen content and acidic pH with minimal systemic exposure. Vaginal prasterone (DHEA) 6.5 mg, authorised by the FDA in November 2016 [44] and by the European Medicines Agency in January 2018 [9], acts as an intracellular precursor converted locally to both estrogens and androgens, an intracrinological rationale that is mechanistically distinct from exogenous estrogen delivery. Oral ospemifene 60 mg, a selective estrogen receptor modulator approved in February 2013 [45], provides a non-hormonal systemic alternative for moderate-to-severe dyspareunia.

In parallel, a large and commercially aggressive market has grown around interventions framed as regenerative. Energy-based devices act by controlled thermal injury: fractional microablative CO₂ laser and non-ablative Er:YAG laser deliver photothermal stimuli to the lamina propria, while monopolar and dynamic quadripolar radiofrequency deliver volumetric heating; both are proposed to induce neocollagenesis, neoangiogenesis, restoration of epithelial thickness and glycogen deposition. Platelet-rich plasma, an autologous concentrate of platelets and their growth factors, is injected submucosally into the vaginal walls and vulvar vestibule with the intention of stimulating fibroblast activity, extracellular matrix remodelling and angiogenesis. Both classes borrow their conceptual framework, and much of their marketing vocabulary, from musculoskeletal orthobiologics.

This creates a specific epistemic hazard. Biological plausibility, responsiveness of surrogate endpoints and durable patient-relevant benefit are three distinct claims, and the literature on regenerative gynaecology systematically conflates them. Uncontrolled before–after series in this field are abundant and almost uniformly positive; when the same interventions are examined against active hormonal comparators the differences shrink, and when examined against double-blind sham procedures several signals disappear entirely [21,25]. The regulatory record is equally divided: the FDA issued a safety communication on 30 July 2018 warning that the safety and effectiveness of energy-based devices for vaginal 'rejuvenation' had not been established [6], and no rescission of that communication could be documented, whereas in

November 2025 the FDA initiated removal of boxed warnings for cardiovascular disease, breast cancer and probable dementia from systemic and vaginal estrogen products, retaining only the endometrial cancer warning [4], with corresponding labelling changes approved in February 2026 [5]. The risk–benefit calculus of the conventional arm has therefore shifted favourably at the precise moment when the regenerative arm remains unvalidated.

Three further methodological problems are specific to this evidence base and motivate a matrix rather than a narrative approach. First, syntheses of energy-based devices reach opposite conclusions depending on whether mixed-comparator or exclusively sham-controlled trials are pooled [20,21,22,24,25]. Second, the same small pool of double-blind participants recirculates across nominally independent reviews, inflating the apparent quantity of evidence. Third, network meta-analyses that rank laser first for vaginal dryness were produced without GRADE assessment and, in the case of the NICE model, alongside an economic analysis in which laser becomes cost-effective only above approximately £270,000 per quality-adjusted life-year [3].

The objective of this review is to lay conventional and regenerative interventions side by side in a single technical matrix using identical outcome definitions, and to convert that matrix into an explicit feasibility framework separating normatively endorsed from experimental therapy, so that the clinical decision can be made on evidence tier rather than on mechanistic narrative.

Methods

Design and reporting

This is a structured umbrella-type synthesis of secondary evidence. The unit of analysis is the systematic review, meta-analysis, network meta-analysis, guideline or position statement, supplemented by pivotal or uniquely informative primary randomised controlled trials and by regulatory assessment reports where these constitute the only source of outcome-level data. The design was chosen because the primary literature on GSM has already been synthesised repeatedly and the operative clinical uncertainty concerns discordance between syntheses rather than absence of them.

Eligibility criteria

Population: postmenopausal women with GSM or vulvovaginal atrophy, including iatrogenically menopausal women and breast cancer survivors, analysed separately where reported. Interventions: (i) low-dose vaginal estrogen in any formulation; (ii) vaginal DHEA/prasterone; (iii) energy-based devices (fractional microablative CO₂ laser, non-ablative Er:YAG laser, monopolar or microablative/dynamic quadripolar radiofrequency); (iv) platelet-rich plasma alone or combined with hyaluronic acid, laser or adipose-derived preparations. Comparators: placebo, saline injection, sham procedure, non-hormonal moisturiser or lubricant, active hormonal therapy, or no treatment. Oral ospemifene was retained as a non-hormonal systemic reference arm because it appears in the same network meta-analyses and provides the only High-certainty GRADE findings in the field. Outcomes: those listed in section 2.4. Publication window: priority to syntheses published in 2024, 2025 and 2026; earlier syntheses and landmark trials were retained when they remain the only source for a given comparison and are explicitly dated as such.

Information sources and selection

Evidence was identified from PubMed and PubMed Central, Cochrane Library, journal platforms (Menopause, Climacteric, Maturitas, Journal of Sexual Medicine, Sexual Medicine Reviews, Lasers in Medical Science, Obstetrics & Gynecology, JAMA Network Open, JAMA Internal Medicine, Annals of Internal Medicine, International Urogynecology Journal, Revista Brasileira de Ginecologia e Obstetrícia), guideline repositories (AUA, NICE Evidence Reviews, The Menopause Society, AUGS, FEBRASGO) and regulatory sources (FDA Drugs@FDA and press announcements, EMA European public assessment reports, Brazilian product labelling). Every quantitative value reported in this article was extracted from the source document itself; where a value could only be obtained from a secondary tabulation, this is stated explicitly in the reference list.

Outcome definitions

- **Vaginal maturation index / value (VMI/VMV)** — cytological composition of the vaginal smear. Reported either as a composite maturation value or as the percentage of superficial, intermediate and parabasal cells. Estrogenic effect is an increase in superficial and a decrease in parabasal cells.
- **Vaginal pH** — a decrease towards 4.5 or below indicates restoration of the lactobacillus-dominant acidic milieu. Reported as mean difference in pH units or as the proportion converting from pH >5 to ≤5.
- **Vaginal Health Index (VHI/VHIS)** — five-domain clinician-scored composite (elasticity, fluid volume, pH, epithelial integrity, moisture), range 5–25; higher is better.
- **Dyspareunia** — severity on visual analogue or four-point ordinal scales; when reported as most bothersome symptom, an MCID of a 2-point decrease was applied [39]. Responder analyses using >50% symptom-severity reduction were recorded where available [25].
- **Female Sexual Function Index (FSFI)** — 19-item instrument, total range 2–36. A relative change of approximately 6% of the total score has been proposed as the MCID in procedural GSM trials [25].
- **Urinary outcomes** — urgency, frequency, incontinence questionnaires, and recurrent urinary tract infection incidence.
- **Histology and biomarkers** — epithelial thickness, collagen density and organisation, glycogen content, vascularity.
- **Safety** — all-cause adverse events, procedure-specific adverse events, serious adverse events, discontinuation, endometrial thickness and histology, and oncological outcomes in breast cancer survivors.

