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Genitourinary Syndrome of Menopause: Management Strategies for the Clinician

Stephanie S. Faubion, MD; Richa Sood, MD; and Ekta Kapoor, MBBS

From the Women's Health Clinic, Division of General Internal Medicine (S.S.F., R.S., E.K.) and Division of Endocrinology, Diabetes, Metabolism, and Nutrition (E.K.), Mayo Clinic, Rochester, MN.

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Learning Objectives: On completion of this article, you should be able to (1) describe the signs and symptoms of genitourinary syndrome of menopause (GSM), (2) list the hormonal and nonhormonal treatment strategies for GSM, and (3) determine appropriate follow-up of patients with GSM.

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Abstract

Genitourinary syndrome of menopause (GSM), previously known as atrophic vaginitis or vulvovaginal atrophy, affects more than half of postmenopausal women. Caused by low estrogen levels after menopause, it results in bothersome symptoms, including vaginal dryness, itching, dyspareunia, urinary urgency and increased frequency, and urinary tract infections. Even though women with GSM can have sexual dysfunction that interferes with partner relationships, women are often embarrassed to seek treatment, and health care professionals do not always actively screen for GSM. As a result, GSM remains underdiagnosed and undertreated. Several effective treatments exist, but low-dose vaginal estrogen therapy is the criterion standard. It is effective and safe for most patients, but caution is suggested for survivors of hormone-sensitive cancers. Newer treatment options include selective estrogen receptor modulators, vaginal dehydroepiandrosterone, and laser therapy. Nonprescription treatments include vaginal lubricants, moisturizers, and dilators. Pelvic floor physical therapy may be indicated for some women with concomitant pelvic floor muscle dysfunction. Sex therapy may be helpful for women with sexual dysfunction. This concise review presents a practical approach to the evaluation and management of GSM for the primary care physician.

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Genitourinary syndrome of menopause (GSM) is a common, underrecognized, and undertreated condition that results from decreased estrogen levels. Affecting nearly 50% of postmenopausal women, GSM also occurs in other low-estrogen states, such as postpartum, during lactation, and with certain medications (eg, aromatase inhibitors [AIs]).[1] Other names for this condition include *vulvovaginal atrophy*, *vaginal atrophy*, and *atrophic vaginitis*.[2] A change in terminology was proposed and endorsed by the North American Menopause Society and the International Society for the Study of Women's Sexual Health in 2014 to (1) acknowledge the involvement of not only the vulvar and vaginal tissues but also the lower urinary tract, (2) identify menopause as an etiologic factor, and (3) avoid the negative connotations associated with the term *atrophy*.[2]

Although vasomotor symptoms typically improve over time, GSM is chronic and progressive, and symptoms are unlikely to resolve without treatment.[1] Findings from the Real Women's Views of Treatment Options for Menopausal Vaginal Changes (REVIVE) survey,[3] involving 3046 postmenopausal women with symptoms of GSM, suggested a lack of awareness that these changes relate to the menopause transition. Further, 59% of respondents reported that their symptoms considerably decreased their enjoyment of sexual activity, and 23% reported an adverse effect on general enjoyment of life.[3] The Women's EMPOWER survey[4] queried 1858 community-dwelling US women and found that women did not bring up the topic with their health care professional because of embarrassment or concerns that the topic was inappropriate for conversation, but most were willing to try a product for symptom relief and would welcome information and treatment suggestions from their health care professional. The Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey reported on 1000 married or cohabitating North American menopausal women with vaginal discomfort and their male partners and the impact of vaginal dryness and low-dose vaginal estrogen therapy (ET) on various parameters.[5] Results revealed that the women and their partners believed that vaginal discomfort had a considerable impact on intimacy. Women avoided intimacy because of vaginal discomfort (58%), experienced loss of libido (64%), and experienced sexual pain (64%). The majority of male partners believed that vaginal dryness caused avoidance of intimacy by their partners (78%), loss of libido (52%), and painful sex (59%). The use of low-dose vaginal ET was associated with less painful sex, greater satisfaction with sex, and an improved sex life.[5]

PRESENTATION AND EVALUATION

Genitourinary syndrome of menopause is a clinical diagnosis, and laboratory testing is usually unnecessary. Although some women with mild GSM remain asymptomatic, many women report symptoms such as vaginal dryness, burning, irritation, decreased lubrication with sexual activity, and dyspareunia with resultant sexual dysfunction.[1] Urinary symptoms of GSM may include frequency, dysuria, and increased risk for urinary tract infections.[1] For some women, symptoms can be severe enough to preclude penetrative sexual activity and to cause discomfort even with sitting or wiping. In women taking AIs, symptoms are more common and may be particularly severe.[1]

