American Urological Association

**APPROVED BY THE AUA BOARD OF DIRECTORS APRIL 2025**

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.



# Genitourinary Syndrome of Menopause: AUA/SUFU/AUGS Guideline

*Endorsed by The International Society for the Study of Women's Sexual Health (ISSWSH) and The Menopause Society (TMS)*

## Guideline Panel

*Melissa R. Kaufman, MD, PhD; A. Lenore Ackerman, MD, PhD; Katherine A. Amin, MD; Marge Coffey, MSW; Stephanie S. Faubion, MD, MBA; Anne Hardart, MD; Irwin Goldstein, MD; Giulia M. Ippolito, MD, MS; Gina M. Northington, MD, PhD; Charles R. Powell, MD; Rachel S. Rubin, MD; O. Lenaine Westney, MD; Tracey S. Wilson, MD; Una J. Lee, MD*

## Staff and Consultants

*Systematic Review prepared by the Minnesota Evidence-based Practice Center Minneapolis, MN. Investigators: Elisheva R. Danan, M.D., M.P.H.; Susan Diem, M.D., M.P.H.; Catherine Sowerby, B.A.; Kristen Ullman, M.P.H.; Kristine Ensrud, M.D., M.P.H.; Adrienne Landsteiner, Ph.D., M.P.H.; Nancy Greer, Ph.D.; Nicholas Zerzan, M.P.H.; Maylen Anthony, M.P.H.; Caleb Kalinowski, M.S.; Mary Forte, Ph.D., D.C.; Hamdi I. Abdi, M.P.H.; Jessica K. Friedman, Ph.D.; Rahel Nardos, M.D., M.S.; Cynthia Fok, M.D., M.P.H.; Philipp Dahm, M.D., M.H.Sc.; Mary Butler, Ph.D., M.B.A.; Timothy J. Wilt, M.D., M.P.H.*

## SUMMARY

### Purpose

Genitourinary syndrome of menopause (GSM) describes the spectrum of symptoms and physical changes resulting from declining estrogen and androgen concentrations in the genitourinary tract during the menopausal transition.[1] There has not been a consensus reached about the number or type of symptoms (vulvovaginal, urinary, or sexual) needed to diagnose GSM, nor a requirement for identifying concurrent physical signs.[2, 3] Furthermore, the urinary symptoms associated with GSM are also linked with other common urologic conditions in older patients, such as overactive bladder, making identification, evaluation, and treatment complex.[4] This guideline provides information to clinicians regarding identification, diagnosis, counseling, and treatment for patients with GSM to optimize symptom control and quality of life while minimizing adverse events. The strategies defined in this document were derived from evidence-based and consensus-based processes; however, shared decision-making is the optimal strategy to individualize level of impact and ultimate interventions. Outreach to the marginalized and underserved GSM population is essential; this guideline will give clinicians across a multitude of disciplines the tools to evaluate, manage, and treat GSM patients.

## Methodology

The systematic review utilized in the creation of this guideline is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ) and funded by the Patient Centered Outcomes Research Institute (PCORI).[5] Low and moderate risk of bias studies were synthesized and provided Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence (COE) ratings for 8 patient-centered outcomes identified by the Core Outcomes in Menopause (COMMA) review[1] as most important to patients and clinicians, including: (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort/irritation, (4) dysuria, (5) change in Most Bothersome Symptom (MBS), (6) distress, bother, or interference of genitourinary symptoms, (7) satisfaction with treatment, and (8) treatment side effects.

After assessing 107 publications for risk of bias (RoB), the EPC extracted and synthesized effectiveness and/or harms outcomes from 68 publications that were rated low, some concerns, or moderate RoB (24 estrogen publications, 35 non-estrogen, 11 energy-based, and 4 moisturizers). Of 39 high, serious, or critical RoB publications, the EPC extracted long-term harms from only 15 uncontrolled studies of energy-based interventions (all serious or critical RoB due to confounding). An additional 66 publications evaluating 46 non-hormonal interventions, including natural products, mind/body practices, and educational interventions, were described in an evidence map. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

# GUIDELINE STATEMENTS

## SHARED DECISION MAKING

1. Clinicians and patients should engage in shared decision-making, taking into consideration the best available evidence and the patient's expressed values, preferences, and goals of GSM care. *(Clinical Principle)*

## SCREENING & DIAGNOSIS

2. Clinicians should screen patients at risk for, or presenting with signs of, GSM for genital, sexual, and/or urinary symptoms using a focused medical, sexual, and psychosocial history. *(Clinical Principle)*

3. Patients with symptoms of GSM should undergo a genitourinary examination. *(Clinical Principle)*

4. Clinicians should educate patients with GSM about genitourinary signs and symptoms that result from decreased sex steroid hormones. *(Clinical Principle)*

5. During evaluation of patients with GSM, clinicians should assess for coexisting genitourinary conditions, utilizing additional testing or referral when appropriate. *(Clinical Principle)*

6. In patients with GSM and psychosocial and/or sexual health concerns, clinicians may refer to a credentialed therapist. *(Expert Opinion)*

7. In patients with GSM and pelvic floor dysfunction, clinicians may refer to a physical therapist specializing in pelvic floor conditions. *(Expert Opinion)*

## HORMONAL INTERVENTIONS

**8.** Clinicians should offer the option of local low-dose vaginal estrogen to patients with GSM to improve vulvovaginal discomfort/irritation, dryness, and/or dyspareunia. *(Strong Recommendation; Evidence Level: Grade C)*

**9.** Clinicians should offer the option of vaginal dehydroepiandrosterone (DHEA) to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Moderate Recommendation; Evidence Level: Grade C)*

**10.** Clinicians may offer the option of ospemifene to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Conditional Recommendation; Evidence Level: Grade C)*

**11.** In patients with GSM who are on systemic estrogen therapy, clinicians should offer the option of local low-dose vaginal estrogen or vaginal dehydroepiandrosterone (DHEA). *(Expert Opinion)*

**12.** In patients with GSM and comorbid genitourinary conditions (e.g., overactive bladder), clinicians may offer the option of local low-dose vaginal estrogen to improve genitourinary symptoms. *(Expert Opinion)*

**13.** In patients with GSM and recurrent urinary tract infections, clinicians should recommend local low-dose vaginal estrogen to reduce the risk for future urinary tract infections. *(Moderate Recommendation; Evidence Level: Grade B)*

## NON-HORMONAL INTERVENTIONS

**14.** Clinicians should recommend the use of vaginal moisturizers and/or lubricants, either alone or in combination with other therapies, to improve vaginal dryness and/or dyspareunia in patients with GSM. *(Moderate Recommendation; Evidence Level: Grade C)*

**15.** Clinicians should counsel patients that the evidence does not support the use of alternative supplements in the treatment of GSM. *(Expert Opinion)*

**16.** Clinicians should counsel patients to avoid vulvovaginal irritants and/or cleansers which may exacerbate the signs and symptoms of GSM. *(Expert Opinion)*

## ENERGY-BASED INTERVENTIONS

**17.** Clinicians should counsel patients that the evidence does not support the use of $CO_2$ laser, ER:YAG laser, or radiofrequency in the treatment of GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, quality of life, change in bothersome symptoms, satisfaction with treatment, or dyspareunia. *(Moderate Recommendation, Evidence Level: Grade C)*

**18.** In the context of shared decision-making, and with the disclosure that these therapies are considered experimental outside of clinical trials, clinicians may consider $CO_2$ laser treatment in patients who are not candidates for, or prefer alternatives to, FDA-approved treatments for GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, and/or dyspareunia. *(Expert Opinion)*

## BREAST AND ENDOMETRIAL CANCER

**19.** Clinicians should inform patients of the absence of evidence linking local low-dose vaginal estrogen to the development of breast cancer. *(Expert Opinion)*

**20.** For patients with GSM who have a personal history of breast cancer, clinicians may recommend local low-dose vaginal estrogen in the context of multi-disciplinary shared decision-making. *(Expert Opinion)*

**21.** Clinicians should counsel patients with GSM that neither vaginal dehydroepiandrosterone (DHEA) nor ospemifene increase the risk for breast cancer. *(Expert Opinion)*

**22.** Clinicians should counsel patients with GSM that local low-dose vaginal estrogen, does not increase the risk for endometrial hyperplasia with atypia or endometrial cancer. *(Moderate Recommendation; Evidence Level: Grade C)*

**23.** Clinicians should counsel patients with GSM that neither vaginal dehydroepiandrosterone (DHEA) nor ospemifene increase the risk for endometrial hyperplasia with atypia or endometrial cancer. *(Moderate Recommendation; Evidence Level: Grade C)*

## ENDOMETRIAL SURVEILLANCE

**24.** Clinicians should not perform endometrial surveillance in patients with GSM solely due to their use of local low-dose vaginal estrogen, vaginal dehydroepiandrosterone (DHEA), or ospemifene. *(Expert Opinion)*

## FOLLOW-UP

**25.** After initiation of treatment, clinicians should reassess patients with GSM to monitor response. *(Clinical Principle)*

**26.** Clinicians should counsel patients receiving therapy for GSM that long-term treatment and follow-up may be required to manage signs and symptoms. *(Clinical Principle)*

# INTRODUCTION[5]

*The source of the Introduction and Methodology text, as well as some text summarizing evidence results, is drawn from the evidence report used to create this Guideline, "Genitourinary Syndrome of Menopause: A Systematic Review," by the Minnesota Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ) and funded by the Patient-Centered Outcomes Research Institute (PCORI®)[5] The use of this report to derive clinical practice guidelines does not imply endorsement by PCORI®, AHRQ, or U.S. Department of Health and Human Services.*

## BACKGROUND

Genitourinary syndrome of menopause (GSM) describes the spectrum of symptoms and physical changes resulting from declining estrogen and androgen concentrations in the genitourinary tract during perimenopause and after menopause.[1] Menopause, which is defined as the phase that begins 12 months after the last menstrual period, is characterized by the natural decline in ovarian function and associated physiological changes that occur in most women in their early 50s.[6] For some individuals, menopause is associated with vasomotor symptoms (i.e., hot flashes/flushes and/or night sweats) and/or genitourinary symptoms, with wide variability in prevalence, duration, and severity.[7]

Since introduction of the term GSM in 2014,[1] no consensus has been reached about the number or type of symptoms (vulvovaginal, urinary, or sexual) needed to diagnose GSM, nor a requirement for identifying concurrent physical signs.[2, 3] Vulvovaginal symptoms associated with menopause include dryness, burning, and irritation.[8] Urinary symptoms include urgency, frequency, dysuria, and recurrent urinary tract infections

(UTI).[9] The vulvovaginal and urinary effects of menopause are often considered the cause of sexual symptoms of GSM, including dyspareunia and bleeding during intercourse, as well as broader impacts on sexual function, such as reduced libido, arousal, and orgasm.[9-11] Physical changes associated with GSM include labial atrophy, reduced moisture, introital stenosis, and clitoral atrophy.[1] The vaginal surface may be friable and hypopigmented, with petechiae, ulcerations, and tears; urethral findings may include caruncles, prolapse, or polyps.[4] However, presence and severity of physical exam findings do not directly correlate with self-reported GSM symptoms.[4, 12, 13]

Clinicians generally diagnose GSM based on symptoms, with or without related physical findings, and after ruling out other etiologies or co-occurring pathologies (e.g., infectious vaginitis, vulvar lichen sclerosus, dermatitis, lichen planus, or an active UTI).[9, 14, 15] Objective measures of postmenopausal vaginal changes include the Vaginal Maturation Index (VMI)[16] and vaginal pH.[17] The VMI demonstrates a shift from superficial cells to parabasal cells as the vaginal epithelium thins, and vaginal pH then rises as fewer superficial epithelial cells exfoliate and break down to release glycogen and glucose, which would typically be broken down into lactic acid by *Lactobacilli* in an estrogenized vagina.[8] Trials have sometimes limited inclusion to patients with moderate to severe GSM symptoms, 5% or fewer superficial cells on VMI, and vaginal pH greater than 5, however these measures are neither required nor commonly used for clinical diagnosis and treatment of GSM.[18]

GSM prevalence estimates in postmenopausal patients vary widely from 13 to 87 percent.[19] This inconsistency stems from many factors including variation in the symptoms and/or signs assessed and evaluated, the symptom assessment tools used, and the demographics and settings of study populations.[19] Unlike vasomotor symptoms of menopause (i.e., hot flashes and/or night sweats), the prevalence and intensity of some genitourinary symptoms, such as vulvovaginal dryness, increase with advancing age.[20, 21] GSM may be associated with reduced quality of life (QoL) and sexual functioning, and a higher likelihood of urinary complaints, all of which may interfere with interpersonal relationships.[22-27] Despite the potentially disruptive nature of GSM, only about half of individuals with GSM symptoms report discussing their symptoms with their clinicians, and of those who did, most said the clinician did not initiate the conversation.[28, 29]

Several organizations recommend identifying GSM through a case-finding approach, by screening patients for symptoms with routine questions.[30-32] However, few tools have been validated for GSM assessment and existing tools are limited to vulvovaginal symptoms.[10, 33] The urinary symptoms associated with GSM are also linked with other common urologic conditions in older patients, such as overactive bladder (OAB), making identification, evaluation, and treatment of these symptoms complex.[4] A causal relationship between reduced hormone levels and urinary symptoms remains controversial.[34-36] Some have even questioned whether GSM meets the definition of a disease syndrome.[37] These questions create uncertainty around the optimal approach to screening, identification, evaluation, and management of GSM.

Nonetheless, the range of GSM treatments has increased substantially in recent years.[32, 38] Traditional therapies, such as vaginal estrogen, moisturizers, and lubricants restore, alleviate symptoms, or avoid friction, respectively. Estrogen binds to receptors in the vagina, vulva, urethra, bladder, and pelvic floor, shifts the vaginal cytology toward superficial cells, away from parabasal cells, and reduces the vaginal pH. Vaginal moisturizers increase the fluid content in the endothelium and reduce the vaginal pH. Personal lubricants can be water, silicone, or oil-based and are primarily used to provide short-term lubrication during sexual activity; lubricants are often used as a placebo or control treatment in clinical trials. Newer hormonal approaches include vaginal dehydroepiandrosterone (DHEA), vaginal oxytocin, selective estrogen receptor modulators (SERMs), and testosterone. DHEA is a precursor to both androgens and estrogens that is transformed into estradiol and testosterone within vaginal cells. Oxytocin is a pituitary hormone primarily implicated in uterine labor contractions and lactation, but vaginal oxytocin gel has also been shown to reduce vaginal pH and increase the proportion of superficial cells in small studies. SERMs have varied estrogen agonist/antagonist effects throughout the body; among SERMs, ospemifene has unique estrogen receptor agonist activity in vaginal tissue. Complementary therapies, including oral and vaginal natural products (e.g., herbal supplements, phytoestrogens, vitamins, probiotics), mind-body practices, pelvic floor physical

therapy (PFPT), and educational interventions, offer various mechanisms of action while appealing to individuals who wish to avoid hormonal treatments. Finally, energy-based treatments such as laser and radiofrequency devices claim to stimulate collagen formation, angiogenesis, and epithelial thickening by causing microtrauma or heating superficial tissue layers.

Some of these treatments aim to improve a broad range of GSM symptoms, while others target a specific bothersome symptom. Randomized controlled trials (RCTs) are typically short term, and lack long-term intervention efficacy, adherence, or harms data. Study populations are often not comparable and confounding variables can impact the validity of the findings. Consequently, guidance for longer-term follow-up and surveillance as well as treatment in special populations, such as patients with a history of hormonally sensitive breast cancer, has relied on expert consensus in the absence of robust evidence.[30, 32, 39]

This guideline endeavors to provide information to clinicians regarding identification, diagnosis, counseling and treatment for patients with GSM to optimize symptom control and improve QoL while minimizing adverse effects (AE). The strategies defined in this document were derived from evidence-based and consensus-based processes. However, shared decision-making (SDM) is the optimal strategy to individualize level of impact and ultimate interventions. As outreach to this marginalized and underserved population is essential, the Panel trusts this document will guide all types of clinicians who evaluate, manage and treat patients with GSM across a multitude of disciplines.

## METHODOLOGY[5]

The systematic review utilized in the creation of this guideline is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ) and funded by the Patient Centered Outcomes Research Institute (PCORI). Searches covered publication dates from database inception through December 11, 2023. To improve applicability of findings to U.S. patients and clinicians, the EPC included only U.S.-available interventions. Where evidence was sufficient without an unacceptable amount of clinical heterogeneity, the EPC conducted pairwise meta-analyses. For studies that evaluated non-hormonal interventions (other than vaginal moisturizers), an evidence map describing study characteristics was created. For hormonal and energy-based interventions, and vaginal moisturizers, low and moderate risk of bias studies were synthesized and the EPC provided Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence (COE) ratings for 8 patient-centered outcomes identified by the Core Outcomes in Menopause (COMMA) review[1] as most important to patients and clinicians, including: (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort/irritation, (4) dysuria, (5) change in Most Bothersome Symptom (MBS), (6) distress, bother, or interference of genitourinary symptoms, (7) satisfaction with treatment, and (8) treatment side effects. The EPC derived COE from statistical rather than clinical significance or effect magnitude, in part because validated measures of clinically meaningful differences do not exist for most outcomes.

### Results

After assessing 107 publications for risk of bias (RoB), the EPC extracted effectiveness and/or harms outcomes from 68 publications describing trials or prospective, controlled observational studies that were rated low, some concerns, or moderate RoB (24 estrogen publications, 35 non-estrogen, 11 energy-based, and 4 moisturizers). Of 39 high, serious, or critical RoB publications, the EPC only extracted long-term harms from 15 uncontrolled studies of energy-based interventions (all serious or critical RoB due to confounding). Among 19 high RoB randomized controlled trials (RCT), the most common source of bias was missing outcome data. An additional 66 publications evaluating 46 non-hormonal interventions are described in an evidence map. Most non-hormonal interventions in the evidence map were focused on natural products (i.e., herbal or botanical supplements, vitamins) and were small in sample size. Five trials[1-3, 6, 7] (9 publications) compared active interventions from more than one category with placebo and are counted more than once in the description above. The relevant arms of each trial are described in their respective sections.