Evidence appraisal and feasibility tiering

Certainty was taken as reported by the source: GRADE certainty ratings where available, AMSTAR-2 confidence where stated, and the evidence grade and strength of recommendation assigned by guideline panels. Because guideline nomenclature differs across bodies, the AUA framework was used as the reference scale, in which Grade A denotes high-quality, well-conducted randomised evidence, Grade B moderate quality, and Grade C low quality, and recommendations may be Strong, Moderate, Conditional or Expert Opinion. Each intervention was then assigned to one of three feasibility tiers:

- **Tier 1 — normatively endorsed (first line).** Positive recommendation from at least one major society or regulator, regulatory approval for the indication, and reproducible effects on both objective and patient-reported outcomes.
- **Tier 2 — signal-positive, not endorsed (conditional second line).** Meta-analytical signal on at least one clinically relevant outcome, acceptable short-term safety, but absent or negative guideline endorsement, low or very low certainty, and instability of effect under sham control.
- **Tier 3 — experimental.** Insufficient controlled evidence to estimate effect with confidence; use confined to registered clinical research.

This tiering is deliberately conservative and is derived from the documents cited rather than from the authors' clinical impression. It is intended to be auditable: each cell of the matrix in Table 1 and each tier assignment in Table 8 can be traced to a numbered reference.

Handling of overlap and heterogeneity

Because overlapping primary studies across reviews inflate the appearance of independent confirmation, syntheses addressing the same intervention were compared for shared primary trials, and the number of unique double-blind participants was recorded where determinable. Statistical heterogeneity is reported as published; pooled estimates with I^2 above 75% are flagged in the tables and treated as descriptive rather than as reliable point estimates. No new meta-analysis was performed.

Results

Conventional hormonal therapy: low-dose vaginal estrogen

Objective endpoints

The largest recent meta-analysis of vaginal estrogen in GSM pooled 18 trials and 4,723 participants [11]. Cytological effects were unambiguous: superficial cells increased by 19.28 percentage points (95% CI 13.40 to 25.16; $p < 0.00001$; $I^2 = 90\%$) and parabasal cells decreased by 24.85 percentage points (95% CI -32.96 to -16.73; $I^2 = 92\%$). The composite maturation value, by contrast, was not significantly different from placebo (MD -1.96; 95% CI -13.20 to 9.28; $p = 0.73$) with $I^2 = 99\%$, an internally inconsistent result that reflects incompatible scaling of the composite across trials rather than absence of biological effect. Vaginal pH fell by 0.94 units (95% CI -1.05 to -0.84; $p < 0.00001$; $I^2 = 96\%$) across eight studies [11]; an independent 2025 meta-analysis of 17 trials and 2,111 participants focused on urinary symptoms reported a concordant pH reduction of 1.29 units (95% CI -1.66 to -0.91; $I^2 = 96\%$) [13].

The MsFLASH randomised trial provides the cleanest individual-trial comparison against both an active non-hormonal arm and placebo. Among 302 participants, 57% of the estradiol 10 µg tablet group achieved more than 5% superficial cells versus 11% with moisturiser and 11% with placebo ($p < 0.001$), and 46% of the estradiol group converted from pH above 5 to 5 or below ($p < 0.001$) versus 9% with moisturiser ($p = 0.60$) and 12% with placebo [39]. Objective epithelial and pH restoration is therefore an estrogen-specific pharmacological effect and not a nonspecific consequence of vaginal application.

Patient-reported endpoints and the objective–subjective dissociation

Pooled dyspareunia benefit was statistically significant but modest (MD -0.52; 95% CI -0.63 to -0.41; $I^2 = 99\%$ across five studies) [11]. The Agency for Healthcare Research and Quality-sponsored systematic

review, covering seven trials and 2,072 participants, concluded that vaginal estrogen produced 'little to no difference' versus placebo in patient-reported symptoms with low certainty of evidence, noting that more than half of the higher-quality trials were null [41]. In MsFLASH, FSFI improvement was +5.4 with estradiol, +3.1 with moisturiser and +4.5 with placebo, none significantly different [39].

This dissociation is the single most important interpretive fact in the field. It demonstrates that in GSM the placebo and vehicle response on symptom scales is large enough to absorb a genuine pharmacological effect, and it establishes the benchmark against which any regenerative intervention must be judged: a positive open-label symptom trajectory carries essentially no discriminative information.

Safety

Overall adverse event risk was not increased (RR 0.95; 95% CI 0.88 to 1.02); mycotic vaginal infection was more frequent (RR 2.82; 95% CI 1.23 to 6.46; $p=0.01$), pruritus was less frequent (RR 0.52; 95% CI 0.31 to 0.89), and urinary tract infection was unchanged (RR 1.13, non-significant) [11]. Endometrial safety data across 10 trials and 1,093 participants identified one case of hyperplasia arising within a polyp and no malignancies, with endometrial thickness increasing by no more than 0.5 mm [41]. In breast cancer survivors, a 2025 meta-analysis found no increase in recurrence overall (RR 0.87; 95% CI 0.67 to 1.11) and lower mortality (RR 0.80; 95% CI 0.75 to 0.86), but a point estimate of concern in women on aromatase inhibitors (RR 2.59; 95% CI 0.74 to 9.09), an interval too wide to exclude either no effect or substantial harm [12].

Conventional hormonal therapy: vaginal DHEA (prasterone)

A 2026 meta-analysis of five trials and 1,611 participants found that vaginal DHEA reduced dyspareunia severity by 0.40 units (95% CI -0.66 to -0.15) [14]. Regulatory data from the European public assessment report document superficial cell increases of 6% and 10% versus approximately 1% and 2% for placebo, parabasal cell reductions of 42% and 47%, and pH reductions of 0.9 and 1.0 units versus 0.2 and 0.3 across two pivotal trials totalling 813 participants [9]; earlier pivotal data for 0.5% DHEA reported a pH change of -1.3 ± 0.13 ($p<0.0001$) [17]. Indirect comparison of intravaginal prasterone 6.5 mg, conjugated estrogens 0.3 mg and estradiol 10 μ g yielded placebo-adjusted dyspareunia improvements of 0.35–1.21, 0.7–1.0 and 0.33 units respectively [16], which is compatible with approximate therapeutic equivalence; however, no head-to-head randomised trial of DHEA versus vaginal estrogen was identified, so non-inferiority remains an indirect inference.