Changes on examination include scant pubic hair, loss of the labial fat pad, thinning and resorption of the labia minora, narrowing of the introitus, and increased vaginal pH.[1] Internal examination findings include reduced vaginal caliber; smooth, shiny, pale mucosa with loss of folds; and a cervix flush with the vaginal vault. With inflammation, the vagina may appear erythematous, develop petechiae, and bleed easily.[1]

A pelvic examination can be helpful to exclude other vulvar and vaginal conditions that may present with symptoms similar to those of GSM, including irritant, infectious, or inflammatory vaginitis; dermatoses; and neoplasia.[1]

MANAGEMENT OF GSM

Lubricants and Moisturizers

Lubricants and moisturizers are used for sexual comfort and pleasure and are particularly useful for women with mild to moderate vaginal dryness and for those who choose

TABLE 1. Hormonal Therapy for Management of GSM

Treatment	Product	Dosage		Comments
		Initial	Maintenance	
Vaginal cream				
Estradiol-17β	Estrace	0.5-1 g daily for 2 wk	0.5-1 g 1-3 times weekly	FDA-approved dose is higher loading dose (2-4 g daily; maintenance dose, 1 g 1-3 times weekly)
Conjugated estrogens	Premarin	0.5-1 g daily for 2 wk	0.5-1 g 1-3 times weekly	FDA-approved dose is higher and administration is cyclical (for GSM: 0.5-2 g daily for 21 d and then off for 7 d; for dyspareunia: 0.5 g daily for 21 d and then off for 7 d *or* 0.5 g twice weekly)
Vaginal insert				
Estradiol hemihydrate	Vagifem, Yuvafem	10-μg insert once daily for 2 wk	1 twice weekly	…
Estradiol-17β softgel capsules	TX-004HR	4, 10, or 25 μg daily for 2 wk	1 twice weekly	This product is not yet FDA approved
DHEA (prasterone)	Intrarosa	6.5 mg once daily	6.5 mg once daily	…
Vaginal ring				
Estradiol-17β	Estring	Insert for 90 d (2 mg releases approximately 7.5 μg daily)	Change every 90 d	…
Estradiol acetate	Femring	Insert for 90 d (12.4 mg or 24.8 mg releases 0.05 mg or 0.1 mg daily, respectively)	Change every 90 d	This product is delivered vaginally but it provides systemic hormone levels to treat VMS and GSM
SERM				
Ospemifene	Osphena	60 mg daily	60 mg daily	FDA approved for dyspareunia

DHEA = dehydroepiandrosterone; FDA = US Food and Drug Administration; GSM = genitourinary syndrome of menopause; SERM = selective estrogen receptor modulator; VMS = vasomotor symptoms; ellipses = no comment.
Adapted from *Menopause*,[1] with permission.

not to use vaginal ET.[6] Lubricants provide short-term relief of vaginal dryness and discomfort with sexual activity. They may be water, silicone, or oil based and are applied to the vulva, vagina, or penis (or to all 3) before sexual activity. Water-based lubricants have the advantage of being nonstaining and are associated with fewer genital symptoms than the silicone-based lubricants.[6] There are limited data on the safety of oils (eg, olive oil, coconut oil, and mineral oil) and petrolatum used as lubricants, although there are concerns about effects on sperm motility, condom integrity, and increased risk for *Candida* species colonization and bacterial vaginosis with the use of these products.[7-9] Vaginal moisturizers are used on a regular basis to maintain vaginal moisture (daily or every 2-3 days as needed on the basis of symptom severity). They provide longer-term relief by increasing mucosal moisture and reducing pH.[6] Hyaluronic acid vaginal gel, used every 3 days, has been associated with improvement in symptoms of vaginal dryness comparable to that seen with estriol cream without a change in pH.[10] Vaginal lubricants and moisturizers can be used as needed in combination with other GSM treatments.