### Key Questions (Appendix A)

No studies evaluated Key Questions (KQ) related to GSM screening (KQ1) or directly addressed appropriate follow-

up intervals (KQ4) or the effectiveness and harms of endometrial surveillance (KQ5).

For efficacy/effectiveness (KQ2) and harms (KQ3), the certainty of evidence for most intervention-comparison-outcome combinations was low or very low; COE was moderate or high for only a few comparisons. Overall, for KQ2 the EPC concluded that vaginal estrogen, vaginal DHEA, vaginal moisturizers, and oral ospemifene, may all improve at least some GSM symptoms, primarily vulvovaginal dryness and, to a lesser extent, dyspareunia. No treatment significantly improved vaginal discomfort/irritation or dysuria. Placebo effect was high, particularly in studies using a lubricating vaginal gel or cream placebo. Evidence does not demonstrate the efficacy of energy-based therapies (carbon dioxide [$CO_2$] or Erbium-doped yttrium aluminum garnet [Er:YAG] laser), vaginal or systemic testosterone, vaginal oxytocin, oral raloxifene, or bazedoxifene for any GSM symptoms.

Compared with placebo, vaginal estrogen may improve vulvovaginal dryness, MBS, and treatment satisfaction (low COE), but probably results in little to no difference in QoL (moderate COE) and may result in little to no difference in dyspareunia or dysuria (low COE). Compared with no treatment, vaginal estrogen may improve vulvovaginal dryness and dyspareunia and may result in little to no difference in vulvovaginal discomfort/irritation or dysuria (low COE).

Among non-estrogen hormonal interventions, vaginal DHEA compared with placebo may improve vulvovaginal dryness, dyspareunia, and QoL (low COE), but may result in more AEs (low COE). Oxytocin compared with placebo probably results in little to no difference in MBS (moderate COE) and may result in little to no difference in serious AEs (low COE). Ospemifene compared with placebo may improve vulvovaginal dryness and dyspareunia (low COE) and results in higher treatment satisfaction (high COE), but results in little to no difference in vulvovaginal discomfort/irritation (high COE) and may result in little to no difference in AEs (low COE). Raloxifene added to vaginal estrogen or moisturizer compared with vaginal estrogen or moisturizer plus placebo may result in little to no difference in vulvovaginal dryness, discomfort/irritation, dysuria, and dyspareunia (low COE). Bazedoxifene may improve QoL less than placebo (low COE). Oral bazedoxifene or raloxifene compared with placebo may result in higher treatment satisfaction (low COE).

Systemic estrogen plus systemic testosterone compared with systemic estrogen alone may result in little to no difference in vulvovaginal dryness and dyspareunia (low COE). Vaginal moisturizers compared with placebo may improve vulvovaginal dryness (low COE) but may result in little to no difference in MBS (low COE). Vaginal moisturizers compared with placebo probably result in little to no difference in AEs (moderate COE). Among energy-based interventions, $CO_2$ laser (compared with sham laser) may result in little to no difference in MBS, dysuria, QoL, or serious AEs (low COE). Compared with vaginal estrogen cream, $CO_2$ laser may result in little to no difference in vulvovaginal dryness, dyspareunia, discomfort/irritation, dysuria, QoL, or serious AEs (low COE). Er:YAG laser compared with sham laser may result in little to no difference in QoL (low COE).

For the eight COMMA outcomes defined above, the evidence was very uncertain (very low COE) for all other studied intervention-comparator-outcome combinations. The full report contains results for additional effectiveness outcomes, including recurrent urinary infections, sexual function, urinary incontinence, physical signs of vulvovaginal atrophy, common AEs, and warnings reported by the U.S. Food and Drug Administration (FDA).

Harms reporting (KQ3) was limited, in part, by studies not being sufficiently powered to evaluate infrequent but serious harms, though most studies did not find evidence of frequent serious harms. Infrequent AEs varied by treatment. For example, vaginal estrogen was associated with vaginal bleeding, discharge, and breast tenderness; vaginal DHEA was associated with increased facial hair, voice changes, and headaches; oral ospemifene was associated with hot flushes and vaginal candidiasis; and $CO_2$ laser was associated with vaginal bleeding, pain, and discharge. For KQ4, limited evidence within studies of effective treatments, suggests that symptoms begin improving within 1-2 months and continue to improve through 12 weeks (average length of study follow-up). For endometrial outcomes (KQ5), among hormonal interventions, ospemifene was associated with thickened endometrial lining, proliferative endometrial histology, and one case of endometrial hyperplasia. In 6 of 10 studies that evaluated endometrial stimulation up to 36 weeks, vaginal estrogen was associated with cases of vaginal

bleeding, a nominal increase in endometrial thickness, proliferative endometrium, and one case of endometrial hyperplasia in a polyp. Limited evidence suggests that vaginal DHEA, vaginal oxytocin, oral bazedoxifene and raloxifene, and vaginal testosterone are not associated with clinically relevant endometrial stimulation as measured by transvaginal ultrasound or endometrial biopsy in primarily short-term studies and 3 year-long studies.

## Determination of Evidence Strength

The GRADE[40] system was used to determine the aggregate evidence quality for each outcome, or group of related outcomes, informing Key Questions. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence is correct. Evidence is categorized as high, moderate, low and very low, and assessment is based on the aggregate risk of bias for the evidence base, plus limitations introduced as a consequence of inconsistency, indirectness, imprecision and publication bias across the studies.[41] Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding would suggest either spurious effects or would reduce the demonstrated effect.

The American Urological Association (AUA) employs a 3-tiered strength of evidence system to underpin evidence-based guideline statements. Table 1 summarizes the GRADE categories, definitions and how these categories translate to the AUA strength of evidence categories. In short, high certainty by GRADE translates to AUA A-category strength of evidence, moderate to B, and both low and very low to C.

TABLE 1: Strength of Evidence Definitions

| AUA Strength of Evidence Category | GRADE Certainty Rating | Definition |
|---|---|---|
| **A** | High | • Very confident that the true effect lies close to that of the estimate of the effect |
| **B** | Moderate | • Moderately confident in the effect estimate<br>• The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| **C** | Low | • Confidence in the effect estimate is limited<br>• The true effect may be substantially different from the estimate of the effect |
| | Very Low | • Very little confidence in the effect estimate<br>• The true effect is likely to be substantially different from the estimate of effect |

## AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens **(Table 2)**. ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional***

***Recommendations*** are non-directive statements used when the evidence indicates there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence is *likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations can also be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, ***Clinical Principles*** or ***Expert Opinions*** are provided via consensus of the Panel. A ***Clinical Principle*** is a statement about a component of clinical care widely agreed upon by urologists or other clinicians for which there may or may not be evidence in medical literature. ***Expert Opinion*** refers to a statement based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature.

## Panel Formation

The GSM Guideline Panel was created in 2022 by the American Urological Association Education and Research, Inc and in in collaboration with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) and the American Urogynecologic Society (AUGS). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members based on an open nomination process. SUFU and AUGS each appointed two panelists. Additionally, the Panel included patient representation. Funding of the Guideline was provided by the AUA; panel members received no remuneration for their work. Funding for the AHRQ systematic review was provided by the PCORI.

## Peer Review

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of Genitourinary Syndrome of Menopause. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from SUFU and AUGS and external content experts. A call for reviewers was placed on the AUA website from September 27 – October 11, 2024, to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and the AUA Public Policy & Advocacy team to open the document further to the patient perspective. The draft guideline document was distributed to 45 nominated peer reviewers, including 8 external reviewers (i.e., peer reviewers who responded to the call for comments), and 5 reviewers nominated by AUGS and SUFU; 40 AUA Committee members (PGC, SQC, BOD) and 16 AUA staff. All peer review comments were blinded and sent to the Panel for review. In total, 43 reviewers provided comments, including 6 external reviewers. At the end of the peer review process, a total of 594 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD, the SUFU Executive Committee; and the AUGS Board of Directors for final approval.

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

| Evidence Grade | Evidence Strength A (High Certainty) | Evidence Strength B (Moderate Certainty) | Evidence Strength C (Low Certainty) |
|---|---|---|---|
| Strong Recommendation<br>(Net benefit or harm substantial) | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is substantial<br>-Applies to most patients in most circumstances and future research is unlikely to change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is substantial<br>-Applies to most patients in most circumstances but better evidence could change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) appears substantial<br>-Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation) |
| Moderate Recommendation<br>(Net benefit or harm moderate) | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is moderate<br>-Applies to most patients in most circumstances and future research is unlikely to change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) is moderate<br>-Applies to most patients in most circumstances but better evidence could change confidence | -Benefits > Risks/Burdens (or vice versa)<br>-Net benefit (or net harm) appears moderate<br>-Applies to most patients in most circumstances but better evidence is likely to change confidence |
| Conditional Recommendation<br>(Net benefit or harm comparable to other options) | -Benefits = Risks/Burdens<br>-Best action depends on individual patient circumstances<br>-Future Research is unlikely to change confidence | -Benefits = Risks/Burdens<br>-Best action appears to depend on individual patient circumstances<br>-Better evidence could change confidence | -Balance between Benefits & Risks/Burdens unclear<br>-Net benefit (or net harm) comparable to other options<br>-Alternative strategies may be equally reasonable<br>-Better evidence likely to change confidence |
| Clinical Principle | a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature | | |
| Expert Opinion | a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature | | |

# GUIDELINE STATEMENTS

## SHARED DECISION-MAKING

1. **Clinicians and patients should engage in shared decision-making, taking into consideration the best available evidence and the patient's expressed values, preferences, and goals of GSM care.** ***(Clinical Principle)***

High-quality, patient-centered care supports implementation of SDM into comprehensive urologic practice.[42] SDM is a patient-centered, dynamic and collaborative process whereby clinicians and patients work together to make healthcare decisions that align with patient's goals while employing evidenced based medicine.[42, 43] SDM can be employed in all healthcare decisions, but is most pertinent in preference-sensitive clinical decisions, where either multiple, equally effective clinical options exist (clinical equipoise) or where there is not data to clearly favor one clinical option.[44] The AUA white paper *Implementation of Shared Decision Making into Urological Practice* provides specific methods on how to incorporate SDM in clinical medicine.[43] GSM care may necessitate multidisciplinary or interprofessional shared decision-making (IP-SDM) which assumes that "at least two healthcare professionals from different health professions collaborate to achieve SDM with the patient either concurrently or not."[45] The patient is central to IP-SDM and this process can be accomplished in several ways: 1) patient having individual SDM conversations with clinicians of differing subspecialties; 2) clinicians reaching consensus on options and one clinician communicating options to a patient in a SDM encounter; and 3) a multidisciplinary SDM encounter involving clinicians and the patient.[46]

GSM represents an ideal preference-sensitive condition in which SDM may be implemented and optimally leveraged.[43] There are several models for SDM; one model endorsed by the AUA white paper[43] is the SHARE approach.[47] Applying the SHARE approach to GSM may include the following steps. First, the clinician should engage patients in their decision making early and often by letting them know that their goals and preferences are an important part of the treatment decision. Second, the clinician should provide appropriate education on the diagnosis of GSM and explore potential harms and benefits of treatment options within the context of the patient's overall medical care and preferences and values. It is important to provide patients with knowledge that they can decline treatment for GSM symptoms. Third, once patients are informed about the condition of GSM and options that are relevant to their clinical situation, elicit their preferences. One robust method is simply asking *"what matters most to you when making this decision?"* Fourth, allow patients time to deliberate on a decision with decision support, and decide on a care plan. Finally, establish a time in the future to review the care plan.

## SCREENING & DIAGNOSIS

2. **Clinicians should screen patients at risk for, or presenting with signs of, GSM for genital, sexual, and/or urinary symptoms using a focused medical, sexual, and psychosocial history.** ***(Clinical Principle)***
3. **Patients with symptoms of GSM should undergo a genitourinary examination.** ***(Clinical Principle)***

Approximately 27% to 84% of postmenopausal women experience symptoms associated with GSM.[26, 32] Additionally, individuals experiencing menopause between ages 40 and 45 years, patients with primary ovarian insufficiency (characterized by hypergonadotropic hypogonadism in women younger than age 40 years), women using medications that may cause GSM symptoms (e.g., oral contraceptives, chemotherapeutic agents), and surgically menopausal patients are at risk for GSM. However, women at any age may have low estrogen levels due to genetic, autoimmune, or other acquired conditions leading to GSM symptoms.[19, 30]

### Screening

GSM may be screened through a focused history and review of genitourinary symptoms (Table 3). Clinical symptoms of GSM that involve the genital tract include vulvar, vestibular and vaginal dryness; irritation; discomfort and/or burning; introital stenosis causing insertional dyspareunia and pain; spontaneous bleeding; and fissuring during intercourse, which could lead to postcoital bleeding. During screening, patients should be queried about bothersome symptoms of GSM, including

urinary symptoms; pain with sex; and vulvar, vestibular, and vaginal irritation or dryness. Although screening for symptoms of GSM are not known to affect outcomes, patients will have the opportunity to discuss genitourinary symptoms that may not have otherwise been brought forward if not elicited by the clinician.[33]

Many patients do not have a complete understanding of the vulvar, vestibular, vaginal, and lower urinary tract changes associated with decreased levels of sex steroid hormones, including atrophy, or that GSM represents a chronic condition. By asking relevant questions of patients, the clinician normalizes the most bothersome symptom a patient may be experiencing, which could provide reassurance that these symptoms are common.[48]

## Focused history

The focused history should document genitourinary symptoms. It is important to understand the chronicity and severity of genitourinary symptoms as well as their impact on QoL, including sexual function.[10] During a detailed history, the clinician should identify potential medications that might cause vaginal dryness (e.g., oral contraceptives, spironolactone, antihistamines, anti-androgens) and ask questions about sexual and psychosocial concerns. The clinician should also seek to identify medical comorbidities (e.g., lichen sclerosus, malignancy requiring radiation or chemotherapy, gender-affirming hormonal treatments, endocrine disorders, diabetes) that are known to cause GSM symptoms in some patients.

Secondary sexual dysfunctions associated with GSM include decreased libido, arousal, genital sensation, and orgasmic responses (e.g., decreased intensity, increased orgasmic latency). Symptoms of introital stenosis and postcoital pain may also be associated with avoidance of annual gynecological examinations and pap smears. Clinical symptoms of GSM that involve the lower urinary tract include urgency, frequency/nocturia, dysuria, stress/urgency incontinence, and/or recurrent UTI (rUTI) (Table 3).

Trauma-informed care is an approach that a clinician may use to recognize the impact of past traumas (psychosocial or physical) on individuals. Knowledge of past traumas could help clinicians successfully create a safe and supportive environment that avoids re-traumatization and promotes healing.[49, 50] Clinicians should utilize trauma-informed care and inquire about a patient's history of trauma, including childhood maltreatment, trauma, or violence, sexual violence/assault, and/or intimate partner violence in a patient's relationship history, as these factors may impact the severity of GSM symptoms.[51, 52]

Validated patient reported outcome measures are available that may be used by clinicians in a clinical setting to document the severity of symptoms and the impact on QoL (e.g., Cervantes-GSM 15-item questionnaire,[53] Vulvovaginal Symptoms Questionnaire [VSQ],[54] and Day-to-Day Impact of Vaginal Aging [DIVA]) questionnaire.

## Physical exam

Prior to performing a pelvic exam, the clinician should obtain informed consent and offer a chaperone for patient comfort, in accordance with their respective state laws and institutional guidance/policy. Furthermore, clinicians should consider the universal application of trauma-informed care approaches, recognizing the potential impact of common traumatic exposures (e.g., current or history of intimate partner violence) and adverse childhood experiences on patients with the utilization of best practices seeking to avoid re-traumatization during the pelvic examination.[49]

During the physical examination of patients presenting with symptoms of GSM, the clinician should perform visual inspection of the genitourinary tissues examining for signs of atrophy, dermatoses, malignancy, or infection (Table 3). The external examination involves the vulva, including the labia majora, labia minora, and interlabial sulci between the two labia. If discrete lesions or ulcerations are noted, referral to gynecology for vulvoscopy may be indicated. To examine the vestibule, which lies between Hart's line and the hymen, as well as the urethral meatus, the labia minora are separated. Evaluation of the vulvar vestibule must include Bartholin's and Skene's glands, typically found at 4 and 8 o'clock on the posterior vestibule and 2 and 10 o'clock on the anterior vestibule. Careful examination of the clitoris and prepuce should be performed to determine the presence of phimosis, agglutination, lesions, and or tenderness.