Safety signals are minor but not absent. The AHRQ review rated adverse events as more frequent with vaginal DHEA than with placebo (low certainty), with serious adverse events in 3.5% versus 0% and discontinuation in 1.5–11.4% versus 1.2–9.5% [41]; the EMA label reports vaginal discharge in up to 1 in 10 users [9]. Mechanistically, DHEA supplementation raises circulating estradiol, a consideration in hormone-sensitive malignancy [18].

For context, oral ospemifene 60 mg reduced dyspareunia by 0.31 units (95% CrI -0.64 to 0.01 in random-effects and -0.31 , 95% CI -0.41 to -0.22 in fixed-effect analysis) in a network meta-analysis of 44 controlled trials and 12,637 participants, with 15 studies at high risk of bias [15], and had the largest FSFI impact in a Bayesian network meta-analysis of nine trials and 8,311 patients [10]. Ospemifene also carries

the only two High-certainty GRADE conclusions in the field, both concerning treatment satisfaction and the absence of a difference in discomfort or irritation [41]. Its trade-off is systemic: serious adverse events up to 1.9%, one probably related deep vein thrombosis, hot flushes in approximately 7%, discontinuation of 4.8–13.5% at 52 weeks, and proliferative endometrium in 30 of 1,237 treated versus 1 of 646 control participants [41,43].

Emerging regenerative interventions: energy-based devices

Pooled effects across all comparators

A 2024 GRADE-assessed meta-analysis of energy-based devices reported a favourable effect on VHI (SMD 0.40; 95% CI 0.16 to 0.64; 8 trials, 528 participants; low certainty) and on dyspareunia (SMD –0.85; 95% CI –1.59 to –0.10; 4 trials, 249 participants; low certainty), no effect on vaginal pH (SMD –1.14; 95% CI –2.60 to 0.32; 3 trials, 198 participants; very low certainty) and no effect on FSFI total score (MD 2.46; 95% CI –3.60 to 8.52; 6 trials, 308 participants; low certainty) [20]. For CO2 laser specifically against sham, the VHI mean difference was 2.21 (95% CI 1.25 to 3.16) [20]. A 2025 meta-analysis of 11 randomised trials found a statistically significant effect on pain during intercourse (SMD 0.51; $p=0.021$) while explicitly noting that clinical significance was unclear [19]. A 2023 meta-analysis of nine trials and 523 participants reported VHI superiority of laser over sham ($p=0.003$) [24], and a 2021 meta-analysis of three Er:YAG trials and 164 participants reported an FSFI mean difference of 9.37 (95% CI 6.59 to 12.14; $p<0.001$) [22].

Effects restricted to double-blind sham-controlled evidence

When analysis is confined to double-blind sham-controlled randomised trials, the picture inverts. In a synthesis of seven such trials and 407 participants, the FSFI difference was not significant (MD 3.92; 95% CI –2.87 to 10.70; $p=0.26$) and became significant only after exclusion of the largest trial (MD 6.29; 95% CI 0.20 to 12.37; $p=0.04$), a fragility that disqualifies the estimate as a basis for practice; dyspareunia showed a 16.3% absolute difference that did not reach significance in an underpowered comparison, and vaginal pH showed no difference [21]. A 2025 appraisal reached the same conclusion and quantified the reason: placebo response accounted for 55.2% of quality-of-life improvement in procedural trials, and approximately 1,384 participants would be needed for an adequately powered laser trial against sham using accepted MCID thresholds — an order of magnitude beyond any trial conducted to date [25]. The International Consultation on Sexual Medicine synthesis likewise found no difference between laser and sham in double-blind studies [10], and the 2025 systematic review supporting the AUA guideline found little or no difference for CO2 laser versus sham (4 trials) and versus conjugated estrogen cream (2 trials), with low certainty [26].

Head-to-head comparison against hormonal therapy shows equivalence rather than superiority: CO2 laser versus vaginal estrogen produced no difference in VMI (MD –0.56; 95% CI –1.14 to 0.02; 6 trials, 270 participants; $I^2 = 35\%$), VHI (MD 0.20; 95% CI –0.56 to 0.97; $I^2 = 83\%$) or FSFI (MD –0.04; 95% CI –0.45 to 0.36) [23]. Interpreted against the sham-controlled data, this equivalence is more plausibly explained by a large shared nonspecific response than by equivalent biological efficacy, since only the estrogen arm reproducibly separates from placebo on cytology and pH.

Radiofrequency

Controlled radiofrequency evidence is markedly thinner than for laser. A three-arm randomised trial with

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histomorphometry in 32 participants found VMI changes of +9.3 percentage points for radiofrequency, +31.3 for vaginal estrogen and -0.5 for moisturiser, with only the estrogen–moisturiser contrast significant ($p<0.001$), and VHI changes of +6.6, +7.3 and +1.5 with both active arms superior to moisturiser ($p<0.001$) [30]. A double-blind placebo-controlled pilot trial of microablative fractional radiofrequency versus vaginal estriol in 30 participants found no between-group difference in pH ($p=0.12156$) at an observed power of 62% [31]. An additional randomised trial of non-ablative radiofrequency has been published [29]. The 2025 AUA evidence base includes essentially a single radiofrequency publication [1]. Radiofrequency therefore cannot be considered interchangeable with laser for evidentiary purposes, despite frequent joint marketing.

Safety and durability

Short-term safety is acceptable. Across 32 studies no serious adverse events were identified [26], and a retrospective cohort of 826 women and 2,129 CO2 laser sessions reported no burns [27]. Procedure-related discomfort is common and differentiates active from sham treatment: post-procedure pain occurred in 2.3–100% of CO2 laser versus 0–10.5% of sham participants, with bleeding or discharge in 0–11.5% versus 2.3–2.6%; for Er:YAG, vaginal pain occurred in 36% versus 4% of sham participants and bleeding in 4% versus 0%, with no serious adverse events across three trials [1]. Case reports nonetheless describe scarring, chronic pain and de novo dyspareunia [25]. The FEBRASGO position statement estimates the duration of effect at 12–18 months, requiring maintenance sessions, and states that no society considers these technologies a gold standard [42]. An uncontrolled Er:YAG pilot study in breast cancer survivors reported VHI rising from 10.75 to 23.38 at one year ($p<0.0001$) in a cohort that shrank from 12 to 8 participants [28] — an instructive example of the design that generates most of the enthusiasm in this field and the least of its usable evidence.

Emerging regenerative interventions: platelet-rich plasma

PRP is the least mature of the four intervention classes and, notably, the only one for which the vaginal maturation index has not been assessed in any identified comparative study [37]. The 2026 systematic review of PRP in vulvovaginal conditions included 18 studies and 480 patients, of whom only 87 had vulvovaginal atrophy, and concluded that adverse events were few and mild [33].