Low-Dose Vaginal ET

Low-dose vaginal ET is the preferred pharmacological treatment if symptomatic GSM is unresponsive to nonprescription therapies.[1] It is more effective and safer than systemic ET for treatment of GSM.[1] In fact, women receiving systemic ET for other menopausal symptoms often have persistent GSM symptoms requiring supplemental vaginal ET.[1] With

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low-dose vaginal ET, systemic estrogen absorption is minimal, and serum estradiol levels (according to studies using older assays) remain in the postmenopausal range.[1]

Multiple US Food and Drug Administration (FDA)—approved vaginal estrogen products with similar efficacy are available (Table 1),[1] and the choice is determined predominantly by patient preference. Estrogen creams provide a soothing and moisturizing effect, but some patients find them messy and dislike the reusable applicators.[4] Also, the amount of cream inserted in the vagina varies because it is not packaged as a dosing unit. This feature may be unacceptable when low-dose vaginal ET is required (eg, in breast cancer survivors). Vaginal estradiol tablets (10-μg dose) may be preferred in situations requiring more controlled dosing of vaginal ET. With creams and tablets, women may use daily dosing for the first 2 weeks followed by twice-weekly maintenance dosing. Ideally, women should be treated with the lowest dose and frequency of vaginal ET that effectively manages their symptoms.[1]

Sustained-release estradiol vaginal rings, which can be inserted and removed by patients, are effective for 90 days. The lower-dose ring (Estring, 2 mg) releases approximately 7.5 μg daily and is useful for GSM only; the higher-dose ring (Femring, 12.4 mg or 24.8 mg releases 0.05 mg or 0.1 mg daily, respectively) produces systemic estradiol levels adequate to treat GSM and vasomotor symptoms.[1] The ring is especially useful for women who prefer not to use a vaginal estrogen product every few days.

A vaginal softgel capsule containing solubilized estradiol-17β (4-, 10-, and 25-μg doses) is an emerging treatment option for GSM (it is not yet FDA approved). It provided statistically significant improvement in GSM symptoms compared with placebo with minimal systemic absorption in a 12-week, randomized placebo-controlled trial (used daily for 2 weeks and then twice weekly).[11,12] Maximum serum concentrations of estradiol in the softgel capsule group were lower when compared with estradiol tablets delivering an equivalent dose ($P=.019$ for 10-μg tablet; $P<.001$ for 25-μg tablet).[13] The estradiol vaginal capsule may be useful for women who dislike creams or who want to minimize exposure to systemic estrogen.

Women may notice improvement in symptoms within a few weeks of initiating treatment,[1,12] but many require 8 to 12 weeks for the full benefit of therapy, which can be continued as long as needed to manage symptoms.[1] Observational data reveal no evidence of harm with extended use, but clinical trial safety data are limited to 1 year.[1]

A progestogen is typically not required for endometrial protection in women receiving low-dose vaginal ET.[14] However, periodic endometrial surveillance or progestogen use is a consideration for women at high risk for endometrial cancer or those who are using vaginal ET in doses that are higher than usual.[1]

Clinical trial data are lacking on the safety of low-dose vaginal ET in survivors of hormone-dependent cancers (breast and endometrial cancers). In general, nonhormonal treatments are preferred initial strategies, but after a careful discussion of the potential benefits and risks, low-dose vaginal ET, possibly for a short duration, may be considered in women with refractory symptoms affecting their quality of life.[14] The goal of AI therapy is to reduce circulating estradiol levels, so low-dose vaginal ET should be used cautiously in women receiving AI therapy for breast cancer treatment. Small but significant increases in estradiol levels have been found in women treated with AIs while they use the 25-μg estradiol tablet (no longer available) or the estradiol ring.[15,16] Women using the new estradiol vaginal capsule at the 4-μg dose did not have any differences in mean serum estradiol concentrations compared with placebo, but women using the 10-μg dose had a difference at day 1, with no difference by day 14.[12]

Vaginal ET does not seem to increase the risk of venous thromboembolism, but data on high-risk patients are lacking.[1] Vaginal ET is contraindicated in any woman with undiagnosed vaginal bleeding. Similarly, any woman who reports vaginal bleeding during treatment with vaginal ET should undergo evaluation, including pelvic imaging and endometrial biopsy if indicated.[1]

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are synthetic nonsteroidal agents

that exert variable mixed estrogen agonist and antagonist effects on target tissues.[17] Of the currently available SERMs, only ospemifene is FDA approved for the treatment of moderate to severe dyspareunia caused by GSM in menopausal women.[1] Ospemifene, when given orally at a dose of 60 mg daily, exerts estrogenic effects on vulvovaginal tissues and results in acidic vaginal pH and improvements in the vaginal maturation index and dyspareunia.[18] Although ospemifene does not appear to stimulate breast tissue,[19-21] its safety in women with or at high risk for breast cancer has yet to be established. Ospemifene is an option for management of dyspareunia in postmenopausal women and may be particularly appealing for those who are unwilling or unable to use low-dose vaginal estrogen.