TABLE 3: GSM symptoms and signs[1]

| Symptoms | Signs |
|---|---|
| Genital dryness | Decreased moisture, loss of vaginal rugae, vaginal pallor/erythema |
| Decreased lubrication with sexual activity | Decreased elasticity, decreased moisture, introital retraction |
| Discomfort or pain with sexual activity | Decreased moisture/introital stenosis, loss of hymenal remnants |
| Discomfort with tight clothing/exercising | Vulvar erythema, vaginal pallor/erythema, introital retraction |
| Post-coital bleeding | Tissue fragility/fissures/petechiae |
| Irritation/burning/itching of vulva or vagina | Vaginal fissures/petechiae/erythema |
| Dysuria | Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections |
| Urinary frequency/urgency/nocturia | Prominence of urethral meatus, urethral caruncle or prolapse, recurrent urinary tract infections |
| Decreased arousal, orgasm, desire | |

Examination of the clitoral glans and corona requires retraction of the prepuce to evaluate for clitoral atrophy and or adhesions. Additional genital signs of GSM include loss and/or thinning of pubic hair, labia majora atrophy, labia minora resorption, introital stenosis, vestibular erythema, pallor, fissures and/or dryness, minor

vestibular gland erythema and/or tenderness, lack of vaginal rugae, reduced vaginal moisture, friable and/or hypopigmented vaginal epithelium with petechiae, ulcerations, and/or tears. The cervix may appear friable and erythematous with a stenosed cervical os on exam. GSM signs that involve the lower urinary tract include urethral meatal telescoping, caruncles, urethral prolapse, and/or polyps. Some women might find using a mirror during the examination helpful to visualize some of the anatomic changes associated with GSM and this could aid in educating them concerning treatment options.

Additional physical changes in the vagina that may indicate GSM and strongly suggestive of vaginal atrophy correlating to decreased serum estradiol levels include a predominance of parabasal cells with few superficial cells on vaginal smear, thinning of the vaginal epithelium, pH greater than 5.0, which indicate fewer lactobacilli and/or dysbiosis in the vagina.[55] Superficial dyspareunia and/or insertional pain can be confirmed by positive cotton-tipped swab testing throughout the vestibule which is also present in women with vestibulodynia. These objective measures, however, are not required to diagnose and/or treat GSM.

4. **Clinicians should educate patients with GSM about genitourinary signs and symptoms that result from decreased sex steroid hormones.** ***(Clinical Principle)***

Clinicians should educate patients using level-appropriate information and in terms that patients can understand about GSM and the structural and physiologic changes, which are a result of biological changes in the genitourinary tract, are related to decreased biosynthesis of sex steroid hormones, androgens (e.g., DHEA, testosterone, and dihydrotestosterone), and estrogens. These changes are related to aging and the natural decline in ovarian function that occur in most women in their early 50's, suddenly after bilateral oophorectomy, or due to other conditions causing low sex steroid levels.

Pathologic conditions affecting genitourinary tissues are due to estrogen deficiency and possibly a decline in androgens as well.[56] Both androgens and estrogens are critical physiologic modulators for development and maintenance of genital tissue structure and function. Androgens are necessary precursors for biosynthesis of estrogens. In the ovaries, adrenal gland, and peripheral tissues, DHEA can be converted to testosterone, which in turn can be converted to the more potent androgen 5α-

dihydrotestosterone by the action of 5α-reductase, or to estradiol by aromatase. In postmenopausal women, circulating DHEA is an important precursor for the local synthesis of testosterone and estradiol in extragonadal tissues. Given that the genitourinary organs are heavily influenced by sex steroids, the absence of sufficient levels of these hormones may cause the clinical signs and symptoms of GSM. However, it is also important to educate patients that documentation of hormone levels is neither necessary nor helpful for the treatment of this condition.

5. **During evaluation of patients with GSM, clinicians should assess for coexisting genitourinary conditions, utilizing additional testing or referral when appropriate.** ***(Clinical Principle)***

A thorough initial assessment of patients with GSM will help direct management. Patients may present with some or all of the signs and symptoms of GSM. In order to obtain an accurate GSM diagnosis, the patient must express bother related to these symptoms and they cannot be accounted for by another diagnosis. Blood levels of sex steroid hormones are not used to make the diagnosis and the clinician should consider other etiologies or co-occurring conditions that mimic GSM symptoms including vaginitis (e.g., desquamative inflammatory vaginitis, vulvar candidiasis, allergic vaginitis), UTI, dermatitis (e.g., vulvar lichen sclerosus, vulvar lichen planus, lichen simplex chronicus), neuroproliferative vestibulodynia, hypertonic pelvic floor dysfunction, pudendal neuropathy, and/or sacral radiculopathy. If these diagnoses are suspected, a referral to a gynecologist, dermatologist, neurologist, pelvic floor physical therapist, spine surgeon, or sexual medicine specialist may be considered, as appropriate.

Depending on the history and physical examination, additional testing may be indicated, including urinalysis with culture and sensitivity for suspected UTI and vaginal smear with culture and sensitivity for suspected vaginitis. If there are concerns for vulvovaginal or cervical cancer based on history or physical exam, an appropriate referral to gynecology/gynecologic oncology should be made.

6. **In patients with GSM and psychosocial and/or sexual health concerns, clinicians may refer to a credentialed therapist.** ***(Expert Opinion)***

GSM is a chronic, progressive condition that increases in severity over time. As a result, GSM may lead to secondary psychosocial concerns, including anxiety and depression, as well as sexual dysfunctions such as desire, arousal, and orgasm disorders. GSM may also adversely affect activities of daily living, reduce QoL, negatively impact self-image and self-esteem, and negatively impact interpersonal relationships.[29, 57] In addition, those patients with pre-existing anxiety and depression may be at risk for more bothersome GSM symptoms.

Patients who have experienced sexual abuse or sexual violence are at higher risk for experiencing bothersome GSM symptoms.[51, 52] In a sample of perimenopausal and postmenopausal women veterans, vaginal symptoms associated with GSM were more common in participants with a history of military sexual assault.[51] In another cross-sectional analysis of data from a cohort of women aged 40 to 80 years, women with a reported history of sexual assault were at increased odds of reporting vaginal symptoms (vaginal dryness: OR:1.41; 95% CI:1.10-1.82; vaginal irritation: OR:1.42; 95% CI:1.04-1.95; pain with intercourse: OR:1.44; 95% CI:1.00-2.06).[52] These studies underscore the importance of approaching patients with GSM through the lens of trauma-informed care and accounting for co-existing mental health conditions and a personal history of sexual violence and/or sexual assault. If appropriate, the clinician should offer the patient with GSM a referral to a credentialed sex therapist or counselor.[58]

7. **In patients with GSM and pelvic floor dysfunction, clinicians may refer to a physical therapist specializing in pelvic floor conditions.** ***(Expert Opinion)***

Many patients with GSM may present with co-existing pelvic floor disorders, such as urinary incontinence, defecatory dysfunction, or pelvic organ prolapse. Pelvic floor muscle training (PFMT) refers to a variety of exercises designed to improve pelvic floor muscle strength, endurance, and relaxation. Myofascial PFMT, performed by physical therapists who have additional training and clinical expertise in the muscles, ligaments, joints, and connective tissue of the pelvis and adjacent structures, has been shown to be an effective treatment for urinary incontinence and pelvic floor dysfunction.[59] Goals of treatment often include strengthening core

TABLE 4: FDA Approved treatments for GSM

| Category | Composition | Commonly used starting dose | Commonly used maintenance dose | Typical serum estradiol level (pg/mL) |
|---|---|---|---|---|
| **Vaginal creams** | 17β-estradiol 0.01% (0.1 mg active ingredient/g) | 0.5-1 grams daily for 2 weeks | 0.5 -1 gram 1-3 times per week | Variable, 3-5a |
| | Conjugated estrogen (0.625 mg active ingredient/g) | 0.5 -1 grams daily for 2 weeks | 0.5 grams 1-3 times/week | Variable |
| **Vaginal inserts** | 17β-estradiol inserts | 4 or 10 µg/d for 2 weeks | 1 insert twice/week | 3.6 (4 µg)<br>4.6 (10 µg) |
| | Estradiol hemihydrate tablets | 4 or 10 µg/d for 2 weeks | 1 insert twice/week | 5.5 |
| | Prasterone (DHEA) inserts | 6.5 mg/day | 1 insert/day | 5 |
| **Vaginal rings** | Silicone polymer with a core containing 2mg estradiol | 7.5 mcg/day for 3 months | 1 ring/three months | 8 |
| **Oral tablet** | Ospemifene | 60 mg/day | 1 tablet by mouth/day | N/A |

muscles, improving collagen fiber elasticity, optimizing muscle tonicity, ameliorating myofascial trigger points, and improving motor control and/or sensory awareness of the pelvic floor. At home devices, such as vaginal dilators, may be used to stretch the pelvic floor muscles and expand vaginal capacity.

There is evidence that PFMT may improve signs and symptoms of GSM. In a recent single-arm feasibility

study, a 12-week PFMT program not only resulted in a significant improvement in the most bothersome GSM symptom for participants, but also there was evidence of increased vaginal secretions, and improved vaginal color observed via examination and the Vaginal Health Assessment scale.[60] One proposed mechanism of action is through improved blood flow in the arteries supplying the vulvar, vestibular, vaginal and lower urinary tract tissues; improved pelvic floor muscle relaxation capacity; and increased genitourinary tissue elasticity.[61]

Given the wide range of symptomatology and associated comorbidities in patients with GSM, the clinician should consider treating a patient with GSM in a multimodal approach with concomitant, rather than stepwise, therapies for optimal relief of symptoms and patient satisfaction. For example, PFMT may be utilized synergistically with local hormonal or nonhormonal therapy as well as sex therapy.

## HORMONAL INTERVENTIONS

While there is a large body of evidence that is supportive of both vaginal and systemic hormonal approaches to the management of GSM, there is insufficient evidence to compare the efficacy of these hormonal interventions against one another. Thus, this guideline is not meant to support a stepwise progression through different hormonal approaches, but instead to provide evidence to support a process of SDM between the clinician and patient in choosing an appropriate therapy. While there is insufficient information to recommend one hormonal t herapy over another, the greatest amount of evidence and experience exists for vaginal estrogen supplementation. The consensus of the Panel is that the choice of agent should be considered not only using evidence of efficacy and AEs, but also of patient preference, accessibility, and ability to use consistently (i.e., patient dexterity, anatomy, social support). There was insufficient evidence to support clinical recommendations for vaginal and systemic testosterone and oxytocin. The existing evidence and its limitations are detailed below.

8. **Clinicians should offer the option of local low-dose vaginal estrogen to patients with GSM to improve vulvovaginal discomfort/irritation, dryness, and/or dyspareunia. *(Strong Recommendation; Evidence Level: Grade C)***

Local low-dose vaginal estrogen may be administered in the form of a cream, tablet, insert, or ring to improve symptoms of GSM. There are different rates of satisfaction and improvements in QoL across the various treatment modalities; therefore, the decision on the specific formulation should be made in the context of SDM, individualized for each patient, and based upon the patient's personal preference.

The evidence on the use of local low-dose vaginal estrogen includes inconsistency and imprecision. In addition to several routes of administration used in treatment arms, the dose that qualifies as local 'low-dose' vaginal estrogen is ill-defined. Table 4 shows the FDA-approved treatments for GSM, including the various formulations and dosing regimens of each.

Despite the limitations of the literature, the Panel recommends local low-dose vaginal estrogen to treat GSM symptoms due to its effectiveness combined with a high margin of safety. The safety of low-dose vaginal estrogen is supported by Mitchell et al.[62] and Constantine et al.,[63, 64] both of whom found significant improvement in GSM symptoms with no increase in serum estradiol levels. Likewise, a 2019 systematic review[63] of 20 RCTs, 10 interventional trials, and 8 observational studies found no increased endometrial hyperplasia or cancer risk in patients on low-dose estrogen (without progestogen).

There has been evidence of safety in breast cancer survivors using low-dose vaginal estrogen as well.[65-67] Finally, an 18-year follow-up of women enrolled in the Nurse's Health Study found no increased risk for chronic disease for low-dose vaginal estrogen when compared to systemic estrogen.[68]

The evidence particularly supports the use of local low-dose vaginal estrogen to treat vaginal dryness. Seven studies[64, 69-74] (n=2072) showed mixed effects of vaginal estrogen on dryness when compared to placebo at 8-12 weeks. One study showed a significant benefit when using 10 mcg of vaginal estrogen, but not 4 mcg.[64] Another study found daily utilization of vaginal estrogen cream was significantly better at improving vaginal dryness compared to twice weekly utilization when compared to placebo.[70] In an RCT without placebo, Eriksen et al.[75] showed significantly more patients experienced resolution of dryness in the vaginal estrogen group (81%) as compared to no treatment (17%) at 36 weeks (p=0.001). Two other RCTs[76, 77] compared vaginal estrogen cream to ring and found equivalence in symptom

improvement between both arms at 12 and 15 weeks. Both trials found higher patient satisfaction and acceptance with the ring compared to vaginal cream. Much of the evidence from RCTs describes vaginal moisturizer as a placebo, which might be expected to have some treatment effect when vaginal dryness is a primary outcome measure, suggesting that a different placebo would enhance observed differences further.

The evidence regarding the effect of vaginal estrogen on vulvovaginal discomfort/irritation is also mixed. Four studies[64, 69, 70, 72] compared vaginal estrogen to placebo. Freedman[72] found significantly more patients with symptom improvement in the vaginal estrogen group compared to placebo, as did Constantine et al. for the 10mcg soft gel capsule but not the 4mcg dose.[64] Two studies found no difference in vaginal discomfort/irritation when compared to placebo.[69, 70]

When examining the effect of vaginal estrogen on dysuria related to GSM, there was no statically significant difference across three different RCTs when compared to placebo for 12 weeks,[69] no treatment for 36 weeks,[75] or vaginal ring for 12 weeks.[76]

Seven RCTs[69-74, 78] (n=2072) found mixed effects of vaginal estrogen compared to placebo on dyspareunia. Constantine et al. found improvement with all doses of vaginal estrogen (4, 10, and 25mcg) compared to placebo;[64] one study[74] found no significant difference between groups; and the third[71] did not report a statistical comparison of change over time between arms. Four studies used a 4-point severity scale, with two[70, 72] noting a significant improvement in vaginal estrogen compared to placebo; while one[69] found no statistically significant difference between groups; and one[73] did not provide a comparison between groups. When comparing vaginal estrogen to no treatment, one RCT[75] (n=108) found patients with vaginal estrogen had significantly more symptom resolution than those without treatment after 36

weeks. Two RCTs[76, 77] (n=390) compared estrogen cream to estrogen ring and found equivalence in dyspareunia between groups.

## Testosterone and Oxytocin

There was insufficient evidence to support clinical recommendations of vaginal and systemic testosterone and vaginal oxytocin for the treatment of GSM symptoms.

### Testosterone

All of the trials included in the evidence report that examined the use of testosterone therapy (n=7) for the treatment of GSM[71, 79-84] primarily focused on sexual rather than COMMA outcomes and included fewer than 100 participants. The addition of systemic testosterone either alone or in combination with systemic estrogen was associated with little or no improvements in dyspareunia or vulvovaginal dryness/lubrication.[81, 83]

Only two trials addressed the specific use of vaginal testosterone. Drawing patients from a menopause clinic, Fernandes et al. found improvements in the orgasm domain of the female sexual function index (FSFI) (measured from 0-6, with 6 being best) with vaginal testosterone in comparison to a vaginal lubricant placebo (3.3 vs 1.8 at 12 weeks (p<0.001) compared to 1.1 vs 1.7 at baseline). Davis et al. recruited women with invasive breast cancer on aromatase inhibitors (AI) (e.g., anastrozole, exemestane, or letrozole) who were experiencing GSM symptoms such as dryness, soreness, irritation, or dyspareunia. They found improvements in sexual function demonstrated by increased scores in comparison to placebo on the FSFI satisfaction subdomain (p=0.043), female sexual dysfunction scale – revised (FSDS-R) scores (p=0.02), sexual concerns (p=0.001), and sexual responsiveness (p=0.001) scores. Serum sex steroid levels did not change.

These trials also evaluated dyspareunia using the FSFI to assess pain during intercourse, though at two different lengths of follow-up (12 or 26 weeks). Fernandes et al. reported a statistically significant improvement in dyspareunia assessed over 12 weeks for vaginal testosterone, however after adjusting for baseline differences, this was no longer significant. Davis et al. did find a statistically significant improvement in dyspareunia over 26 weeks when assessed using the Profile of Female Sexual Function (PFSF) 4-point severity scale.[85]

Davis et al.[80] did find improvements in vaginal dryness using vaginal testosterone compared with placebo (p=0.009) as did Fernandes et al.[71] Using the FSFI lubrication domain, Davis et al. failed to find a statistically significant difference from baseline when compared to placebo (p=0.12), while Fernandes et al. reported a significant mean improvement from baseline to week 12 in the testosterone arm (1.6 to 3.9; p=0.03) compared with the lubricant arm (1.9 to 2.9).

As vaginal testosterone cream may improve sexual function and dyspareunia in comparison with placebo or lubricant, clinicians may choose to offer patients, in the context of SDM, vaginal testosterone for treatment of GSM. However, while few adverse events were noted in these trials, the Panel cannot recommend this treatment as it was not possible to draw reliable conclusions regarding their efficacy due to the small number of trials, very low COE, low accrual, and mixed results.

### Oxytocin

Two RCTs [86, 87] (n=243) evaluated the efficacy of vaginal oxytocin gel versus placebo on symptoms related to GSM. Mixed results were obtained regarding vaginal dryness and dyspareunia. One study showed improvement in vaginal discomfort or irritation,[87] while a second study showed no significant improvement in self-identified MBS (i.e., vaginal dryness, vulvovaginal irritation/itching, dysuria, dyspareunia) at 12 weeks.[87] No studies evaluated effect of vaginal oxytocin on QoL or treatment satisfaction. One trial showed significant improvement in sexual function after 8 weeks of treatment with vaginal oxytocin versus placebo.[88] The most common serious AEs associated with vaginal oxytocin were vaginal discharge, UTI, and vaginal odor; however, vaginal oxytocin may result in little to no difference in serious AEs compared to placebo. Lastly, there were no safety concerns of vaginal oxytocin with regards to endometrial thickness. Vaginal oxytocin is not commercially available in the United States but may be obtained through compounding pharmacies. Given the limitations of the reviewed body of evidence, with significant inconsistency and imprecision, the Panel was not able to make recommendations on the use of vaginal oxytocin.