One double-blind randomised controlled trial provides the only placebo-controlled estimate. In 60 participants randomised to intravaginal PRP or saline, the FSFI total score was 19.0 ± 4.5 versus 9.7 ± 4.3 at four months ($p<0.001$) and the pain domain score was 5.18 ± 0.59 versus 2.51 ± 1.63 ($p<0.001$) [32]. The magnitude of this reported gain exceeds that of any hormonal therapy in the field, including the ospemifene estimates derived from more than 12,000 participants [15], which is itself grounds for caution rather than encouragement: an effect of that size in a 60-participant single-centre trial, in a condition with a documented 55.2% placebo contribution to quality-of-life improvement [25], requires independent replication before it can inform practice.

The remaining evidence is observational. A retrospective comparison of 66 patients receiving PRP or topical estrogen reported superiority of PRP for dyspareunia at week 12 ($p=0.005$) and for FSFI ($p=0.004$), without assessment of VMI [37]. Uncontrolled series of PRP with hyaluronic acid and of PRP alone report VHI improvement ($p<0.0001$ and $p<0.001$) in cohorts of 20, 47 and 236 participants [34,35,36,38], and

PRP combined with fractional CO₂ laser has been used to reduce surgical intervention in symptomatic vaginal mesh-related complications, a different indication [47]. No regulator or professional society was identified that approves or recommends PRP for GSM; the intervention is absent from the 2025 AUA/SUFU/AUGS guideline [1], the 2020 Menopause Society position statement [7] and the 2025 FEBRASGO position statement [42]. Product characterisation — platelet concentration, leucocyte content, activation method, injection anatomy, volume and schedule — is inconsistently reported across the series, which precludes dose–response analysis and independent replication.

Comparative matrix

(Table 1) presents the integrated technical matrix. (Tables 2 to 6) disaggregate it by outcome domain with the corresponding synthesis, sample size, heterogeneity and certainty. (Table 7) summarises regulatory and guideline status, and (Table 8) presents the feasibility tiering.

Domain	Vaginal estrogen	Vaginal DHEA (prasterone)	Energy-based devices (CO ₂ / Er:YAG / RF)	Platelet-rich plasma
Mechanism	Direct estrogen receptor agonism; epithelial maturation, glycogen, lactobacilli	Intracrine local conversion to estrogens and androgens	Controlled photothermal or volumetric thermal injury; neocollagenesis, neoangiogenesis	Autologous growth-factor delivery; fibroblast activation, matrix remodelling
VMI / cytology	Superficial +19.28 pp (13.40–25.16); parabasal –24.85 pp (–32.96 to –16.73) [11]	Superficial +6% / +10%; parabasal –42% / –47% [9]	No difference vs vaginal estrogen (MD –0.56; –1.14 to 0.02) [23]; RF +9.3 pp vs estrogen +31.3 pp [30]	Not assessed in any comparative study [37]
Vaginal pH	MD –0.94 (–1.05 to –0.84) [11]; –1.29 (–1.66 to –0.91) [13]	–0.9 / –1.0 vs placebo –0.2 / –0.3 [9]; –1.3 ± 0.13 [17]	SMD –1.14 (–2.60 to 0.32), not significant [20]; no difference vs sham [21]	Not reported
VHI / VHIS	Not pooled in the largest meta-analysis [11]	Improved in pivotal trials [9,17]	SMD 0.40 (0.16–0.64) [20]; vs sham MD 2.21 (1.25–3.16) [20]; null in double-blind-only pooling [21,10]	Improved in uncontrolled series (p<0.0001 / p<0.001) [34,35,36,38]
Dyspareunia	MD –0.52 (–0.63 to –0.41) [11]; 'little to no difference', low certainty [41]	MD –0.40 (–0.66 to –0.15) [14]	SMD –0.85 (–1.59 to –0.10) [20]; not significant vs sham [21,25]	Pain domain 5.18 vs 2.51 saline (p<0.001), single trial [32]
FSFI total	+5.4 vs +4.5 placebo, not significant [39]	Improved; ospemifene ranked highest in NMA [10]	MD 2.46 (–3.60 to 8.52), not significant [20]; sham-controlled MD 3.92, p=0.26 [21]	19.0 ± 4.5 vs 9.7 ± 4.3 saline (p<0.001), single trial [32]
Urinary outcomes	Recurrent UTI prevention: Grade B, Moderate recommendation [1]; pooled urinary benefit [13]	Limited data	Best-ranked for incontinence in one NMA [40]; no guideline support [1]	Not established
Histology	Increased epithelial thickness and glycogen [30,39]	Epithelial maturation on cytology [9]	Histomorphometric change reported with RF and laser [30]	Not systematically reported
Key adverse events	Mycotic infection RR 2.82 (1.23–6.46); overall AE RR 0.95 [11]; 1 hyperplasia in polyp / 1,093 [41]	More AEs than placebo (low certainty); serious AEs 3.5% vs 0% [41]; discharge ≤1/10 [9]	Procedural pain 2.3–100% vs 0–10.5% sham; no serious AEs in 32 studies [1,26]; case reports of scarring and chronic pain [25]	Few and mild across 18 studies / 480 patients [33]
Sessions / durability	Continuous maintenance dosing; effect persists while treated	Daily insert; continuous	1–3 sessions plus maintenance; effect 12–18 months [42]	Not standardised; product characterisation inconsistent [33]
Highest certainty attained	Low (patient-reported) [41]; large objective effects with I ² 90–99% [11]	Low to moderate [41,14]	Low to very low [20,26]	Very low; one small RCT [32,33]
Guideline position	Strong recommendation, Grade C; Grade B for recurrent UTI [1]	Moderate recommendation, Grade C [1]	'Evidence does not support use'; experimental outside trials [1]	Absent from all identified guidelines [1,7,42]
Feasibility tier	Tier 1 — first line	Tier 1 — first line	Tier 2 — conditional second line	Tier 3 — experimental

Table 1: Integrated technical comparative matrix of conventional hormonal and emerging regenerative interventions for genitourinary syndrome of menopause.

AE, adverse event; CI, confidence interval; DHEA, dehydroepiandrosterone; FSFI, Female Sexual Function Index; MD, mean difference; NMA, network meta-analysis; pp, percentage points; RF, radiofrequency; RR, risk ratio; SMD, standardised mean difference; UTI, urinary tract infection; VHI, Vaginal Health Index; VMI,

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vaginal maturation index. All confidence intervals are 95% unless otherwise stated.