None of the other available SERMs are FDA approved for treatment of GSM. These SERMs include tamoxifen (approved for breast cancer prevention and treatment), raloxifene (approved for osteoporosis and breast cancer treatment), and bazedoxifene (approved for use in combination with conjugated equine estrogens for treatment of vasomotor symptoms and for osteoporosis prevention).[17] Tamoxifen exerts mixed vaginal effects and may cause dyspareunia, increased vaginal discharge, or vaginal dryness.[17] Raloxifene and bazedoxifene do not exert any direct positive effects on the vagina.[17] However, the combination of bazedoxifene and conjugated equine estrogens (20/0.45 mg daily) has improved symptoms and signs of GSM without causing endometrial hyperplasia.[22,23]

Lasofoxifene, a third-generation SERM currently under development and not approved by the FDA, has been reported to prevent bone loss and is effective for GSM.[17]

Vaginal Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid prohormone in the biosynthetic pathway of testosterone and estradiol. Short-term clinical trials with daily use of vaginal DHEA have found improvements in GSM symptoms (including dyspareunia), vaginal pH, and the vaginal maturation index.[24,25] Vaginal DHEA is thought to exert its effect by local conversion to testosterone and estradiol; it has not been found to increase systemic steroid hormone levels, presumably because of local inactivation.[25] Therefore, it may be a safer alternative to vaginal ET in patients with contraindications to estrogen use (eg, breast cancer survivors). Additionally, with the lack of the aromatase enzyme in the endometrium, vaginal DHEA is not converted to estradiol in the endometrium and does not exert any endometrial proliferative effects.[26] Used as a daily vaginal insert, DHEA (Intrarosa, 6.5 mg), was recently approved by the FDA for the treatment of GSM.

Laser Treatments

Laser therapy for GSM has been tested in smaller, uncontrolled clinical trials with positive results.[27] Although the carbon dioxide laser has been cleared by the FDA for "incision, excision, ablation, vaporization, and coagulation of body soft tissues in medical specialties, including aesthetic (dermatology and plastic surgery), podiatry, otolaryngology (ENT), gynaecology" and other specialties and the YAG laser has been cleared for "incision, excision, ablation, vaporization of soft tissue for General Dermatology, Dermatologic and General Surgical procedures for coagulation and hemostasis," vulvovaginal atrophy or GSM is not specifically listed as an indication for treatment.[28]

The microablative carbon dioxide laser used for vaginal epithelial resurfacing activates heat shock proteins that in turn activate growth factors, resulting in an increase in vascularity, collagen, extracellular matrix production, and thickness of vaginal epithelium.[29] In a 12-week single-group study involving 50 women, 3 carbon dioxide pulsed laser treatments were administered 1 month apart, with results indicating statistically significant improvements in self-reported vaginal dryness, burning, itching, dyspareunia, and dysuria and in Vaginal Health Index scores (examiner assessments of elasticity, fluid secretion type, pH, epithelial mucosa, and moisture), with few reported adverse effects.[30]

The erbium:YAG laser has also been studied for GSM. In an 18-month study with 50 women, when laser treatment was compared with intravaginal estriol, the laser treatment improved symptoms of GSM with minimal adverse effects, and the benefits were more pronounced and longer lasting compared with estriol.[31] The large multicenter Vaginal

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TABLE 2. Nonhormonal Treatment Strategies for GSM

Treatment strategy	Specific therapy	Typical use	Comments
Education	Provide education on potential vulvar and vaginal changes associated with menopause or other low-estrogen states Offer therapy as indicated	General patient education	Education should be offered to women regardless of partner status Regular, painless sexual activity or vaginal stimulation can help maintain sexual function
Lubricants	Examples of lubricants: YES, JO, Good Clean Love, Pink, and Uberlube	Used as needed for sexual activity	Used to increase comfort and pleasure Avoid irritants (eg, glycerin, parabens, and propylene glycol) Can be used with other therapies (hormonal and nonhormonal)
Moisturizers	Examples of moisturizers: Replens, RepHresh, Sliquid Satin, and Hyalo Gyn	Used daily or every few days on a regular basis to maintain vulvar and vaginal moisture	Mimic normal vaginal secretions Do not reverse cellular and pH changes of GSM Can be used with other therapies (hormonal and nonhormonal)
Use of dilators and vibrators	Multiple types available	Used as needed	Gently stimulate and stretch the vulvar and vaginal tissues to maintain function
Pelvic floor physical therapy	Provide education as indicated on kinesthetic awareness, pelvic floor muscle relaxation, manual therapies, and biofeedback	Used as needed for nonrelaxing pelvic floor muscle dysfunction	Identify a physical therapist who specializes in pelvic floor disorders (http://www.womenshealthapta.org/)[36]
Topical lidocaine	4% aqueous lidocaine	Applied to the vestibule a few minutes before sexual activity	Can be used as an adjunct to other therapies, including lubricants, moisturizers, and physical therapy
Laser therapy	Carbon dioxide laser Erbium:YAG laser	Administered as a series of 3 treatments a few weeks apart	Use is limited by a lack of studies examining long-term safety and efficacy and comparing laser therapy with estrogen therapy and sham control