9. **Clinicians should offer the option of vaginal dehydroepiandrosterone (DHEA) to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Moderate Recommendation; Evidence Level: Grade C)***

Limitations in the retrieved body of evidence include inadequate sample sizes, variable definitions of clinical outcomes, and limited follow up; however, four trials (n=1472) found statistically significant improvements in GSM symptoms of vulvovaginal dryness and dyspareunia in those who were prescribed vaginal DHEA compared to those who were randomized to placebo.[89-92] A single industry-sponsored trial reported a significant difference in the high-dose (1% versus 0.25%, 0.5%) vaginal DHEA treatment arm compared to placebo when assessing vulvovaginal discomfort/irritation using a 4-point severity scale.[91] Similar improvements did not manifest with DHEA dose reduction. Several studies (n=659), demonstrated improvement in a patient's MBS following vaginal DHEA treatment.[89, 91, 92] While a single study on vaginal DHEA (n=216) demonstrated an uncertain effect on QoL,[91] three trials did demonstrate improvements in sexual function following 12 weeks of vaginal DHEA treatment.[89, 90, 92] Additional trials revealed decreases in vaginal pH and improvements in vaginal epithelial anatomy or vaginal atrophy following DHEA as compared to placebo.[89, 91, 92] Three trials (n=1256) of vaginal DHEA versus placebo found that vaginal DHEA may result in flushing and vaginal discharge.[89, 90, 92] No AEs were noted on endometrial biopsy in two studies (n=471).[89, 91] Evidence is uncertain on the efficacy or AEs associated with oral (i.e., systemic) administration of DHEA.[93, 94]

10. **Clinicians may offer the option of ospemifene to patients with GSM to improve vulvovaginal dryness and/or dyspareunia. *(Conditional Recommendation; Evidence Level: Grade C)***

Although there were inconsistencies in outcome measures, the evidence indicates that ospemifene may improve vulvovaginal dryness and dyspareunia in patients with GSM. Three trials (n=1,171) found improvements in vulvovaginal dryness at 12 weeks,[95-97] although the findings were statistically significant in only two trials.[95, 96] Three trials[95, 96, 98, 99] (n=2,062) evaluated the effect of ospemifene versus placebo on dyspareunia at 12 weeks and found a significant ($p<0.05$) improvement in symptoms after 60 mg ospemifene compared with placebo. One trial[95] (n=419) evaluated treatment satisfaction after 12 weeks of oral ospemifene versus placebo and found that patients receiving ospemifene were more likely to rate their satisfaction with treatment as "very/moderately satisfied" compared with placebo.[95] Assessment of treatment-associated AEs showed little or no difference versus placebo, with a small increase in hot flushes,[95, 96, 100] vaginal discharge, and vaginal fungal infections.[100] Endometrial hyperplasia was seen in one study participant across all ospemifene trials;[100] no endometrial cancer was observed. Three studies provided more detailed endometrial biopsy outcomes at follow-up,[95, 100, 101] and proliferative endometrial findings (weakly proliferative, active proliferative, atypical epithelial proliferation, and proliferative pattern, disordered type) were found almost exclusively in ospemifene participants (30 cases across 3 studies), compared with 1 case of weakly proliferative endometrium in placebo. This concern is raised in the boxed warning by the FDA attached to ospemifene, which also includes the risk for thrombotic events and stroke. Clinicians should determine which GSM treatment is appropriate for the individual in the context of SDM and patient preferences. Some patients may prefer to use an oral therapy over a local vaginal therapy or may have physical or other limitations that preclude the use a vaginal product.

11. **In patients with GSM who are on systemic estrogen therapy, clinicians should offer the option of local low-dose vaginal estrogen or vaginal dehydroepiandrosterone (DHEA). *(Expert Opinion)***

Some patients using systemic estrogen therapy for management of vasomotor symptoms or protection of osteoporosis, who also have GSM symptoms, may not achieve adequate relief of their GSM symptoms with systemic estrogen therapy alone. Although data are limited, in patients with GSM, the Panel recommends consideration of concurrent use of local low-dose vaginal estrogen or vaginal DHEA to manage GSM symptoms. Because these low-dose therapies are applied directly to the affected tissues, they are preferred over systemic therapy when only GSM symptoms are present.[32] Clinicians should be aware that there are no data investigating the potential risk associated with the addition of local low-dose vaginal estrogen or DHEA to systemic estrogen therapy.

12. **In patients with GSM and comorbid genitourinary conditions (e.g., overactive bladder), clinicians may offer local low-dose vaginal estrogen to improve genitourinary symptoms. *(Expert Opinion)***

The urinary symptoms associated with GSM are also linked with other common urinary conditions in older patients, such as OAB, making identification, evaluation, and treatment of these and other symptoms complex.[4] *The AUA/SUFU Guideline on the Diagnosis and Treatment of Idiopathic Overactive Bladder*[102] directs clinicians to assess a patient for signs of GSM on physical exam during the workup for OAB and recommends local low-dose vaginal estrogen as a treatment option for OAB.

Two trials[103, 104] evaluated the impact of low dose vaginal estrogen on urinary symptoms in women with OAB. Nelken et al.[103] found improvement at 12 weeks follow- up for both vaginal estradiol ring and oral oxybutynin, with no significant difference between treatment groups. Tseng et al. reported significant improvement (p<0.001) in daytime urinary frequency, UDI-6, and IIQ-7 scores in tolterodine plus estrogen compared to tolterodine alone over 11 months, but no placebo was evaluated.[104] There was no difference in urgency incontinence episodes.

13. **In patients with GSM and recurrent urinary tract infections, clinicians should recommend local low-dose vaginal estrogen to reduce the risk for future urinary tract infections. *(Moderate Recommendation; Evidence Level: Grade B)***

Recurrent UTI is not classified as a COMMA symptom, yet there is compelling evidence that low-dose vaginal estrogen therapy prevents rUTI in perimenopausal and postmenopausal patients, those who have ovarian dysfunction, and those who are post-oophorectomy.[105-109] In 1993, Raz et al.[110] published the first RCT comparing vaginal estrogen to placebo. In a study of 93 postmenopausal women with a history of UTI, patients were randomized to 0.5 estrogen cream (n=50) to be used once a night for two weeks and then twice a week for eight months or to placebo (n=43) on the same application schedule. At four months the likelihood that a patient was UTI-free in the estrogen group was 0.95 (95% CI: 0.88-1.00) as compared to 0.30 (95% CI: 0.16 -0.46) in the placebo arm. At the end of follow-up, the median incidence rate of UTI was 0.5 per patient year in the treatment arm versus 5.9 per patient year in the placebo group (p<0.001).

In 1999, Eriksen et al.[75] also demonstrated reduction in rUTI in a study of 108 postmenopausal women with documented UTI who were randomized to a 2mg vaginal ring (n=53) or placebo (n=55). At the end of the 36-week follow-up, 45% of patients in the treatment arm were disease free versus 20% in the control group.[75] Ferrante et al. (2021)had similar but not as robust results.[111] Thirty-five postmenopausal women with rUTI were followed for 6 months after being randomized to vaginal ring or cream (n=18) or placebo (n=17). At the end of follow-up, the intention-to-treat analysis showed that 11/18 patients in the treatment had documented UTI versus 16/17 in the placebo arm, (p=0.041). The as treated analysis yielded similar results: 8/15 in the treatment arm and 10/15 in the placebo arm had an UTI by the end of follow-up (p=0.036).[111]

In 2013, a systematic review of 44 papers that studied postmenopausal women with GSM showed that local low-dose vaginal estrogen lowered the incidence rate of UTI.[108] All commercially available local low-dose vaginal estrogen products were used in the treatments arm across all studies, including estriol products that are not available in the United States; comparators were placebo, no treatment, systemic estrogen therapy, lubricants, and moisturizers. Outcome measures were self-reported common genitourinary signs and symptoms associated with GSM (vaginal dryness, itching or burning, MBS, dysuria, urinary urgency, frequency nocturia, urge and stress urinary incontinence), including UTI. Of the 14 placebo-controlled studies (n=4232 patients), which included the Raz[110] and Eriksen[75] papers discussed above, the frequency of UTI was reduced. In the 18 studies that compared one type of estrogen to another (n=2236), however, there was insufficient evidence to determine which estrogen intervention was better at reducing the frequency of UTI.

The *Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline* (2022) also recommends the use of local low-dose vaginal estrogen to reduce the risk for rUTI in peri- and postmenopausal women.[105] The evidence used to support the rUTI guideline likewise found that local low-dose vaginal estrogen decreased the number of occurrences of rUTI. Given the lack of superiority data of one formulation of

vaginal estrogen over the other, the decision on what kind of estrogen to be used should be made in the context of SDM with the patient.

Finally, a multicenter retrospective review of mostly (93.4%) postmenopausal women (n=5,600) in the Kaiser Permanente Southern California System showed that vaginal estrogen prescriptions reduced rUTI.[112] Specifically, the mean UTI frequency in the year following enrollment in the study decreased to 1.8 (p<.001) from 3.9 the year prior to enrollment (a reduction of 52%).All forms local low-dose vaginal estrogen replacement were represented (ring, cream, and tablet), although it was impossible to know how patients used the medication (i.e., the frequency or location of application). The number of times a patient filled the prescription was used as a proxy for adherence. Those who never refilled the prescription after the initial index prescription were assessed as low-adherence; moderate adherence was defined 1 refill after the index prescriptions; high adherence was defined as filling 2 refills after the index prescription. It was assumed that patients who refilled the prescription were using it as instructed. Patients who never filled the initial prescription were excluded. Baseline UTI frequency was nearly identical among the low, moderate, and high adherences groups (3.8. 3.9, 3.9 respectively; p=.03); however, the data showed that those who were in the low adherence group had the most significant reduction in UTI occurrence (1.6) as compared to the moderate and high adherence groups (2.1 and 2.2 respectively). The authors surmised that this paradox could be a result of unmeasured confounding.

## NON-HORMONAL INTERVENTIONS

14. **Clinicians should recommend the use of vaginal moisturizers and/or lubricants, either alone or in combination with other therapies, to improve vaginal dryness and/or dyspareunia in patients with GSM. (*Moderate Recommendation; Evidence Level: Grade C)***

Moisturizers (a gel product applied regularly and is intended to mimic the natural secretions in an estrogenized vagina independent of the timing of sexual activity)[107] and lubricants (used at the time of sexual activity to provide short-term relief of discomfort during sexual activity and can be water, silicone, or oil based) have both been recommended to help alleviate several symptoms of GSM, though few clinical studies have been conducted on the long-term safety and efficacy of these products. Regular use of lubricants has been associated with increase in pleasure and ease of orgasm. Both lubricants and moisturizers can be used in combination with hormonal therapies to aid in symptom relief and ingredients should be evaluated for chemical irritants, osmolality, as well as condom and fertility compatibility depending on intended use. The World Health Organization recommends lubricants have an osmolarity of less than 1,200mOsm/kg[113] and a pH between 5.0-7.0. Very little data exists on the safety of lubricants that contain flavors, warming elements, or preservatives such as propylene glycol and parabens.

The systematic review used to develop this guideline looked at six heterogeneous trials that examined the effects of lactic acid-based vaginal gel,[114] hyaluronic acid-based vaginal gel,[115] bio adhesive polycarbophil-based vaginal gel,[74] and polyacrylic acid vaginal cream,[71] compared with placebo or lubricant gels. Lubricants are often used as a placebo or control treatment in clinical trials for GSM treatments, which is important to note as they are not truly a placebo, but a commonly recommended treatment strategy. In the systematic review used to develop this guideline, all moisturizers, including hyaluronic acid-based moisturizers, were grouped together.

### Vaginal Dryness

The systematic review indicated that vaginal moisturizers and placebo lubricant gel both improve vulvovaginal dryness. Four trials[71, 74, 114, 115] (n=418) evaluated the effect of vaginal moisturizer versus placebo on vaginal dryness at 12 weeks with mixed results. Nearly all studies showed improvement in vaginal dryness using different scales.

### Dyspareunia

Three trials[71, 74, 114] (n=338) evaluated the effect of vaginal moisturizer versus placebo lubricant on dyspareunia at 12 weeks with mixed results.

Lee[114] (n=98) used the vaginal assessment scale (VAS) (0 [best] to 10 [worst]) and found that among breast cancer survivors there was a statistically significant (p<0.05) greater reduction in the VAS for dyspareunia

from baseline to 12 weeks (lactic acid 8.23 to 5.48 versus placebo 8.11 to 6.11). It is important to note while there was a reduction in dyspareunia, the patients still reported pain in greater than 5/10 on VAS.

Mitchell[74] (n=200) measured change in MBS in postmenopausal women with at least one moderate to severe symptom of GSM (i.e., vulvovaginal itching, pain, dryness, irritation, pain with penetration). Patients were randomized to either 10-µg vaginal estrogen tablet plus placebo gel (n = 102), placebo tablet plus vaginal moisturizer (n = 100), or dual placebo (n = 100). All treatment groups had similar mean reductions in MBS severity over 12 weeks, and no significant differences were seen between the moisturizer and placebo arms.

Fernandes[71] measured change in female sexual function using the FSFI scale in postmenopausal women (n=80) who were randomized to treatment with vaginal estrogen, topical testosterone, polyacrylic acid, or lubricant alone. After 12 weeks, there were improvements in the FSFI domains of sexual desire, lubrication, reduced pain during intercourse, and total score in the polyacrylic acid group as compared with lubricant alone. Treatment with topical estrogen in comparison with lubricant alone showed an improvement in the FSFI field of desire. There was not a statistical test comparing the change over time between treatment arms.

## Satisfaction with Treatment

Two trials[74, 115] (n=280) evaluated the effect of vaginal moisturizers versus placebo on treatment satisfaction at 12 weeks or 3 months. Mitchell[74] (n=200) used a study-specific, 11-point Likert scale (0=not satisfied to 10=completely satisfied) and reported mean treatment satisfaction was similar between groups (7.7 vs 8.1) without a statistical comparison. They also reported the percentage of participants who reported "meaningful benefit" and found no significant (p>0.05) difference between the vaginal moisturizer arm (58%) and the placebo arm (65%).

Nappi (p=80) measured treatment satisfaction with the Patients' Global Assessment of Overall Satisfaction 4-point scale (0=dissatisfied or very dissatisfied to 3=greatly satisfied) and reported that "overall, patients were highly satisfied with treatment," with 100% of participants in the moisturizer arm "very/greatly satisfied," at 3 months and no information provided about the placebo arm.[115]

*Sexual Function*

Sexual function outcomes using the FSFI were evaluated in 3 studies. All three showed improvements in global sexual function scores with the use of both placebo lubricant gels as well as moisturizers.[71, 74, 115]

## Adverse Events

Studies on moisturizers and placebo lubricants show documented AEs. These included increased vaginal secretions, breast tenderness, body rash, vaginal itching, spotting or bleeding, vaginal candidiasis, vaginal discharge, vaginal odor, UTI, non-cancer breast disorders and gastrointestinal signs and symptoms and were not different among the treatment groups.[74] Among breast cancer survivors, there were no significant differences in AEs (irritation, itching, discharge) for lactic acid versus placebo gel, and all AEs were deemed mild or moderate.[114] Other AE reporting was sparse or incomplete.[71, 115] It is important to note that moisturizers or lubricants may irritate the thin vulvovaginal tissues. Often treating the patient with local vaginal hormones can improve the tolerance of moisturizers and lubricants and improve the patient experience.

## Vaginal Moisturizers and/or Lubricants to Treat or Prevent Urinary Symptoms

To the Panel's knowledge, there are no studies showing the vaginal lubricants or moisturizers improve urinary frequency, urgency, leakage, or prevent recurrent urinary tract infections. Data do not support the use of moisturizers and lubricants as preventative interventions for urinary symptoms of GSM and therefore should not be considered first line therapy. The Panel therefore recommends that moisturizers and lubricants should be synergistically with hormonal therapies to treat or to prevent urinary symptoms related to GSM.

15. **Clinicians should counsel patients that the evidence does not support the use of alternative supplements in the treatment of GSM. *(Expert Opinion)***

Many botanicals and naturally occurring organic compounds have estrogenic and antiestrogenic effects mediated by direct receptor actions or indirect mechanisms.[116] The effect of a given compound on the

individual is heavily influenced by estrogen status and receptor concentration. The most recognized and studied agents are phytoestrogens, vitamins, and minerals. These preparations are formulated outside FDA regulation; thus, the concentrations and quality of the active ingredient may vary, making a standardized analysis difficult. Further, mixed herbal supplements are particularly unpredictable, regarding the balance of ingredients. The literature falling into this category was not formally evaluated for a level of evidence or RoB; thus, no strict interpretation of evidence quality is available.

In the review of over 40 natural product studies included in the literature search, the majority had small sample sizes (n=61=99). Regardless of subject numbers, the majority were double-blinded RCTs. The highest number of comparable products by primary ingredient category were: soy (isoflavone) vaginal and oral preparations (5),[73, 117-120] vitamin E & D/E vaginal creams (4),[121-124] oral vitamin D (3),[125-127] fenugreek vaginal cream (2),[128, 129] red clover vaginal cream (isoflavone) (2)[130, 131] and licorice vaginal cream (2).[132, 133] While the selected outcomes varied, the majority utilized the FSFI, VMI, and pH. Urinary symptoms were assessed in just over 25% of the reports. Only a few papers reported psychological symptoms or general QoL. Less than half (20) explicitly reported AEs. The outcomes described below were not evaluated or synthesized by the evidence report systematically, rather they were presented in an evidence map constructed by the EPC;5 the selected outcomes here were extracted by the Panel.