Intervention / comparison	Effect estimate	Source synthesis	Trials / participants	I ²	Certainty
Vaginal estrogen vs placebo — maturation value	MD -1.96 (-13.20 to 9.28); p=0.73	Ali 2024, J Menopausal Med [11]	18 / 4,723	99%	Not graded
Vaginal estrogen vs placebo — superficial cells	MD +19.28 pp (13.40 to 25.16); p<0.00001	Ali 2024 [11]	18 / 4,723	90%	Not graded
Vaginal estrogen vs placebo — parabasal cells	MD -24.85 pp (-32.96 to -16.73)	Ali 2024 [11]	18 / 4,723	92%	Not graded
Estradiol 10 µg tablet — >5% superficial cells	57% vs 11% placebo; p<0.001	Mitchell 2018, MsFLASH [39]	1 / 302	—	Randomised trial
Vaginal moisturiser — same endpoint	11% vs 11% placebo (no effect)	Mitchell 2018 [39]	1 / 302	—	Randomised trial
Prasterone 6.5 mg	Superficial +6% / +10% vs ~1% / ~2%; parabasal -42% / -47%	EMA public assessment report [9]	2 / 813	—	Regulatory
CO2 laser vs vaginal estrogen	MD -0.56 (-1.14 to 0.02); not significant	Jang 2022, JAMA Netw Open [23]	6 / 270	35%	Not graded
Radiofrequency vs estrogen vs moisturiser	+9.3 / +31.3 / -0.5 pp; estrogen vs moisturiser p<0.001	Moraes 2024, Menopause [30]	1 / 32	—	Small randomised trial
Platelet-rich plasma	Not assessed	Atlihan 2025, Front Med [37]	66 (retrospective)	—	—

Table 2: Vaginal maturation index and cytological outcomes.

Intervention / comparison	Effect estimate	Source synthesis	Trials / participants	I ²	Certainty
Vaginal estrogen vs placebo	MD -0.94 (-1.05 to -0.84); p<0.00001	Ali 2024 [11]	8 studies	96%	Not graded
Vaginal estrogen (urinary-symptom review)	MD -1.29 (-1.66 to -0.91)	Porcari 2025, Climacteric [13]	17 / 2,111	96%	Not graded
Estradiol tablet / moisturiser / placebo — pH >5 to ≤5	46% (p<0.001) vs 9% (p=0.60) vs 12%	Mitchell 2018 [39]	1 / 302	—	Randomised trial
Prasterone 6.5 mg	-0.9 / -1.0 vs placebo -0.2 / -0.3	EMA [9]	2 / 813	—	Regulatory
DHEA 0.5%	-1.3 ± 0.13; p<0.0001	Pięta 2021 [17]	Pivotal data	—	Narrative review
Energy-based devices	SMD -1.14 (-2.60 to 0.32); not significant	Pessoa 2024, RBGO [20]	3 / 198	—	Very low (GRADE)
Laser vs sham	No difference	Prodromidou 2023, J Pers Med [21]	7 / 407	—	Not graded
Microablative radiofrequency vs estriol	Between-group p=0.12156 (observed power 62%)	Zunino 2025, RBGO [31]	1 / 30	—	Pilot trial

Table 3: Vaginal pH outcomes.

Intervention / comparison	Effect estimate	Source synthesis	Trials / participants	Certainty
Energy-based devices, pooled	SMD 0.40 (0.16 to 0.64)	Pessoa 2024 [20]	8 / 528	Low (GRADE)
CO2 laser vs sham	MD 2.21 (1.25 to 3.16)	Pessoa 2024 [20]	Subset	Low
Laser vs sham	p=0.003	Mao 2023, Lasers Med Sci [24]	9 / 523	Not graded
Laser vs sham, double-blind trials only	No difference	Prodromidou 2023 [21]; ICSM 2026 [10]	7 / 407	Not graded
CO2 laser vs vaginal estrogen	MD 0.20 (-0.56 to 0.97); not significant (I ² = 83%)	Jang 2022 [23]	6 / 270	Not graded
Radiofrequency vs estrogen vs moisturiser	+6.6 / +7.3 / +1.5; both active arms vs moisturiser p<0.001	Moraes 2024 [30]	1 / 32	Small randomised trial
Er:YAG laser, uncontrolled	10.75 to 23.38 at 1 year; p<0.0001	Ferreira 2025 [28]	12 enrolled, 8 completed	Very low

Intervention / comparison	Effect estimate	Source synthesis	Trials / participants	Certainty
PRP + hyaluronic acid / PRP alone, uncontrolled	Improved ($p < 0.0001$ / $p < 0.001$)	Waghe 2024 [34]; Hersant 2018 [35]; Saleh 2022 [36]; Moccia 2023 [38]	20; 47; 236	Very low
Vaginal estrogen	Not pooled in the largest meta-analysis	Ali 2024 [11]	—	—

Table 4: Vaginal Health Index outcomes.

Outcome / intervention	Effect estimate	Source synthesis	Trials / participants	Certainty
Dyspareunia				
Vaginal estrogen vs placebo	MD -0.52 (-0.63 to -0.41); $I^2 = 99\%$	Ali 2024 [11]	5 studies	Not graded
Vaginal estrogen vs placebo	'Little to no difference'; majority of higher-quality trials null	Danan 2024, Ann Intern Med [41]	7 / 2,072	Low (GRADE)
Vaginal DHEA	MD -0.40 (-0.66 to -0.15)	Lemos 2026, Menopause [14]	5 / 1,611	Not graded
Prasterone vs CEE vs estradiol	0.35–1.21 vs 0.7–1.0 vs 0.33 units over placebo	Archer 2017 [16]	Indirect comparison	Low
Ospemifene 60 mg	MD -0.31 (CrI -0.64 to 0.01) random effects; -0.31 (-0.41 to -0.22) fixed effect	Simon 2023, Menopause [15]	44 / 12,637	15 studies high risk of bias
Energy-based devices	SMD -0.85 (-1.59 to -0.10)	Pessoa 2024 [20]	4 / 249	Low (GRADE)
Laser / radiofrequency, pain during intercourse	SMD 0.51; $p = 0.021$; clinical significance unclear	Vizán-Chaguaceda 2025, Obstet Gynecol [19]	11 randomised trials	Not graded
Laser vs sham	Not significant; 16.3% absolute difference, underpowered	Prodromidou 2023 [21]; Climacteric 2025 [25]	7 / 401–407	Not graded
CO2 laser vs sham / vs conjugated estrogen cream	Little to no difference	Zerzan 2025, Menopause [26]	k = 4; k = 2	Low (GRADE)
PRP vs saline, pain domain	5.18 ± 0.59 vs 2.51 ± 1.63 ; $p < 0.001$	Abdel Hamid 2025, BMC Womens Health [32]	1 / 60	Single small trial
PRP vs topical estrogen	$p = 0.005$ at week 12	Atlihan 2025 [37]	66 (retrospective)	Very low
FSFI total score				
Estradiol tablet / moisturiser / placebo	+5.4 / +3.1 / +4.5; all not significant	Mitchell 2018 [39]	1 / 302	Randomised trial
Ospemifene	Largest FSFI impact in Bayesian network meta-analysis	ICSM 2026 [10]	9 / 8,311	Ranking only
Energy-based devices	MD 2.46 (-3.60 to 8.52); not significant	Pessoa 2024 [20]	6 / 308	Low (GRADE)
Laser vs sham	MD 3.92 (-2.87 to 10.70); $p = 0.26$. Excluding one trial: 6.29 (0.20 to 12.37); $p = 0.04$	Prodromidou 2023 [21]	7 / 407	Fragile
Er:YAG laser	MD 9.37 (6.59 to 12.14); $p < 0.001$	Khamis 2021, Menopause [22]	3 / 164	Not graded
CO2 laser vs vaginal estrogen	MD -0.04 (-0.45 to 0.36); not significant	Jang 2022 [23]	6 / 270	Not graded
PRP vs saline placebo	19.0 ± 4.5 vs 9.7 ± 4.3; $p < 0.001$ at 4 months	Abdel Hamid 2025 [32]	1 / 60	Requires replication
PRP vs topical estrogen	$p = 0.004$	Atlihan 2025 [37]	66 (retrospective)	Very low