GSM = genitourinary syndrome of menopause.

Erbium Laser Academy Study (VELAS)[32] is evaluating the safety and efficacy of laser for treatment of GSM and stress urinary incontinence.

Longer-term safety and efficacy studies using sham controls are needed before laser treatments can be recommended as a standard therapy for GSM.

OTHER THERAPEUTIC CONSIDERATIONS

Education is important so that women know about the genitourinary changes that occur with the loss of estrogen associated with menopause. Patients should be advised that GSM symptoms are unlikely to improve without treatment, and counseling should include a review of treatment options, both nonhormonal and hormonal. Women who are sexually active are often aware of these gradual changes, which may cause discomfort with sexual activity, but sexually inactive women who have GSM and who resume sexual activity may be surprised that it is painful (or not even possible).[1] Regular, painless sexual activity can help maintain vaginal health. A vibrator can be used therapeutically to stimulate blood flow and maintain vaginal function in women with or without a partner.[1] Similarly, either a lubricated vibrator or vaginal dilator can be used to gently stretch the vaginal tissues. In women who experience vaginismus (ie, the involuntary contraction of the muscles surrounding the vagina), the progressive use of vaginal dilators with relaxation

and mindfulness exercises can facilitate reinitiation of painless penetrative sexual activity.[33]

Pelvic floor physical therapy, ideally provided by a physical therapist with specialized training in pelvic floor disorders, may be useful for treatment of women with nonrelaxing or high-tone pelvic floor muscle dysfunction triggered by painful sexual activity related to GSM.[34]

Topical lidocaine applied to the introitus a few minutes before sexual activity has reduced pain with sexual activity in breast cancer survivors and may serve as an adjunct to other therapies (eg, vaginal moisturizers, lubricants, and physical therapy) for management of GSM.[35] Table 2 summarizes nonhormonal treatment options.

FOLLOW-UP

Low-dose vaginal ET is a highly effective therapy for GSM, and most women respond well to treatment. In nonresponders, adherence must be assessed. An analysis of US prescription renewal data revealed that a large proportion of women discontinued vaginal ET within 2 to 4 months after initiating therapy.[37] Common reasons for discontinuation included messiness of the creams, inconvenience of the applicator, vaginal discharge, and concerns about long-term safety.[4]

Women who remain symptomatic despite the use of low-dose vaginal ET should be reevaluated with consideration given to alternative or concomitant diagnoses, such as infection, inflammatory or autoimmune diseases, dermatoses, allergic conditions, neoplasia, vulvodynia, or other medical or psychological contributors.[1] In women with ongoing deep dyspareunia despite adequate treatment of GSM, nonrelaxing pelvic floor muscle dysfunction should be considered, and evaluation and treatment by a physical therapist is indicated.[34] Genitourinary syndrome of menopause with or without pelvic floor muscle dysfunction can adversely affect sexual function, and referral to a sex therapist may also be useful.[34]

CONCLUSION

Genitourinary syndrome of menopause is underrecognized and undertreated and seriously affects quality of life, but many effective treatment strategies are available. Low-dose vaginal ET is the criterion standard therapy, but other treatments are also effective, including ospemifene and intravaginal DHEA. The laser holds promise, but additional studies are needed. Health care professionals should ask menopausal women about symptoms and offer education and therapy as indicated.

Abbreviations and Acronyms: **AI** = aromatase inhibitor; **DHEA** = dehydroepiandrosterone; **ET** = estrogen therapy; **FDA** = US Food and Drug Administration; **GSM** = genitourinary syndrome of menopause; **SERM** = selective estrogen receptor modulator

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Correspondence: Address to Stephanie S. Faubion, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (faubion.stephanie@mayo.edu).

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