Eleven trials included randomization of agents against conjugated estrogen (CE) cream. In six reports, hop extract gel, glycine max (soy) gel, Vitamin E, and Vitamin D/E showed no significant difference in FSFI scores, VMI, and pH between the agent under evaluation and CE. [73, 121-124, 134] Lima et al. performed a double-blind RCT trial in which 90 patients were randomized to soy vaginal gel, placebo gel, and CE cream for 12 weeks. Patients completed serial vulvovaginal symptom questionnaire, vaginal cytologies, transvaginal ultrasounds, and serum estradiol and FSH levels. The soy and CE groups demonstrated similar improvements in dryness, dyspareunia, and VMI compared to the placebo group.[73] A further five studies studying fenugreek (2), licorice (2), and pueraria mirifica (1) showed statistical improvement from baseline in the aforementioned measures but were inferior to vaginal estrogen cream.[128, 129, 132, 133, 135]

In the remaining studies, the following agents were randomized against oral or gel/cream placebos: chamomile gel, fennel cream, genistein vaginal suppository, nettle cream, pureria murifica, red clover cream , sea buckthorn oil, squill oil,and tribulus terrestris.[130, 131, 136-148] The most commonly utilized parameters were again FSFI scores and VMI. In a triple-blind randomized placebo-controlled trial of vaginal nettle cream, Karimi et al.[140] studied 84 postmenopausal women allocating the subjects between nettle and placebo vaginal creams. The subjects were evaluated at week 4 and 8 for VAS (i.e., burning, dryness, itching and dyspareunia), vaginal maturation scale, and pH. At the end of the intervention, the nettle cream group improved significantly in all vaginal symptom domains in comparison to the placebo group.

Regarding harm, some reports included hormonal evaluation and endometrial thickness to gauge response to the preparation, demonstrating no significant change compared to CE.[73, 118] However, the length of these studies, 8-12 weeks, limits the ability to make definitive statements regarding long-term harm or overall risk. Vaginal irritation related to the natural cream or gel compounds was similar to CE cream and placebo preparations.[118, 119, 133]

Despite the variability in the quality, ingredients, and estrogenic effect in the wide range of natural compounds, these products are highly attractive to patients who are reluctant to utilize regulated sex hormone preparations. Thus, patients should be counseled regarding the potential risks and benefits while monitoring for AEs with long-term use.

16. **Clinicians should counsel patients to avoid vulvovaginal irritants and/or cleansers which may exacerbate the signs and symptoms of GSM.** ***(Expert Opinion)***

Patients being treated for GSM should be counseled to avoid excessive cleansing with soap or harsh cleansers, and chemicals. Vulvovaginal irritants can worsen the symptoms of GSM including dryness and dyspareunia. Common vulvovaginal irritants include urine, sweat, feces, soaps, cleaners, douches, spermicides, pads, and

liners. Allergens may include perfumes, lanolin, chlorhexidine, benzocaine, neomycin, preservatives, and latex. Extreme rashes may require consultation with dermatology and/or patch testing.[149]

## ENERGY-BASED INTERVENTIONS

17. **Clinicians should counsel patients that the evidence does not support the use of $CO_2$ laser, ER:YAG laser, or radiofrequency in the treatment of GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, quality of life, change in bothersome symptoms, satisfaction with treatment, or dyspareunia.** ***(Moderate Recommendation, Evidence Level: Grade C)***

18. **In the context of shared decision-making, and with the disclosure that these therapies are considered experimental outside of clinical trials, clinicians may consider $CO_2$ laser treatment in patients who are not candidates for, or prefer alternatives to, FDA-approved treatments for GSM-related vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, and/or dyspareunia.** ***(Expert Opinion)***

The FDA provides clearance of energy-based interventions in surgical applications requiring the ablation, vaporization, excision, incision, and coagulation in medical specialties. However, the FDA has not approved energy-based interventions (laser or radiofrequency ablation) use for "vaginal rejuvenation" nor for treatment of sexual dysfunction. The FDA specifically released a statement and notifications to device manufacturers regarding inappropriate and deceptive marketing of vaginal laser devices for "vaginal rejuvenation."[150] The use of energy-based interventions within the United States for symptoms of GSM is currently recommended only in robust clinical trials utilized by appropriately trained clinicians. Within this context, the panel appraised the available trials providing data regarding vaginal energy-based interventions for GSM. Much of this data originates from studies performed outside of the United States.

Eleven clinical trials with low to some risk for bias have examined the impact of energy based interventions ($CO_2$ laser, Er:YAG laser, radiofrequency) on GSM symptoms.[151-158] Of these, the majority of data (8 studies) focus on $CO_2$ laser, whereas only 3 provide data for Er:YAG and 1 for radiofrequency (compared to $CO_2$). Overall, the study designs and the outcomes of the studies are heterogenous, with short follow-up time (most reporting 3-month follow-up only) and the certainty of evidence based on this pooled data is low or very low.

Studies directly comparing $CO_2$ laser to sham laser, find that $CO_2$ laser may result in little to no difference in dysuria, change in MBS, or change in QoL, as compared to sham laser.[152, 153, 155, 156] The data is very uncertain to the effect of $CO_2$ laser compared to sham laser on vulvovaginal dryness, vulvovaginal discomfort/irritation, dyspareunia, satisfaction with treatment.

In studies comparing $CO_2$ laser to vaginal CE creams, $CO_2$ laser may result in little to no difference in vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, dyspareunia, and QoL.[151, 154] Two studies compared $CO_2$ laser to vaginal CE creams (n=119), one of these studies was ended early due to FDA requirements.[154] Both studies found that there was not a significant difference between $CO_2$ laser and vaginal CE cream for vulvovaginal dryness.

The data is very uncertain to the effect of $CO_2$ laser compared to vaginal estrogen cream for satisfaction with treatment.[151, 154]

Data on adverse effects was limited by short duration of follow-up (3-12 months) and very low certainty of evidence. There were no serious adverse effects reported in any of the trials involving $CO_2$ laser. Among the four trials provided data on AEs of $CO_2$ laser compared to sham laser, the most common AEs reported on by the studies were pain after procedure (3 studies; 2.3%-100% versus 0%-10.5%), vaginal bleeding/discharge (2 studies; 0%-11.5% versus 2.3%-2.6%), and dyspareunia (2 studies; 0% versus 0%).[152, 153, 155, 156] There were no serious AEs in any arms of the three trials evaluating ER:YAG lasers. One study reported AEs of ER:YAG laser compared to sham, the most common AE was vaginal pain (36% versus 4%), vaginal bleeding (4% versus 0%) and vaginal abrasions (0% versus 0%).[159]

## BREAST AND ENDOMETRIAL CANCER

**19. Clinicians should inform patients of the absence of evidence linking local low-dose vaginal estrogen to the development of breast cancer. *(Expert Opinion)***

In 2003, the FDA required a warning placed on all estrogen products regarding an increased risk for endometrial cancer, cardiovascular disorders, breast cancer, and dementia.[160] Since that time, there has been a growing body of evidence that local low-dose vaginal estrogen does not increase the risk for primary breast cancer[161] or recurrence of breast cancer in women with a personal history of breast cancer.[65, 66, 162, 163]

While breast cancer was not an endpoint in the evidence report used to develop this guideline, existing data supports conclusions that local low-dose vaginal estrogen does not increase breast cancer risk in individuals without a history of breast cancer and at average risk (less than 15%) for developing breast cancer. Per the National Cancer Institute, a woman's lifetime risk for developing breast cancer is 12.9%.[164] There are various risk models assessing individual risk for breast cancer that can modify this risk. Individuals with less than a 15% lifetime risk are considered average risk and those with >20% lifetime risk are considered high risk and include individuals with BRCA mutations and strong family histories.

In a secondary review of the Women's Health Initiative Observational Study that included 45,633 women without prior history of breast or endometrial cancer and not on systemic estrogen therapy, those with self-reported use of local low-dose vaginal estrogen during the follow up period did not have higher risk for breast cancer, stroke, endometrial cancer, colorectal cancer, or venous thromboembolism. The risk for coronary artery disease and all-cause mortality were likewise lower in the local low-dose vaginal estrogen users.[161]

While there are no data stratifying the risk for breast cancer in users of local low-dose vaginal estrogen who have an above average or high risk for breast cancer, data suggest that local low-dose vaginal estrogen does not increase the risk for recurrence or of breast cancer mortality in women with a personal history of breast cancer.[65, 66, 162, 163, 165]

There is a dearth of data on patients who are at moderate to high risk for breast cancer (i.e., those with BRCA gene mutations or a strong family history) and their risk for developing breast cancer as a result of using local low-dose vaginal estrogen. There are data to suggest that systemic estrogen in this group does not further increase the risk for breast cancer in individuals with BRCA mutations.[30] Although systemic levels of estradiol may increase briefly and to a small degree after starting local low-dose vaginal estrogen (theoretically via the atrophic vaginal epithelium), the levels return to menopausal levels after 12 weeks.[166] Serum levels with 10mcg tablet and vaginal ring remain in the menopausal range.[167, 168] Estradiol cream or conjugated equine estrogen cream could result in elevated serum levels, particularly if used incorrectly. In general, however, local low-dose vaginal estrogen for GSM, unlike systemic estrogen used to treat vasomotor and other systemic symptoms, results in negligible serum levels of estradiol, and thus does not increase risk for breast cancer.

**20. For patients with GSM who have a personal history of breast cancer, clinicians may recommend local low-dose vaginal estrogen in the context of multi-disciplinary shared decision-making. *(Expert Opinion)***

Patients with a personal history of breast cancer are at high risk for developing GSM,[169] sexual dysfunction, and issues with vaginal health.[169-172] Endocrine therapies, including tamoxifen and AI, are an important component of the treatment on estrogen-dependent breast cancers, which make up 80% of all breast cancers. Because these therapies lower estrogen levels, the symptoms of GSM in breast cancer patients are more magnified.[173]

These patients also have concerns regarding cancer recurrence. Including the patient's medical oncologist in the SDM model of care is recommended to improve QoL, address symptoms, alleviate concerns, and minimize risks.

An analysis of data on 49,237 women with breast cancer from two national registries in Scotland and Wales showed no increase in cancer-specific mortality was seen among women in the cohort who used vaginal estrogen.[66]

In a 2024 systematic review and metanalysis, which included eight observational studies of breast cancer survivors with GSM, there was no increased risk for breast cancer recurrence (OR: 0.48; n=24,060) in users of vaginal estrogen, nor was there an increase in breast cancer mortality (OR: 0.60; n=61695), or overall mortality (OR: 0.46 %; n=59724).[174]

A nested case control study of 13,479 women in the UK with breast cancer showed women who used local estrogen and tamoxifen or local estrogen and AI were not more likely to experience recurrence than women who did not use local hormone therapy. The data were based mostly on tamoxifen, since the AI + vaginal estrogen group was underpowered. Nevertheless, there were no recurrences in the AI + vaginal estrogen group.[165] A Danish cohort study of 8461 patients diagnosed with early stage estrogen-positive breast cancer[162] showed no increase in breast cancer mortality in users of local estrogen, and no increase in recurrence of breast cancer in women who used local estrogen while on tamoxifen or no endocrine therapy. Users of local estrogen with AI, however, had an increased risk for recurrence (HR: 1.39) but not of mortality.[30]

Women taking tamoxifen, as opposed to AI, are less likely to be at increased risk for breast cancer from the use of vaginal estrogen used to treat GSM. The goal of AI is to suppress estrogen levels, while tamoxifen is a SERM that competes at the level of the estrogen receptors in the breast. While there are no data on the use of local estrogen in women with triple negative breast cancers (i.e., cancers that are not sensitive to estrogen), the use of local estrogen may be less of a concern to patients and their oncologists in this subgroup of breast cancer survivors.

Because of the scarcity of data on local estrogen in women taking AIs, multidisciplinary SDM is particularly recommended in this scenario. The 10mcg vaginal estradiol tablet, 4mcg gel insert, or the low-dose estradiol ring may have a lower systemic absorption and may thus be preferable in women with a personal history of breast cancer, particularly those on AIs.[30]

21. **Clinicians should counsel patients with GSM that neither vaginal dehydroepiandrosterone (DHEA) nor ospemifene increase the risk for breast cancer. *(Expert Opinion)***

Vaginal DHEA is FDA approved for dyspareunia associated with menopause. It is an inactive hormone that is transformed to an active androgen in peripheral tissues, such as the vagina, where it is aromatized into estrogen. Because it is metabolized intracellularly via “intracrine” as opposed to endocrine metabolism, it has minimal effect on serum levels.[175] Studies of vaginal DHEA reported a small increase in serum estradiol that remained within the normal menopausal range.[176, 177] There is little data on vaginal DHEA in breast cancer survivors; therefore, clinicians may recommend vaginal DHEA, which is not associated with increased circulating levels of estradiol, in the context of multidisciplinary SDM, for treatment of GSM for individuals with a personal history of breast cancer.

Ospemifene is an oral SERM and both an estrogen agonist and antagonist that displays antiestrogenic effect on the breast. Although it is not known to increase the risk for breast cancer, there are few studies on its use in individuals with a history of breast cancer. Though there is no contraindication to its use in Europe for those with a history of breast cancer, the FDA warns that ospemifene “should not be used in women with known or suspected breast cancer” because it has not been adequately studied in women with breast cancer. However, ospemifene is FDA approved for the treatment of vaginal dryness and moderate to severe dyspareunia. Clinicians may recommend ospemifene for patients with GSM and a personal history of breast cancer, using informed SDM and involving the treating oncologist in the discussion.[173]

22. **Clinicians should counsel patients with GSM that local low-dose vaginal estrogen does not increase the risk for endometrial hyperplasia with atypia or endometrial cancer. *(Moderate Recommendation; Evidence Strength: Level C)***

The evidence report used to develop this guideline included seven trials[64, 71, 73-75, 82, 178] (n=1105 women) that evaluated endometrial safety in users of vaginal estrogen compared to placebo or no treatment. There was minimal effect on the endometrium, and neither endometrial cancer nor hyperplasia was found after 8 to 36 weeks. One large, randomized placebo-controlled study (n=561) that included endometrial biopsy at 12 weeks on all subjects showed no hyperplasia or endometrial cancer.[64]

Another three studies evaluated endometrial safety with different doses of vaginal estrogen. Goetsch et al.[179]

evaluated endometrial thickness via transvaginal ultrasound in 50 patients who used either 50mcg or 100mcg of nightly vaginal estrogen. There was no significant increase from baseline to 12-weeks (0.1 mm increase in the 50mcg group and no increase in the 100mcg group) or difference between the groups. Two other studies[76, 77] identified proliferative endometrium or hyperplasia in an endometrial polyp (n=1) in 4 estradiol ring users and endometrial proliferation in 4 estrogen cream users, though the studies used higher dosing than is common in current practice.

Outside of the evidence report, Crandall's analysis of the Women's Health Initiative Observational Study, which included 45,663 women with no prior history of breast or endometrial cancer, those who used local low-dose vaginal estrogen, with a median follow up of 7.2 years, did not have higher risk for endometrial cancer.[180]

23. **Clinicians should counsel patients with GSM that neither vaginal dehydroepiandrosterone (DHEA) nor ospemifene increase the risk for endometrial hyperplasia with atypia or endometrial cancer.** ***(Moderate Recommendation; Evidence Level: Grade C)***

Limited data from the evidence report suggests that DHEA is not associated with endometrial stimulation.[89] Because the mechanism of DHEA is intracellular conversion to estradiol and testosterone, systemic levels of estradiol are not increased. Trials of vaginal DHEA reported no difference in endometrial outcomes (measured by endometrial biopsy in two trials (n=255[89] and n=216[91]) and by transvaginal ultrasound in another (n=156)[93] between treatment and control participants. No adverse endometrial effects were observed.

Ospemifene is an oral SERM that has an estrogen agonist effect on the vaginal epithelium and on bone. Because this is a systemic medication, there exists some potential for affecting other sites such as the endometrium. Ospemifene is an antagonist for the breast but has a minimal proliferative effect on the endometrium. Clinicians who prescribe oral ospemifene for GSM should counsel their patients that this treatment may cause proliferation of the endometrium, but that endometrial cancer or hyperplasia with atypia have not been seen in studies. In the evidence report, among four placebo control trials with 2411 subjects, one case of simple hyperplasia without atypia was noted in the ospemifene arm and no endometrial cancers were observed.[100] While there was some estrogenic effect on the endometrium, there were no precancerous changes or malignancies. As with all women with postmenopausal bleeding, women using ospemifene for GSM should notify their clinicians if they experience bleeding and undergo evaluation.

## ENDOMETRIAL SURVEILLANCE

24. **Clinicians should not perform endometrial surveillance in patients with GSM solely due to their use of local low-dose vaginal estrogen, vaginal dehydroepiandrosterone (DHEA), or ospemifene.** ***(Expert Opinion)***

There is no data to suggest that screening for endometrial hyperplasia or cancer in average risk patients with GSM on local hormone treatment is beneficial. Furthermore, screening for endometrial cancer is not recommended for women on systemic hormone therapy or tamoxifen, both of which have an agonist effect on the endometrium. Endometrial evaluation, whether by ultrasound or by endometrial sampling, does present risks and no identified benefits in these groups, and thus endometrial surveillance in users of local low-dose vaginal estrogen, which has a much lower and transient effect on the endometrium, should not be recommended. A 2014 Practice Bulletin from the American College of Obstetricians and Gynecologists (ACOG) affirms that local low-dose vaginal estrogen therapy does not require endometrial surveillance.[181]

Most cases of endometrial cancer (85%) are diagnosed at low stage because of symptoms, usually bleeding, and survival rates are high. Patients with any postmenopausal bleeding (PMB), who are using local low-dose vaginal estrogen for GSM, should notify their clinician and undergo evaluation. Transient bleeding after starting hormonal treatment for GSM can occur, and while it may resolve, it should be addressed. PMB may occur in patients regardless of their use of GSM treatment (including hormonal, non-hormonal and laser treatment.) Causes of PMB include uterine sources (e.g., atrophic endometrium, polyps, hyperplasia, cancer, cervical polyps) and non-uterine sources (e.g., vaginal abrasions or tears [from pessary use or other foreign body], laser use, excoriations from prolapse, vulvar lesions, urethral

lesions). While many causes of PMB are benign, it is incumbent on the clinician to assess the risk and to investigate if appropriate including referral to specialists when needed.