Table 5: Dyspareunia and Female Sexual Function Index outcomes.

Intervention	Safety data	Source
Vaginal estrogen	Overall AE RR 0.95 (0.88–1.02); mycotic infection RR 2.82 (1.23–6.46), $p = 0.01$; pruritus RR 0.52 (0.31–0.89); UTI RR 1.13, not significant	Ali 2024 [11]
Vaginal estrogen — endometrium	10 trials / 1,093 participants: 1 hyperplasia within a polyp, 0 malignancies; thickness increase ≤ 0.5 mm	Danan 2024 [41]
Vaginal estrogen — breast	Recurrence RR 0.87 (0.67–1.11); mortality RR 0.80 (0.75–0.86); with	Santos 2025, RBGO [12]

Intervention	Safety data	Source
cancer survivors	aromatase inhibitor RR 2.59 (0.74–9.09)	
Vaginal DHEA	More AEs than placebo (low certainty); serious AEs 3.5% vs 0%; discontinuation 1.5–11.4% vs 1.2–9.5%; vaginal discharge ≤1/10	Danan 2024 [41]; EMA [9]
Ospemifene	Serious AEs ≤1.9%; 1 probably related deep vein thrombosis; hot flushes ~7%; discontinuation 4.8–13.5% at 52 weeks; proliferative endometrium 30/1,237 vs 1/646	Danan 2024 [41]; Kim 2025 [43]
CO2 laser vs sham	Post-procedure pain 2.3–100% vs 0–10.5%; bleeding or discharge 0–11.5% vs 2.3–2.6%	AUA/SUFU/AUGS 2025 [1]
Er:YAG laser vs sham	Vaginal pain 36% vs 4%; bleeding 4% vs 0%; no serious AEs across 3 trials	AUA/SUFU/AUGS 2025 [1]
Energy-based devices, aggregate	Few AEs and no serious AEs across 32 studies; no burns in 2,129 CO2 laser sessions	Zerzan 2025 [26]; Hatta 2026 [27]
Energy-based devices — case reports	Scarring, chronic pain, de novo dyspareunia	Climacteric 2025 [25]
Platelet-rich plasma	Few and mild AEs across 18 studies and 480 patients (87 with vulvovaginal atrophy)	De Ponte 2026, J Sex Med [33]

Table 6: Adverse events and safety signals.

Body / source	Intervention	Position	Strength / grade
AUA / SUFU / AUGS 2025 [1]	Low-dose vaginal estrogen	Recommend	Strong recommendation; Grade C
AUA / SUFU / AUGS 2025 [1]	Vaginal estrogen for recurrent UTI	Recommend	Moderate recommendation; Grade B (highest grade in the guideline)
AUA / SUFU / AUGS 2025 [1]	Vaginal DHEA	Recommend	Moderate recommendation; Grade C
AUA / SUFU / AUGS 2025 [1]	Ospemifene	May offer	Conditional recommendation; Grade C
AUA / SUFU / AUGS 2025 [1]	Moisturisers and lubricants	Recommend	Moderate recommendation; Grade C
AUA / SUFU / AUGS 2025 [1]	CO2 and Er:YAG laser, radiofrequency	'Evidence does not support the use'	Moderate recommendation; Grade C
AUA / SUFU / AUGS 2025 [1]	CO2 laser	Experimental outside clinical trials	Expert Opinion
FDA, Drugs@FDA [44]	Prasterone 6.5 mg vaginal insert (NDA 208470)	Approved 16 November 2016	Prescription
FDA, CDER [45]	Ospemifene 60 mg (NDA 203505)	Approved 26 February 2013	Prescription
FDA Safety Communication, 30 July 2018 [6]	Energy-based devices for vaginal 'rejuvenation'	Safety and effectiveness not established	Warning; no rescission identified
FDA, 10 November 2025 [4]	Systemic and vaginal estrogen	Removal of boxed warnings for cardiovascular disease, breast cancer and probable dementia initiated; endometrial cancer warning retained	Regulatory action
FDA, February 2026 [5]	Menopausal hormone therapy including topical vaginal estrogen	Labelling changes approved for 6 products across 4 categories	Regulatory action
EMA [9]	Prasterone pessary (EMA/H/C/004138)	Marketing authorisation 8 January 2018	Authorised
ANVISA-market labelling [46]	Promestriene vaginal cream 10 mg/g	Marketed in Brazil (registration number not retrievable from the label consulted)	Prescription
FEBRASGO Position Statement 2025 [42]	Energy-based technologies	Alternative or complementary only; ANVISA-registered equipment and trained gynaecologists; effect duration 12–18 months; not a gold standard for any society	Position statement
The Menopause Society 2020 [7]	Energy-based therapies	Insufficient placebo-controlled trials to make recommendations	Position statement
AUGS Clinical Consensus 2022 [8]	Vaginal energy-based devices	28 of 40 statements reached consensus; 12 failed for insufficient evidence	Consensus statement
ACOG / AUGS / Menopause Society, as summarised in Kim 2025 [43]	Laser and radiofrequency	Advise against routine use	Guideline summary
Any regulator or society	Platelet-rich plasma for GSM	No approval or recommendation identified; absent from AUA 2025, Menopause Society 2020 and FEBRASGO 2025	None [1,7,42]

Table 7: Regulatory and guideline status.