While the risk for endometrial hyperplasia or cancer is low with local low-dose vaginal estrogen therapy, any vaginal bleeding in a postmenopausal patient should be evaluated regardless of whether the individual is using local low-dose vaginal estrogen.

Endometrial surveillance in women using hormonal treatments for GSM was a Key Question in this evidence report. Ten trials[64, 71, 73-77, 82, 178, 179] proactively evaluated the effect of vaginal estrogen on endometrial stimulation using either endometrial biopsy,[64, 71, 73, 77, 82, 178, 179] transvaginal ultrasound,[71, 73, 77, 82, 178, 179] progesterone challenge,[76, 77] or passively assessed for vaginal bleeding.[74-76, 179] Estrogen was given as 4 or 10mcg soft-gel capsules,[64] 2mg ring,[75-77] CE (0.625mg/g; 0.5g dose nightly,[73] 1g nightly for 3 weeks, then 1 week free of treatment,[76] 1g dose three times per week,[71] 1g dose nightly for 2 weeks, then twice weekly,[82] or 2g dose three times weekly[77]), 50 or 100mcg vaginal cream,[179] or 25mcg gel.[178]

Transvaginal ultrasound was performed at baseline and 8 or 12 weeks in four trials that compared vaginal estrogen with placebo;[71, 73, 82, 178] 1 trial that compared 50 or 100µg of vaginal estrogen;[179] and 1 trial that compared vaginal estrogen ring to cream (7.5µg vaginal ring and 2g cream 3 times a week).[77] Endometrial thickness in patients who received estrogen increased by 0.08 to 0.5 mm in three trials[71, 82, 179] and decreased by 0.5 to 1 mm in the other two;[73, 178] placebo participant average changes ranged from -0.47 to 0.1.

Two older trials[76, 77] assessed endometrial stimulation using progesterone challenge and reported vaginal bleeding in 3 to 4 percent of vaginal estrogen ring users (2mg in both trials) and 9 to 21 percent of vaginal estrogen cream users. Notably, vaginal estrogen cream doses in these trials were higher than common current doses: 1g nightly for three weeks followed by one week free of treatment (n=194)[76]and 2g three times per week (n=196).[77] Subsequent endometrial biopsies identified proliferative endometrium or hyperplasia in an endometrial polyp (n=1) for 4 estradiol ring users and endometrial proliferation for 4 estrogen cream users.

Four[74-76, 179] trials used passive surveillance to identify patients who experienced vaginal bleeding after being randomized to vaginal estrogen. One trial compared 10mcg estrogen to placebo for 12 weeks (n=202),[74] 1 trial compared 2mg estrogen ring to no-treatment for 36 weeks (n=108),[75] and 2 compared estrogen formulations for 12 weeks (2mg estrogen ring versus 0.625 mg CE (n=195)[76] or 50mcg versus 100 mcg estrogen cream[179]). Patients experienced bleeding in three of these trials.[75, 76, 179]

In one large study[64] (n=574) in which active surveillance was performed with scheduled endometrial biopsy on all participants with a uterus (~ 60% of participants) at 12 weeks, no endometrial hyperplasia or malignancy was found in participants who were given 4 or 10mcg soft-gel estrogen capsules.

No studies were found that evaluated the benefits or harms of endometrial surveillance.

## FOLLOW-UP

25. **After initiation of treatment, clinicians should reassess patients with GSM to monitor response.** ***(Clinical Principle)***

No studies evaluated Key Questions related to either GSM screening or appropriate follow-up intervals. The Panel recommends that patients who are undergoing therapy for GSM should be followed to determine if the most bothersome symptoms are mitigated by interventions. For effective treatments, limited evidence and clinician experience suggests that symptoms begin improving within 1-2 months of initiating treatment and continue to improve through 12 weeks (average length of study follow-up).

Patients should be offered counseling regarding adherence to therapies and alternative therapies when appropriate. If patients fail to respond to primary treatment, repeat physical exam and possible further diagnostics, such as vulvar biopsy, or referral to a clinician who can further evaluate concerning findings is appropriate. Although the Panel did not recommend a tiered strategy for interventions, as a global principle, the least invasive means should be employed. It is critical to explore barriers to adoption of therapies, particularly

concerns regarding topical hormone interventions, and to educate patients and consulting clinicianss.[182]

26. **Clinicians should counsel patients receiving therapy for GSM that long-term treatment and follow-up may be required to manage signs and symptoms.** ***(Clinical Principle)***

Symptoms associated with GSM may be variable and progressive over time and modifications of strategy are often necessitated. Clinicians may choose to tailor treatment based on specific outcomes of concern, intervention side effects, personal risk factors (e.g., cancer history), insurance coverage or cost, patient preference for route or type of therapy, and treatment availability. Patients would benefit from interval follow up with their clinician to ensure treatments continue to mitigate symptoms and new onset genitourinary issues are addressed in a timely manner.

Future studies would be strengthened by a standard definition and uniform diagnostic criteria for GSM, a common set of validated outcome measures and reporting standards, and attention to clinically relevant populations and intervention comparisons. Long-term follow-up for efficacy, tolerability, and safety represents a critical gap needed to guide treatment longer than one year.

# FUTURE DIRECTIONS

Comparable to other functional urologic conditions, GSM is a symptom and sign-based diagnosis made after careful clinical evaluation and at the exclusion of other causes. The hormonal imbalances that drive development of GSM manifest differently in each patient so tailoring individualized management strategies is fundamental for establishing goals of care. Thus, there is no single intervention for GSM which is universally effective or acceptable. Indeed, additional urologic and gynecologic conditions, such as OAB or sexual dysfunction, may co-exist with GSM and may need additional diagnosis-specific targeted treatment to meet the patient's goals.

Understanding the concept of trauma-informed care for the GSM patient and utilizing language that supports patient choice and safety is important for clinicians during history-taking, performing physical exams, and providing treatment. Defining mechanisms for standardizing clinical training regarding counseling and logistics of examinations to preserve a patient's dignity and avoiding negative triggers will empower both clinicians and patients. Given the intimate and impactful nature of GSM, patients should be cared for in a wholistic manner where diagnostic and treatment strategies are implemented in a compassionate and patient-centered manner.

In addition to the aforementioned need for standardized diagnostic criteria and outcomes, further exposure across disciplines to the terminology of GSM would assist to demystify the condition and further expand opportunities for access to care, as well as development of future interventions. Mandated within the framework of definitions would be standardized reporting for AE associated with treatments, or lack thereof, for patients with GSM.

Qualitative studies of the patient perspective on GSM[183] have identified themes including: the need for education on medications including usage instructions, discussion on potential side effects, interest in alternative therapies, and needing support for and validation of GSM and GSM symptoms from health care clinicians. Understanding and overcoming patient-centered barriers to common treatments is critical for driving both compliance and policy.[184] This guideline serves to begin the conversation to increase awareness and establish evidence-based best practices for clinicians. Future studies should continue to explore and include patient's knowledge, attitudes, and beliefs, so that the medical community can better meet GSM patients' needs.

With a standard language for GSM, it is important to collaborate and codify across disciplines to be able to accurately express symptoms such that they may be objectively measured. Broadly, phenotyping our patients to describe the manifestations of GSM on vaginal, urinary, and general pelvic health domains is critical to provide clinically meaningful and standardized research outcomes. A future direction may involve differentiation of the symptoms associated with GSM to best define what is implied by a syndrome.

With regards to expanding the relevance of research outcomes, intentional, community-engaged efforts to

recruit clinically relevant and racialized, minoritized, and systematically excluded patient populations who have been historically left out of clinical trials and research studies must be implemented to increase the relevance and robustness of research outcomes. Including a broader, more inclusive population to reflect the real-world experience of patients and clinicians is key to increase the generalizability of research findings. Contemporary outreach efforts engaging local organizations and implementing telehealth strategies may facilitate inclusive engagement. Additionally, defining best practices with regards to time of follow up, including more long-term evaluation, is critically important for a condition that typically worsens or is subject to influence of comorbid conditions over time. The panel expressed the need for evaluation of otherwise marginalized populations outside of the traditional postmenopausal patient for inclusion in research to explore and establish best practices. This includes transgender patients, patients on systemic estrogen, young women using oral contraceptives, breast- or chest-feeding patients, individuals with hypothalamic amenorrhea, patient on gonadotropin regulating hormone for endometriosis or uterine fibroids, post-oophorectomy patients, and further analysis of the impact of interventions on cancer survivors. Further understanding of the wide manifestation of sex steroid deficiencies, including low and elevated follicle stimulating hormone impacts[19, 30] should expand inclusion and drive recruitment in future clinical trials to serve patients with GSM.

Even with commonly accepted treatment strategies that have been outlined in these guidelines, there remain significant gaps in the comparative effectiveness of interventions. As the treatment decisions are individualized, these types of safety and efficacy parameters become a critical aspect of patient counseling. As outlined in earlier sections, the panel appreciates the impact of current boxed warning of estrogen products and advocates for national efforts to update these labels to reflect contemporary literature, particularly regarding low-dose vaginal estrogen. Development of studies defining and standardizing dosing and scheduling of interventions are important to reduce variation and comparison of therapies. Patient engagement and advocacy will help drive research on issues and research questions that matter most to patients with GSM. Comparative effectiveness studies and studies utilizing patient-centered outcome measures are essential to provide patients with information they need to make informed decisions about their health.

A singular limitation of the data interrogated in this guideline is the lack of high-level data detailing GSM treatment on commonly coexistent bladder symptoms and signs including OAB and recurrent UTIs. Future research in this arena is essential to determine best practices for prevention of conditions that negatively affect the QoL of an aging population. Additionally, future research efforts should be directed to understand the influence of local low-dose vaginal estrogen in patients being concurrently treated with systemic estrogen therapies as this represents a substantial population of high-impact.

And with regards to cost and access, this guideline does not address financial impact of either GSM or the treatments thereof. However, the panel acknowledges the potential financial burden for patients and expresses to the need to explore the issues of cost and access in future research.[182]

In conclusion, the GSM is a common and undertreated condition affecting patients across the lifespan. Safe and effective treatments exist that alleviate bothersome symptoms and improve QoL. Increased education and awareness is critical to reach those affected by GSM. While there are evidence-based best practices in the area of GSM, future research is needed to deepen our understanding of this condition.

# ABBREVIATIONS

| | |
|---|---|
| AEs | Adverse effects |
| AHRQ | Agency for Healthcare Research and Quality |
| AI | Aromatase inhibitors |
| AUA | American Urological Association |
| AUGS | American Urogynecologic Society |
| BOD | Board of Directors |
| CE | Conjugated estrogen |
| $CO_2$ | Carbon dioxide |
| COE | Certainty of evidence |
| COMMA | Core Outcomes in Menopause |
| DHEA | Dehydroepiandrosterone |
| DIVA | Day-to-Day Impact of Vaginal Aging |
| EPC | Evidence-based practice center |
| Er:YAG | Erbium-doped yttrium aluminum garnet |
| FDA | U.S. Food and Drug Administration |
| FSFI | Female sexual function index |
| GSM | Genitourinary syndrome of menopause |
| GRADE | The Grading of Recommendations Assessment, Development, and Evaluation |
| IIQ-7 | Incontinence Impact Questionnaire |
| IP-SDM | Interprofessional shared decision-making |
| KQ | Key Question |
| MBS | Most bothersome symptom |
| OAB | Overactive bladder |
| PCORI | Patient Centered Outcomes Research Institute |
| PGC | Practice Guidelines Committee |
| PFMT | Pelvic floor muscle training |
| PMB | Postmenopausal bleeding |
| QoL | Quality of life |
| RCT | Randomized controlled trial |
| RoB | Risk of bias |
| rUTI | Recurrent UTI |
| SERMS | Selective estrogen receptor modulators |
| SDM | Shared decision making |
| SQC | Science and Quality Council |
| SUFU | Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction |
| UDI-6 | Urogenital Distress Inventory |
| UTI | Urinary tract infection |
| VAS | Vaginal assessment scale |
| VMI | Vaginal Maturation Index |
| VSQ | Vulvovaginal Symptoms Questionnaire |

# Genitourinary Syndrome of Menopause: AUA/SUFU/AUGS Guideline Panel, Consultants, and Staff

## Panel

Melissa R. Kaufman, MD, PhD; Chair
Vanderbilt University Medical Center
Nashville, Tennessee

Una J. Lee, MD; Vice Chair
Virginia Mason Franciscan Health
Seattle, Washington

Charles R. Powell, MD; PGC Representative
Indiana University School of Medicine
Avon, Indiana

A. Lenore Ackerman, MD, PhD
University of California Los Angeles Health System: UCLA Health
Los Angeles, California

Katherine A. Amin, MD
University of Miami Miller School of Medicine
Miami, Florida

Marge Coffey, MSW (Patient Advocate)
Frederick, Maryland

Stephanie S. Faubion, MD, MBA
Mayo Clinic
Jacksonville, Florida

Anne Hardart, MD
Westchester Medical Center Health Network
Valhalla, NY

Irwin Goldstein, MD
Westchester Medical Center Health Network
Valhalla, NY

Giulia M. Ippolito, MD, MS
University of Michigan, Ann Arbor
Ann Arbor, Michigan

Gina M. Northington, MD, PhD
Emory University School of Medicine Atlanta, Georgia

Rachel S. Rubin, MD
Rachel Rubin Medicine
North Bethesda, Maryland

O. Lenaine Westney, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas

Tracey S. Wilson, MD
University of Alabama, Birmingham
Birmingham, Alabama

## Consultants

Systematic Review prepared by the Minnesota Evidence-based Practice Center Minneapolis, MN.

Elisheva R. Danan, M.D., M.P.H.
Susan Diem, M.D., M.P.H.
Catherine Sowerby, B.A.
Kristen Ullman, M.P.H.
Kristine Ensrud, M.D., M.P.H.
Adrienne Landsteiner, Ph.D., M.P.H.
Nancy Greer, Ph.D.
Nicholas Zerzan, M.P.H.
Maylen Anthony, M.P.H.
Caleb Kalinowski, M.S.
Mary Forte, Ph.D., D.C.
Hamdi I. Abdi, M.P.H.
Jessica K. Friedman, Ph.D.
Rahel Nardos, M.D., M.S.
Cynthia Fok, M.D., M.P.H.
Philipp Dahm, M.D., M.H.Sc.
Mary Butler, Ph.D., M.B.A.
Timothy J. Wilt, M.D., M.P.H.

**Staff**
Erin Kirkby, MS
Sennett K. Kim
Lauren J. Pak, MHS, MS
Leila Rahimi, MHS

## CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic– and non -topic-

related relationships. Panel members not listed below have nothing to disclose.

**Consultant/Advisor: A. Lenore Ackerman,** Watershed Medical, Abbvie, Deseret Harvest; **Irwin Goldstein,** Coloplast Corporation, Immugen Pharma, Winsantor, Palatin, TRT, Endo International; **Melissa R. Kaufman**, Boston Scientific, Laborie; **Gina M. Northington,** American Board of Obstetrics and Gynecology, Chinese Medical Board; **Rachel S. Rubin,** Sprout Pharmaceuticals, Freya; **O. Lenaine Westney,** Urotronic, Bluewind.

**Scientific Study or Trial**: **A. Lenore Ackerman**, MicrogenDx; **Katherine A. Amin,** Urovant, SpineX, K12 Calabresi Research Career Development Program; **Stephanie S. Faubion,** Cancer Alliance; **Irwin Goldstein**, BTL; **Melissa R. Kaufman**, Medtronic; **Charles R. Powell**, Micron Medical, Medtronic, Neuspera; **O. Lenaine Westney**, Laborie; **Tracey S. Wilson**, Patient-Centered Outcomes Research Initiative, Bluewind Medical.

**Meeting Participant/Lecturer: Irwin Goldstein,** TRT,Coloplast, Vitaris; **Una J. Lee,** Medtronic, Axonics; **O. Lenaine Westney**, Boston Scientific

**Health Publishing**: Irwin Goldstein, Endo International; Melissa R. Kaufman, Journal of Urology; Gina M. Northington, American College of Obstetricians and Gynecologist; Charles R. Powell, Neurourology and Urodynamics – Wiley, Oakstone Publishing- Practical Reviews in Urology.

**Leadership Position**: **Stephanie S. Faubion,** The North American Menopause Society; **Irwin Goldstein**, ISSWSH; **Giulia M. Ippolito,** SUFU Research Network; **Gina M. Northington,** American Urogynecologic Society; Rachel S. Rubin, ISSWSH; **Tracey S. Wilson**, SUFU

**Other**: **Melissa R. Kaufman,** Cook Myosite

# PEER REVIEWERS

We are grateful to the persons listed below who contributed to the Guideline by providing comments during the peer review process. Their reviews do not necessarily imply endorsement of the Guideline.

**AUA (BOD, SQC, PGC, Journal of Urology)**

Damara Lee Kaplan, MD, PHD
Jennifer Ulanda Miles-Thomas, MD
Hassan Razvi, MD
Stephen A. Boorjian, MD
David Alan Ginsberg, MD
Ramy Said Goueli, MD, MHS
Landon Trost, MD
Angela B. Smith, MD

**External Reviewers (Non-AUA Affiliates)**
Laila Agrawald, MD
Maude Carmel, MD
Gary Lemack, MD
Humphrey Atiemo, MD
Alex Gomelsky, MD
Ramzy Burns, MD
Sue Goldstein
Heather S. Howard, MD
Janeane Anderson, MD
Jewel Kling, MD
Roberta Renzelli-Cain
Estela Citrin, MD
Megan Falsetta, MD
Jill Krapf, MD
Cheryl Kinney, MD
Laurie Jeffers, MD
Carolyn Gibson, MD
Holly Thomas, MD
Makeba Williams, MD
Ekta Kapoor, MD
Monica Christmas, MD
Scott Smilen, MD
Jerry Lowder, MD
Sara Cichowski, MD
Michael Krychman, MD
Rossella E. Nappi, MD
Nirit Rosenblum, MD
Ariana Smith, MD

**Public Commenters (Via public notice on AUA website)**
Sandra Elmer, MD
Susan Glover, MD
Cassio Riccetto, MD
Suzette E. Sutherland, MD
Ashay Arun Patil, MD
Nancy Phillips, MD

# DISCLAIMER

This document was written by the Genitourinary Syndrome of Menopause Panel of the American Urological Association Education and Research, Inc., which was created in 2022. The PGC of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the panel included specialists with specific expertise on this syndrome. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the evaluation, diagnosis, and treatment of GSM.

Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (off label") that are not approved by the FDA, or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management that are too new to be addressed by this guideline as necessarily experimental or investigational.

# REFERENCES

1. Portman, D. J., Gass, M. L., Vulvovaginal Atrophy Terminology Consensus Conference, P.: Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. J Sex Med, 11: 2865, 2014
2. Castelo-Branco, C., Peralta, S., Ferrer, J. et al.: The dilemma of menopause and hormone replacement--a challenge for women and health-care providers: knowledge of menopause and hormone therapy in Spanish menopausal women. Climacteric, 9: 380, 2006
3. Cucinella, L., Martini, E., Tiranini, L. et al.: Genitourinary syndrome of menopause: Should we treat symptoms or signs? Current Opinion in Endocrine and Metabolic Research, 26: 100386, 2022
4. Mitchell, C. M., Waetjen, L. E.: Genitourinary Changes with Aging. Obstet Gynecol Clin North Am, 45: 737, 2018
5. Danan, E., Diem, S., Sowerby, C. et al.: Genitourinary Syndrome of Menopause. Comparative Effectiveness Review No. 272. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 75Q80120D00008.) AHRQ Publication No. 24-EHC022. PCORI® Publication No. 2024-SR-02 Rockville, MD: Agency for Healthcare Research and Quality. July 2024. DOI: https://doi.org/10.23970/AHRQEPCCER272. Posted final reports are located on the Effective Health Care Program search page.
6. Greendale, G. A., Lee, N. P., Arriola, E. R.: The menopause. Lancet, 353: 571, 1999
7. Hickey, M., Hunter, M. S., Santoro, N. et al.: Normalising menopause. BMJ, 377: e069369, 2022
8. Mayo Clinic Proceedings: Vulvovaginal atrophy. 2010
9. Gandhi, J., Chen, A., Dagur, G. et al.: Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. Am J Obstet Gynecol, 215: 704, 2016
10. Gabes, M., Knuttel, H., Stute, P. et al.: Measurement properties of patient-reported outcome measures (PROMs) for women with genitourinary syndrome of menopause: a systematic review. Menopause, 26: 1342, 2019
11. Kingsberg, S., Kellogg, S., Krychman, M.: Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy. Int J Womens Health, 1: 105, 2010
12. Greendale, G. A., Zibecchi, L., Petersen, L. et al.: Development and validation of a physical examination scale to assess vaginal atrophy and inflammation. Climacteric, 2: 197, 1999
13. Phillips, N. A., Bachmann, G. A.: The genitourinary syndrome of menopause. Menopause, 28: 579, 2021
14. Faubion, S. S., Sood, R., Kapoor, E.: Genitourinary Syndrome of Menopause: Management Strategies for the Clinician. Mayo Clin Proc, 92: 1842, 2017
15. Lewis, F. M.: Vulval symptoms after the menopause - Not all atrophy! Post Reprod Health, 21: 146, 2015
16. McEndree, B.: Clinical application of the vaginal maturation index. Nurse Pract, 24: 48, 1999
17. Roy, S., Caillouette, J. C., Roy, T. et al.: Vaginal pH is similar to follicle-stimulating hormone for menopause diagnosis. Am J Obstet Gynecol, 190: 1272, 2004
18. Weber, M. A., Limpens, J., Roovers, J. P.: Assessment of vaginal atrophy: a review. Int Urogynecol J, 26: 15, 2015
19. Mili, N., Paschou, S. A., Armeni, A. et al.: Genitourinary syndrome of menopause: a systematic review on prevalence and treatment. Menopause, 28: 706, 2021
20. Cagnacci, A., Xholli, A., Sclauzero, M. et al.: Vaginal atrophy across the menopausal age: results from the ANGEL study. Climacteric, 22: 85, 2019
21. Kingsberg, S. A., Wysocki, S., Magnus, L. et al.: Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med, 10: 1790, 2013
22. Moral, E., Delgado, J. L., Carmona, F. et al.: The impact of genitourinary syndrome of menopause on well-being, functioning, and quality of life in postmenopausal women. Menopause, 25: 1418, 2018

23. Nappi, R. E., Kingsberg, S., Maamari, R. et al.: The CLOSER (CLarifying Vaginal Atrophy's Impact On SEx and Relationships) survey: implications of vaginal discomfort in postmenopausal women and in male partners. J Sex Med, 10: 2232, 2013

24. Nappi, R. E., Kokot-Kierepa, M.: Women's voices in the menopause: results from an international survey on vaginal atrophy. Maturitas, 67: 233, 2010

25. Nappi, R. E., Palacios, S.: Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. Climacteric, 17: 3, 2014

26. Parish, S. J., Nappi, R. E., Krychman, M. L. et al.: Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. Int J Womens Health, 5: 437, 2013

27. Pinkerton, J. V., Bushmakin, A. G., Komm, B. S. et al.: Relationship between changes in vulvar-vaginal atrophy and changes in sexual functioning. Maturitas, 100: 57, 2017

28. Kingsberg, S. A., Krychman, M., Graham, S. et al.: The Women's EMPOWER Survey: Identifying Women's Perceptions on Vulvar and Vaginal Atrophy and Its Treatment. J Sex Med, 14: 413, 2017

29. Simon, J. A., Kokot-Kierepa, M., Goldstein, J. et al.: Vaginal health in the United States: results from the Vaginal Health: Insights, Views & Attitudes survey. Menopause, 20: 1043, 2013

30. Faubion, S. S., Larkin, L. C., Stuenkel, C. A. et al.: Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause, 25: 596, 2018

31. Stuenkel, C. A., Davis, S. R., Gompel, A. et al.: Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 100: 3975, 2015

32. Panel., T. N. G. P. S. E.: The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause, 27: 976, 2020

33. Huang, A. J., Gregorich, S. E., Kuppermann, M. et al.: Day-to-Day Impact of Vaginal Aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. Menopause, 22: 144, 2015

34. Augoulea, A., Moros, M., Kokras, N. et al.: Association of menopausal symptoms with sociodemographic factors and personality traits. Prz Menopauzalny, 18: 191, 2019

35. Christmas, M. M., Iyer, S., Daisy, C. et al.: Menopause hormone therapy and urinary symptoms: a systematic review. Menopause, 30: 672, 2023

36. Hamer, M. A., Kallen, K., Lidfeldt, J. et al.: Serum estradiol does not differentiate stress, mixed and urge incontinent women around menopause. A report from the Women's Health in the Lund Area (WHILA) study. Eur J Obstet Gynecol Reprod Biol, 159: 209, 2011

37. Vieira-Baptista, P., Marchitelli, C., Haefner, H. K. et al.: Deconstructing the genitourinary syndrome of menopause. Int Urogynecol J, 28: 675, 2017

38. Kagan, R., Kellogg-Spadt, S., Parish, S. J.: Practical Treatment Considerations in the Management of Genitourinary Syndrome of Menopause. Drugs Aging, 36: 897, 2019

39. Gelfand, M. M.: It might be wise to consider adding androgen to the estrogen or estrogen-progestin regimens in the appropriate patients. Menopause, 11: 505, 2004

40. Guyatt, G., Oxman, A. D., Akl, E. A. et al.: GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol, 64: 383, 2011

41. Balshem, H., Helfand, M., Schünemann, H. J. et al.: GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol, 64: 401, 2011

42. National Quality Partners™ Shared Decision Making Action Team: National Quality Partners Playbook™: Shared Decision Making in Healthcare. 2018

43. Makarov, D., Fagerlin, A., Finkelstein, J. et al.: Implementation of Shared Decision Making into Urological Practice. 2022

44. Elwyn, G., Frosch, D., Rollnick, S.: Dual equipoise shared decision making: definitions for decision and behaviour support interventions. Implement Sci, 4: 75, 2009

45. Legare, F., Stacey, D., Pouliot, S. et al.: Interprofessionalism and shared decision-making in primary care: a stepwise approach towards a new model. J Interprof Care, 25: 18, 2011

46. https://decisionaid.ohri.ca/ip-sdm.html: https://decisionaid.ohri.ca/docs/develop/IP-SDM-Model.pdf

47. The SHARE Approach. Content last reviewed October 2024. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/sdm/share-approach/index.html

48. Parish, S. J., Hahn, S. R.: Hypoactive Sexual Desire Disorder: A Review of Epidemiology, Biopsychology, Diagnosis, and Treatment. Sex Med Rev, 4: 103, 2016

49. Felitti, V. J., Anda, R. F., Nordenberg, D. et al.: REPRINT OF: Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. Am J Prev Med, 56: 774, 2019

50. Rouch, I., Strippoli, M. F., Dorey, J. M. et al.: Early-life adversity predicting the incidence of multisite chronic pain in the general population. Eur Psychiatry, 67: e67, 2024

51. Travis, K. J., Huang, A. J., Maguen, S. et al.: Military Sexual Trauma and Menopause Symptoms Among Midlife Women Veterans. J Gen Intern Med, 39: 411, 2024

52. Gibson, C. J., Huang, A. J., McCaw, B. et al.: Associations of Intimate Partner Violence, Sexual Assault, and Posttraumatic Stress Disorder With Menopause Symptoms Among Midlife and Older Women. JAMA Intern Med, 179: 80, 2019

53. Baquedano, L., Rejas-Gutierrez, J., Coronado, P. J.: Development and psychometric properties of a measurement to ascertain the impact of genitourinary symptoms on health-related quality of life in menopausal women: the Cervantes-GSM questionnaire. Menopause, 30: 512, 2023

54. Erekson, E. A., Yip, S. O., Wedderburn, T. S. et al.: The Vulvovaginal Symptoms Questionnaire: a questionnaire for measuring vulvovaginal symptoms in postmenopausal women. Menopause, 20: 973, 2013

55. Streicher, L. F.: Diagnosis, causes, and treatment of dyspareunia in postmenopausal women. Menopause, 30: 635, 2023

56. Harlow, S. D., Gass, M., Hall, J. E. et al.: Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab, 97: 1159, 2012

57. Levine, K. B., Williams, R. E., Hartmann, K. E.: Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. Menopause, 15: 661, 2008

58. https://www.aasect.org/referral-directory.

59. Dumoulin, C., Hay-Smith, J., Habee-Seguin, G. M. et al.: Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women: a short version Cochrane systematic review with meta-analysis. Neurourol Urodyn, 34: 300, 2015

60. Mercier, J., Morin, M., Zaki, D. et al.: Pelvic floor muscle training as a treatment for genitourinary syndrome of menopause: A single-arm feasibility study. Maturitas, 125: 57, 2019

61. Mercier, J., Morin, M., Tang, A. et al.: Pelvic floor muscle training: mechanisms of action for the improvement of genitourinary syndrome of menopause. Climacteric, 23: 468, 2020

62. Mitchell, C. M., Larson, J. C., Crandall, C. J. et al.: Association of Vaginal Estradiol Tablet With Serum Estrogen Levels in Women Who Are Postmenopausal: Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open, 5: e2241743, 2022

63. Constantine, G. D., Graham, S., Lapane, K. et al.: Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. Menopause, 26: 800, 2019

64. Constantine, G. D., Simon, J. A., Pickar, J. H. et al.: The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause, 24: 409, 2017

65. Agrawal, P., Singh, S. M., Able, C. et al.: Safety of Vaginal Estrogen Therapy for Genitourinary Syndrome of Menopause in Women With a History of Breast Cancer. Obstet Gynecol, 142: 660, 2023

66. McVicker, L., Labeit, A. M., Coupland, C. A. C. et al.: Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer. JAMA Oncol, 10: 103, 2024

67. Meaidi, A., Pourhadi, N., Lokkegaard, E. C. et al.: Association of vaginal oestradiol and the rate of breast cancer in Denmark: registry based, case-control study, nested in a nationwide cohort. BMJ Med, 3: e000753, 2024

68. Bhupathiraju, S. N., Grodstein, F., Stampfer, M. J. et al.: Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. Menopause, 26: 603, 2018

69. Archer, D. F., Kimble, T. D., Lin, F. D. Y. et al.: A Randomized, Multicenter, Double-Blind, Study to Evaluate the Safety and Efficacy of Estradiol Vaginal Cream 0.003% in Postmenopausal Women with Vaginal Dryness as the Most Bothersome Symptom. J Womens Health (Larchmt), 27: 231, 2018

70. Bachmann, G., Bouchard, C., Hoppe, D. et al.: Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause, 16: 719, 2009

71. Fernandes, T., Costa-Paiva, L. H., Pinto-Neto, A. M.: Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med, 11: 1262, 2014

72. Freedman, M., Kaunitz, A. M., Reape, K. Z. et al.: Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy. Menopause, 16: 735, 2009

73. Lima, S. M., Yamada, S. S., Reis, B. F. et al.: Effective treatment of vaginal atrophy with isoflavone vaginal gel. Maturitas, 74: 252, 2013

74. Mitchell, C. M., Reed, S. D., Diem, S. et al.: Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. JAMA Intern Med, 178: 681, 2018

75. Eriksen, B.: A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol, 180: 1072, 1999

76. Ayton, R. A., Darling, G. M., Murkies, A. L. et al.: A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. Br J Obstet Gynaecol, 103: 351, 1996

77. Nachtigall, L. E.: Clinical trial of the estradiol vaginal ring in the U.S. Maturitas, 22 Suppl: S43, 1995

78. Kingsberg, S. A., Derogatis, L., Simon, J. A. et al.: TX-004HR Improves Sexual Function as Measured by the Female Sexual Function Index in Postmenopausal Women With Vulvar and Vaginal Atrophy: The REJOICE Trial. J Sex Med, 13: 1930, 2016

79. Chaikittisilpa, S., Soimongkol, K., Jaisamrarn, U.: Efficacy of oral estrogen plus testosterone gel to improve sexual function in postmenopausal women. Climacteric, 22: 460, 2019

80. Davis, S. R., Robinson, P. J., Jane, F. et al.: Intravaginal Testosterone Improves Sexual Satisfaction and Vaginal Symptoms Associated With Aromatase Inhibitors. J Clin Endocrinol Metab, 103: 4146, 2018

81. Penteado, S. R., Fonseca, A. M., Bagnoli, V. R. et al.: Effects of the addition of methyltestosterone to combined hormone therapy with estrogens and progestogens on sexual energy and on orgasm in postmenopausal women. Climacteric, 11: 17, 2008

82. Raghunandan, C., Agrawal, S., Dubey, P. et al.: A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. J Sex Med, 7: 1284, 2010

83. Tungmunsakulchai, R., Chaikittisilpa, S., Snabboon, T. et al.: Effectiveness of a low dose testosterone undecanoate to improve sexual function in postmenopausal women. BMC Womens Health, 15: 113, 2015

84. Melisko, M. E., Goldman, M. E., Hwang, J. et al.: Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA Oncol, 3: 313, 2017

85. McHorney, C. A., Rust, J., Golombok, S. et al.: Profile of Female Sexual Function: a patient-based, international, psychometric instrument for the assessment of hypoactive sexual desire in oophorectomized women. Menopause, 11: 474, 2004

86. Fianu Jonasson, A., Bixo, M., Sundstrom Poromaa, I. et al.: Safety and Efficacy of an Oxytocin Gel and an Equivalent Gel but Without Hormonal Ingredients (Vagivital((R)) Gel) in Postmenopausal Women with Symptoms of Vulvovaginal Atrophy: A Randomized, Double-Blind Controlled Study. Med Devices (Auckl), 13: 339, 2020

87. Zohrabi, I., Abedi, P., Ansari, S. et al.: The effect of oxytocin vaginal gel on vaginal atrophy in postmenopausal women: a randomized controlled trial. BMC Womens Health, 20: 108, 2020

88. Abedi, P., Zohrabi, I., Ansari, S. et al.: The Impact of Oxytocin Vaginal Gel on Sexual Function in Postmenopausal Women: A Randomized Controlled Trial. J Sex Marital Ther, 46: 377, 2020

89. Archer, D. F., Labrie, F., Bouchard, C. et al.: Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). Menopause, 22: 950, 2015

90. Barton, D. L., Sloan, J. A., Shuster, L. T. et al.: Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). Support Care Cancer, 26: 643, 2018

91. Labrie, F., Archer, D., Bouchard, C. et al.: Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause, 16: 907, 2009

92. Labrie, F., Archer, D. F., Koltun, W. et al.: Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause, 25: 1339, 2018

93. Panjari, M., Bell, R. J., Jane, F. et al.: A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. J Sex Med, 6: 2579, 2009