Discussion

No intervention reaches Level A evidence

The central finding of this synthesis is negative and should be stated plainly: no intervention for GSM currently rests on Level A / Grade A evidence. In the 2025 AUA/SUFU/AUGS guideline, the highest evidence grade assigned to any GSM intervention is Grade B, and it applies to a single indication — vaginal estrogen for prevention of recurrent urinary tract infection. Every other recommendation, including the Strong recommendation for low-dose vaginal estrogen itself, rests on Grade C evidence [1]. The only High-certainty GRADE conclusions identified anywhere in the field concern ospemifene, and both are about treatment satisfaction and the absence of a difference in discomfort or irritation rather than about symptom efficacy [41].

This has a direct consequence for how the conventional–regenerative comparison should be framed. The relevant contrast is not 'proven' versus 'unproven' but a gradient of evidentiary maturity in which conventional therapy occupies a position of guideline-endorsed low-to-moderate certainty and the regenerative interventions occupy positions of low-to-very-low certainty without endorsement. Arguments that dismiss the regenerative arm by appeal to Level A hormonal evidence misstate the record; arguments that promote the regenerative arm on the grounds that hormonal evidence is also imperfect commit a false-equivalence error, because the two arms differ decisively in comparator rigour, regulatory approval status and reproducibility of objective effects.

Objective and patient-reported endpoints diverge, and the direction of divergence differs by intervention

Vaginal estrogen and prasterone produce large, replicated, mechanistically coherent changes in cytology and pH while yielding small or null pooled effects on symptom scales [11,39,41]. Energy-based devices show the opposite pattern: no reliable effect on pH [20,21], no advantage over vaginal estrogen on VMI [23], yet a positive pooled signal on the clinician-scored VHI and on dyspareunia when all comparators are combined [19,20]. PRP shows the most extreme version of this asymmetry, with no VMI data at all and the largest reported FSFI gain in the literature from a single 60-participant trial [32,37].

The interpretive rule that follows is that endpoint concordance, not endpoint magnitude, is the marker of a genuine tissue-level effect. An intervention that restores epithelial maturation and acidifies the vaginal milieu but improves symptoms modestly is behaving as a pharmacological agent operating against a high nonspecific response. An intervention that improves symptom scores and clinician-scored composites without moving cytology or pH is not yet distinguishable from an elaborate procedural placebo. This distinction cannot be resolved by larger uncontrolled series; it requires sham control with objective co-primary endpoints.

Comparator rigour explains the discordance between syntheses

Syntheses of energy-based devices published between 2021 and 2025 are not interchangeable, and their disagreement is systematic rather than random. Reviews pooling mixed comparators report benefit [19,20,22,24]; reviews restricted to double-blind sham-controlled trials report none [10,21,25], and the 2025 evidence review supporting the AUA guideline aligns with the latter [1,26]. Two features make the negative syntheses more credible for decision-making. First, the sham-controlled estimates are fragile in

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the direction of the null under leave-one-out analysis, not away from it [21]. Second, the quantified placebo contribution of 55.2% of quality-of-life improvement in procedural trials provides a mechanism for the positive results seen in unblinded designs [25].

Overlap compounds the problem. The same pool of roughly 401 to 407 double-blind participants recurs across three nominally independent syntheses, and the figure of 8,311 patients appears in more than one network meta-analysis of the same underlying trials [10,21,25,40]. A clinician counting reviews rather than unique participants will substantially overestimate the evidence base. Umbrella-level appraisal of overlap is therefore not a methodological refinement in this field but a prerequisite for correct interpretation.

Network meta-analytical rankings conflict with guideline positions

Two network meta-analyses rank laser first for vaginal dryness and, in one case, for dyspareunia, incontinence, pH and VHI [3,40]. These rankings should not be read as efficacy conclusions. The NICE evidence review that produced the dryness ranking (laser > laser plus estrogen > SERM > DHEA > conjugated estrogen > estradiol) states that the laser estimate rests on small numbers, that GRADE assessment was not undertaken, and that in its own economic model laser becomes cost-effective only above approximately £270,000 per quality-adjusted life-year, with estriol the preferred option (incremental net monetary benefit £346) [3]. Ranking probabilities derived from sparse, indirectly connected networks with unblinded nodes are highly sensitive to the very placebo effects that sham control is designed to neutralise. The FEBRASGO position statement effectively reverses the ranking on clinical grounds [42].

The risk–benefit balance of conventional therapy has improved

The 2025 and 2026 FDA actions removing boxed warnings for cardiovascular disease, breast cancer and probable dementia from systemic and vaginal estrogen products, while retaining the endometrial cancer warning, and the subsequent approval of labelling changes, remove a major source of patient and prescriber hesitancy that had no basis in the low-dose vaginal data [4,5]. Combined with meta-analytical endometrial safety data showing one case of hyperplasia within a polyp and no malignancies across 1,093 participants [41], and oncological data in breast cancer survivors showing no increase in recurrence and lower mortality [12], the practical argument for reaching first for a device or an injectable because 'hormones are risky' is now considerably weaker than it was three years ago. The one genuine unresolved safety question in the conventional arm concerns concurrent aromatase inhibitor therapy, where the meta-analytical point estimate of 2.59 with a confidence interval from 0.74 to 9.09 mandates shared decision-making with the treating oncologist rather than either reassurance or prohibition [12].

What would make PRP credible for GSM

PRP occupies a distinctive position in this matrix: it is the intervention with the strongest single reported effect and the weakest evidentiary foundation. Four deficiencies must be corrected before it can enter routine practice. First, replication: one 60-participant trial cannot support a claim of superiority over therapies evaluated in thousands of patients [15,32]. Second, objective endpoints: the absence of any VMI or pH data means there is currently no biological corroboration of the reported symptomatic benefit [37]. Third, product and procedure characterisation: platelet and leucocyte concentration, activation method, injection anatomy and depth, volume, number of sessions and interval are inconsistently

reported, which makes the intervention irreproducible in the strict sense and prevents dose–response analysis [33]. Fourth, adequate power against sham: the 1,384-participant estimate derived for laser trials is the appropriate order of magnitude for any procedural intervention in this condition when accepted MCID thresholds are applied [25].

A defensible next trial would therefore be a multicentre, double-blind, saline-sham randomised trial of standardised, fully characterised PRP with co-primary endpoints combining an objective measure (VMI or pH) and a patient-reported measure (most bothersome symptom or FSFI), a minimum follow-up of 12 months to test durability, prespecified responder analysis using a 2-point most-bothersome-symptom reduction [39] or a 6% FSFI change [25], and mandatory reporting of the full product specification. Until such data exist, PRP for GSM should be offered only within registered research.

Clinical feasibility and a decision structure

(Table 8) operationalises the matrix into feasibility tiers. The resulting decision structure is sequential rather than menu-based.