94. Scheffers, C. S., Armstrong, S., Cantineau, A. E. et al.: Dehydroepiandrosterone for women in the peri- or postmenopausal phase. Cochrane Database Syst Rev, 1: CD011066, 2015

95. Archer, D. F., Goldstein, S. R., Simon, J. A. et al.: Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial. Menopause, 26: 611, 2019

96. Bachmann, G. A., Komi, J. O., Ospemifene Study, G.: Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause, 17: 480, 2010

97. Portman, D., Palacios, S., Nappi, R. E. et al.: Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial. Maturitas, 78: 91, 2014

98. Constantine, G., Graham, S., Portman, D. J. et al.: Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric, 18: 226, 2015

99. Portman, D. J., Bachmann, G. A., Simon, J. A. et al.: Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause, 20: 623, 2013

100. Goldstein, S. R., Bachmann, G. A., Koninckx, P. R. et al.: Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric, 17: 173, 2014

101. Simon, J. A., Lin, V. H., Radovich, C. et al.: One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause, 20: 418, 2013

102. Cameron, A. P., Chung, D. E., Dielubanza, E. J. et al.: The AUA/SUFU Guideline on the Diagnosis and Treatment of Idiopathic Overactive Bladder. J Urol, 212: 11, 2024

103. Nelken, R. S., Ozel, B. Z., Leegant, A. R. et al.: Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. Menopause, 18: 962, 2011

104. Tseng, L. H., Wang, A. C., Chang, Y. L. et al.: Randomized comparison of tolterodine with vaginal estrogen cream versus tolterodine alone for the treatment of postmenopausal women with overactive bladder syndrome. Neurourol Urodyn, 28: 47, 2009

105. Anger, J., Lee, U., Ackerman, A. L. et al.: Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol, 202: 282, 2019

106. Lethaby, A., Ayeleke, R. O., Roberts, H.: Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev, 2016: CD001500, 2016

107. Nappi, R. E., Davis, S. R.: The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. Climacteric, 15: 267, 2012

108. Rahn, D. D., Carberry, C., Sanses, T. V. et al.: Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol, 124: 1147, 2014

109. The 2022 Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel: The 2022 hormone therapy position statement of The North American Menopause Society. Menopause, 29: 767, 2022

110. Raz, R., Stamm, W. E.: A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med, 329: 753, 1993

111. Ferrante, K. L., Wasenda, E. J., Jung, C. E. et al.: Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women: A Randomized Clinical Trial. Female Pelvic Med Reconstr Surg, 27: 112, 2021

112. Tan-Kim, J., Shah, N. M., Do, D. et al.: Efficacy of vaginal estrogen for recurrent urinary tract infection prevention in hypoestrogenic women. Am J Obstet Gynecol, 229: 143 e1, 2023

113. Organization, W. H.: WHO/United Nations Population Fund (UNFPA) specifications for plain lubricants. . WHO Drug Information, 33: 562, 2019

114. Lee, Y. K., Chung, H. H., Kim, J. W. et al.: Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial. Obstet Gynecol, 117: 922, 2011

115. Nappi, R. E., Kotek, M., Brestansky, A. et al.: Treatment of vulvo-vaginal atrophy with hyaluronate-based gel: a randomized controlled study. Minerva Obstet Gynecol, 74: 480, 2022

116. Piersen, C. E.: Phytoestrogens in botanical dietary supplements: implications for cancer. Integr Cancer Ther, 2: 120, 2003

117. Carmignani, L. O., Pedro, A. O., Montemor, E. B. et al.: Effects of a soy-based dietary supplement compared with low-dose hormone therapy on the urogenital system: a randomized, double-blind, controlled clinical trial. Menopause, 22: 741, 2015

118. Kim, H. I., Kim, M. K., Lee, I. et al.: Efficacy and Safety of a Standardized Soy and Hop Extract on Menopausal Symptoms: A 12-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Altern Complement Med, 27: 959, 2021

119. Lima, S. M., Bernardo, B. F., Yamada, S. S. et al.: Effects of Glycine max (L.) Merr. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial. Maturitas, 78: 205, 2014

120. Ribeiro, A. E., Monteiro, N. E. S., Moraes, A. V. G. et al.: Can the use of probiotics in association with isoflavone improve the symptoms of genitourinary syndrome of menopause? Results from a randomized controlled trial. Menopause, 26: 643, 2018

121. Azari, N., Mehrabi, E., Javadzadeh, Y. et al.: Comparison of the effect of vaginal vitamin E cream with conjugated estrogen vaginal cream on vulvovaginal atrophy and overactive bladder syndrome: a randomized controlled trial. African Journal of Urology, 29: 35, 2023

122. Golmakani, N., Parnan Emamverdikhan, A., Zarifian, A. et al.: Vitamin E as alternative local treatment in genitourinary syndrome of menopause: a randomized controlled trial. Int Urogynecol J, 30: 831, 2019

123. Keshavarzi, Z., Janghorban, R., Alipour, S. et al.: The effect of vitamin D and E vaginal suppositories on tamoxifen-induced vaginal atrophy in women with breast cancer. Support Care Cancer, 27: 1325, 2019

124. Radnia, N., Hosseini, S. T., Vafaei, S. Y. et al.: The effect of conjugated estrogens vaginal cream and a combined vaginal cream of vitamins D and E in the treatment of genitourinary syndrome. J Family Med Prim Care, 12: 507, 2023

125. Arjmand, M., Abbasi, H., Behforouz, A.: The effect of vitamin D on urgent urinary incontinence in postmenopausal women. Int Urogynecol J, 34: 1955, 2023

126. Kamronrithisorn, T., Manonai, J., Vallibhakara, S. A. et al.: Effect of Vitamin D Supplement on Vulvovaginal Atrophy of the Menopause. Nutrients, 12, 2020

127. Markland, A., Tangpricha, V., Mark Beasley, T. et al.: Comparing Vitamin D Supplementation Versus Placebo for Urgency Urinary Incontinence: A Pilot Study. J Am Geriatr Soc, 67: 570, 2019

128. Mazalzadeh, F., Hekmat, K., Namjouyan, F. et al.: Effect of Trigonella foenum (fenugreek) vaginal cream on vaginal atrophy in postmenopausal women. J Family Med Prim Care, 9: 2714, 2020

129. Safary, M., Hakimi, S., Mobaraki-Asl, N. et al.: Comparison of the Effects of Fenugreek Vaginal Cream and Ultra Low- Dose Estrogen on Atrophic Vaginitis. Curr Drug Deliv, 17: 815, 2020

130. Hidalgo, L. A., Chedraui, P. A., Morocho, N. et al.: The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: A randomized, double-blind, placebo-controlled study. Gynecological Endocrinology, 21: 257, 2005

131. Khayatan, J., Iravani, M., Moghimipour, E. et al.: The effect of red clover vaginal cream on sexual function in postmenopausal women: a randomized, controlled clinical trial. Iranian Journal of Obstetrics, Gynecology and Infertility, 22: Pe26, 2019

132. Ahmadizad, P., Shohani, M., Direkvand Moghadam, A. et al.: Comparison of the effect of licorice vaginal cream and estrogen vaginal cream on sexual function of postmenopausal women: An RCT. Int J Reprod Biomed, 20: 963, 2022

133. Sadeghi, M., Namjouyan, F., Cheraghian, B. et al.: Impact of Glycyrrhiza glabra (licorice) vaginal cream on vaginal signs and symptoms of vaginal atrophy in postmenopausal women: A randomized double blind controlled trial. J Tradit Complement Med, 10: 110, 2020

134. Vahedpoorfard, Z., Ferdosi, S., Rahimi, H. et al.: Effect of Humulus lupulus L. (Hop) on Postmenopausal Sexual Dysfunction: A Randomized Clinical Trial. Int J Clin Pract, 2023: 9528335, 2023

135. Suwanvesh, N., Manonai, J., Sophonsritsuk, A. et al.: Comparison of Pueraria mirifica gel and conjugated equine estrogen cream effects on vaginal health in postmenopausal women. Menopause, 24: 210, 2017

136. Abedi, P., Najafian, M., Yaralizadeh, M. et al.: Effect of fennel vaginal cream on sexual function in postmenopausal women: A double blind randomized controlled trial. J Med Life, 11: 24, 2018

137. Bosak, Z., Iravani, M., Moghimipour, E. et al.: Effect of Chamomile Vaginal Gel on the Sexual Function in Postmenopausal Women: A Double-Blind Randomized Controlled Trial. J Sex Med, 19: 983, 2022

138. Bosak, Z., Iravani, M., Moghimipour, E. et al.: Evaluation of the influence of chamomile vaginal gel on dyspareunia and sexual satisfaction in postmenopausal women: A randomized, double-blind, controlled clinical trial. Avicenna J Phytomed, 10: 481, 2020

139. Karimi, F., Babazadeh, R., Zojaji, A. et al.: Squill oil for decreasing dyspareunia and increasing sexual satisfaction in menopausal women: A triple-blind randomized controlled trial. Avicenna J Phytomed, 11: 464, 2021

140. Karimi, F. Z., Nazari, N., Rakhshandeh, H. et al.: The effect of nettle vaginal cream on subjective symptoms of vaginal atrophy in postmenopausal women. Eur J Obstet Gynecol Reprod Biol, 285: 41, 2023

141. Larmo, P. S., Yang, B., Hyssala, J. et al.: Effects of sea buckthorn oil intake on vaginal atrophy in postmenopausal women: a randomized, double-blind, placebo-controlled study. Maturitas, 79: 316, 2014

142. Le Donne, M., Caruso, C., Mancuso, A. et al.: The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause. Arch Gynecol Obstet, 283: 1319, 2011

143. Manonai, J., Chittacharoen, A., Theppisai, U. et al.: Effect of Pueraria mirifica on vaginal health. Menopause, 14: 919, 2007

144. Postigo, S., Lima, S. M., Yamada, S. S. et al.: Assessment of the Effects of Tribulus Terrestris on Sexual Function of Menopausal Women. Rev Bras Ginecol Obstet, 38: 140, 2016

145. Sritonchai, C., Manonai, J., Sophonsritsuk, A. et al.: Comparison of the effects of Pueraria mirifica gel and of placebo gel on the vaginal microenvironment of postmenopausal women with Genitourinary Syndrome of Menopause (GSM). Maturitas, 140: 49, 2020

146. Vale, F. B. C., Boroni, J. D., Geber, G. et al.: Effect of Tribulus Terrestris in the Treatment of Female Sexual Dysfunction and Clitoral Vascularization. Results of a Randomized Study Comparing Two Different Dosage Regimes. J Sex Marital Ther, 47: 696, 2021

147. Warinsiriruk, P., Tantitham, C., Cherdshewasart, W. et al.: Effects of Pueraria mirifica on vaginal artery vascularization in postmenopausal women with genitourinary syndrome of menopause. Maturitas, 160: 4, 2022

148. Yaralizadeh, M., Abedi, P., Najar, S. et al.: Effect of Foeniculum vulgare (fennel) vaginal cream on vaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled trial. Maturitas, 84: 75, 2016

149. Margesson, L. J.: Contact dermatitis of the vulva. Dermatologic Therapy, 17: 20, 2004

150. FDA Commissioner Scott Gottlieb, M. D.: Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for "vaginal rejuvenation", July 30, 2018

151. Eftekhar, T., Forooghifar, T., Khalili, T. et al.: The Effect of the CO(2) Fractional Laser or Premarin Vaginal Cream on Improving Sexual Function in Menopausal Women: A Randomized Controlled Trial. J Lasers Med Sci, 11: 292, 2020

152. Li, F. G., Maheux-Lacroix, S., Deans, R. et al.: Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial. Jama, 326: 1381, 2021

153. Page, A. S., Verbakel, J. Y., Verhaeghe, J. et al.: Laser versus sham for genitourinary syndrome of menopause: A randomised controlled trial. Bjog, 130: 312, 2023

154. Paraiso, M. F. R., Ferrando, C. A., Sokol, E. R. et al.: A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. Menopause, 27: 50, 2020

155. Ruanphoo, P., Bunyavejchevin, S.: Treatment for vaginal atrophy using microablative fractional CO2 laser: a randomized double-blinded sham-controlled trial. Menopause, 27: 858, 2020

156. Salvatore, S., Pitsouni, E., Grigoriadis, T. et al.: CO(2) laser and the genitourinary syndrome of menopause: a randomized sham-controlled trial. Climacteric, 24: 187, 2021

157. Alvisi, S., Lami, A., Baldassarre, M. et al.: Short-Term Efficacy and Safety of Non-Ablative Laser Treatment Alone or with Estriol or Moisturizers in Postmenopausal Women with Vulvovaginal Atrophy. J Sex Med, 19: 761, 2022

158. Eftekhar, T., Ghorbani, L., Ghanbari, Z. et al.: Comparison of the Effect of Radiofrequency and Laser Treatment on Mixed Urinary Incontinence and Vulvovaginal Atrophy in Iranian Menopausal Women: A Randomized Controlled Trial. International Journal of Women's Health and Reproduction Sciences, 9: 061, 2019

159. Chiengthong, K., Bunyavejchevin, S.: Efficacy of Erbium YAG laser treatment in overactive bladder syndrome: a randomized controlled trial. Menopause, 30: 414, 2023

160. Stephenson, J.: FDA Orders Estrogen Safety Warnings: Agency Offers Guidance for HRT Use. JAMA, 289: 537, 2003

161. Crandall, C. J., Hovey, K. M., Andrews, C. A. et al.: Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause, 25: 11, 2018

162. Cold, S., Cold, F., Jensen, M. B. et al.: Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. J Natl Cancer Inst, 114: 1347, 2022

163. Hussain, I., Talaulikar, V. S.: A systematic review of randomised clinical trials - The safety of vaginal hormones and selective estrogen receptor modulators for the treatment of genitourinary menopausal symptoms in breast cancer survivors. Post Reprod Health, 29: 222, 2023

164. Howlader, N., Noone, A., Krapcho, M. et al.: SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD,. https://seer.cancer.gov/csr/1975_2017/ based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

165. Le Ray, I., Dell'Aniello, S., Bonnetain, F. et al.: Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Res Treat, 135: 603, 2012

166. Crandall, C. J., Diamant, A., Santoro, N.: Safety of vaginal estrogens: a systematic review. Menopause, 27: 339, 2020

167. Crean-Tate, K. K., Faubion, S. S., Pederson, H. J. et al.: Management of genitourinary syndrome of menopause in female cancer patients: a focus on vaginal hormonal therapy. Am J Obstet Gynecol, 222: 103, 2020

168. Santen, R. J.: Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. Climacteric, 18: 121, 2015

169. Gupta, P., Sturdee, D. W., Palin, S. L. et al.: Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life. Climacteric, 9: 49, 2006

170. Falk, S. J., Bober, S.: Vaginal Health During Breast Cancer Treatment. Curr Oncol Rep, 18: 32, 2016

171. Robison, K., Kulkarni, A., Dizon, D. S.: Sexual Health in Women Affected by Gynecologic or Breast Cancer. Obstet Gynecol, 143: 499, 2024

172. Kingsberg, S. A., Larkin, L., Krychman, M. et al.: WISDOM survey: attitudes and behaviors of physicians toward vulvar and vaginal atrophy (VVA) treatment in women including those with breast cancer history. Menopause, 26: 124, 2019

173. Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer: Clinical Consensus. Obstet Gynecol, 138: 950, 2021

174. Beste, M. E., Kaunitz, A. M., McKinney, J. A. et al.: Vaginal estrogen use in breast cancer survivors: a systematic review and meta-analysis of recurrence and mortality risks. Am J Obstet Gynecol, 232: 262, 2025

175. Simon, J. A., Goldstein, I., Kim, N. N. et al.: The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. Menopause, 25: 837, 2018

176. Labrie, F., Derogatis, L., Archer, D. F. et al.: Effect of Intravaginal Prasterone on Sexual Dysfunction in Postmenopausal Women with Vulvovaginal Atrophy. J Sex Med, 12: 2401, 2015

177. Barton, D. L., Shuster, L. T., Dockter, T. et al.: Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). Support Care Cancer, 26: 1335, 2018

178. Tanmahasamut, P., Jirasawas, T., Laiwejpithaya, S. et al.: Effect of estradiol vaginal gel on vaginal atrophy in postmenopausal women: A randomized double-blind controlled trial. J Obstet Gynaecol Res, 46: 1425, 2020

179. Goetsch, M. F., Garg, B., Lillemon, J. et al.: Treating where it hurts-a randomized comparative trial of vestibule estradiol for postmenopausal dyspareunia. Menopause, 30: 467, 2023

180. Pinkerton, J. V., Kaunitz, A. M., Manson, J. E.: Vaginal estrogen in the treatment of genitourinary syndrome of menopause and risk of endometrial cancer: an assessment of recent studies provides reassurance. Menopause, 24: 1329, 2017

181. ACOG Practice Bulletin No. 141: management of menopausal symptoms. Obstet Gynecol, 123: 202, 2014

182. Stair, S., Chyu, J., Rangwala, S. et al.: PD24-12 BARRIERS TO PERI- AND POST-MENOPAUSAL WOMEN USING VAGINAL ESTROGEN THERAPY INCLUDE COST AND FEAR OF SIDE EFFECTS. Journal of Urology, 211, 2024

183. Stair, S. L., Palmer, C. J., Lee, U. J.: Wealth of Knowledge and Passion: Patient Perspectives on Vaginal Estrogen as Expressed on Reddit. Urology, 182: 79, 2023

184. Stair, S. L., Chyu, J., Rangwala, S. et al.: Experiences With Genitourinary Syndrome of Menopause and Barriers to Vaginal Estrogen Usage Reported by a National Sample of 1500 Women. Urology, 196: 115, 2025