Tier	Intervention	Basis for tier assignment	Clinical role	Consent and documentation requirements
Tier 1 — normatively endorsed	Low-dose vaginal estrogen; vaginal DHEA (prasterone)	Regulatory approval for the indication [9,44]; positive society recommendations [1]; reproducible objective effects [9,11,39]; favourable and now formally relaxed safety labelling [4,5,41]	First line for moderate-to-severe GSM, with moisturisers and lubricants as adjuncts or for mild symptoms [1]	Standard informed consent. Document retained endometrial cancer warning [4] and, in breast cancer survivors on aromatase inhibitors, joint decision with oncology [12]
Tier 1 (systemic alternative)	Oral ospemifene 60 mg	Approved 2013 [45]; largest evidence base [15]; only High-certainty GRADE findings [41]; conditional recommendation [1]	Alternative for moderate-to-severe dyspareunia when vaginal administration is unacceptable	Disclose thromboembolic and vasomotor risk, endometrial proliferation data and discontinuation rates [41,43]
Tier 2 — signal-positive, not endorsed	Fractional microablative CO2 laser; non-ablative Er:YAG laser	Positive pooled VHI and dyspareunia signals at low certainty [19,20]; null under double-blind sham control [10,21,25]; societies advise against routine use [1,42,43]; acceptable short-term safety [26,27]	Conditional second line only after contraindication, intolerance or documented failure of Tier 1, ideally within a registry or trial	Explicit written disclosure that major societies do not support routine use and that the AUA classifies CO2 laser as experimental outside trials [1]; that effect duration is estimated at 12–18 months with maintenance sessions [42]; and that procedural pain, bleeding and rare scarring or chronic pain have been reported [1,25]
Tier 2 (lower position)	Non-ablative and microablative radiofrequency	Almost no controlled evidence; single publication in the AUA evidence base [1]; two underpowered randomised trials [30,31]	Not recommended outside research; should not be presented as equivalent to laser	As above, with additional disclosure of the near-absence of controlled data
Tier 3 — experimental	Platelet-rich plasma, alone or combined with hyaluronic acid, laser or adipose-derived preparations	One 60-participant sham-controlled trial [32]; 87 patients with vulvovaginal atrophy across an 18-study review [33]; no VMI or pH data [37]; absent from all identified guidelines [1,7,42]	Registered clinical research only	Research consent under ethics committee approval; no fee-for-service provision as established therapy; full product characterisation recorded

Table 8: Clinical feasibility analysis by evidence tier.

Applied sequentially, this structure yields four practical rules. First, offer Tier 1 therapy to every symptomatic patient without contraindication, and treat the recently revised labelling as an opportunity to correct exaggerated risk perceptions [4,5]. Second, define failure explicitly before escalating: an adequate trial of low-dose vaginal estrogen or prasterone means at least 12 weeks of documented adherence with objective reassessment of pH and, where available, cytology, since apparent non-response is frequently non-adherence. Third, when escalating to a Tier 2 device, do so as a time-limited

therapeutic trial with predefined response criteria and objective reassessment, and record the disclosures listed in (**Table 8**); a device that has not produced MCID-level improvement after a full protocol should be discontinued rather than repeated indefinitely. Fourth, confine PRP to research, and resist the transfer of orthobiologic marketing language into gynaecological practice where the controlled data do not yet exist.

Strengths and limitations

The strengths of this synthesis are the deliberate separation of mixed-comparator from sham-controlled estimates, the explicit treatment of overlap between reviews, the use of the issuing bodies' own grades rather than a re-derived certainty scale, and the traceability of every matrix cell to a numbered source.

Several limitations must be acknowledged. No new meta-analysis was performed, so pooled estimates are reported as published, including several with I^2 between 88% and 99% that should be read descriptively [11,13]. Some quantitative values were available only from regulatory assessment reports or from secondary tabulations within reviews rather than from the primary publications, and these instances are flagged in the reference list. Four categories of information could not be confirmed from any source consulted: per-session monetary costs for laser, radiofrequency and PRP; Brazilian ANVISA registration numbers and approved indications for the relevant products; the text of the 2018 ISSVD–ICS statement; and any post-2018 FDA update on energy-based devices. Direct comparison of vaginal DHEA with vaginal estrogen rests on indirect evidence only. Finally, formal AMSTAR-2 appraisal of each included review was not undertaken, and the tiering framework, although derived from cited documents, involves judgement in the assignment of radiofrequency to a lower position within Tier 2.

Conclusion

Conventional hormonal therapy and emerging regenerative interventions for genitourinary syndrome of menopause are not evidentiary equals, and the comparative matrix assembled here identifies precisely where they differ. Low-dose vaginal estrogen and vaginal DHEA reproducibly restore epithelial maturation and acidify the vaginal milieu, hold regulatory approval for the indication, carry positive society recommendations, and have recently benefited from formal relaxation of estrogen labelling; their limitation is a modest pooled effect on symptom scales against a large nonspecific response. Energy-based devices generate a low-certainty signal on the Vaginal Health Index and dyspareunia that does not survive restriction to double-blind sham-controlled trials, do not alter vaginal pH, offer no advantage over vaginal estrogen on cytology, last an estimated 12 to 18 months, and are explicitly not supported for routine use by the bodies that have examined them. Platelet-rich plasma rests on one small sham-controlled trial and a set of uncontrolled series, has never been assessed against the vaginal maturation index, and appears in no guideline.

No intervention in this field has achieved Level A evidence; the highest grade attained anywhere is Grade B, for vaginal estrogen in the prevention of recurrent urinary tract infection. Clinical decisions should therefore be made on evidence tier rather than on mechanistic appeal: Tier 1 hormonal therapy first, Tier 2 devices as a conditional, explicitly disclosed and time-limited second line after documented Tier 1 failure or contraindication, and Tier 3 platelet-rich plasma within registered research only. The field's most valuable next contribution would be a single adequately powered, sham-controlled trial of a fully

characterised regenerative product with concordant objective and patient-reported co-primary endpoints — a study that would settle more than the accumulated weight of the uncontrolled literature it would replace.

Declarations

Ethics approval and consent to participate

Not applicable. This article is a synthesis of previously published aggregate data and does not involve human participants, human material or human data collected by the authors.

Consent for publication

Not applicable.

Availability of data and materials

All data analysed in this review are contained in the publications and regulatory documents listed in the references. The extraction matrix is available from the corresponding author on reasonable request.

Competing interests

This research has no relationship with manufacturers of vaginal energy-based devices, platelet-rich plasma systems or menopausal hormone therapy products.

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Confirm that the author(s) verified all extracted values against the primary sources and accept full responsibility for the content.

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