CME

A practical guide to managing genitourinary syndrome of menopause in primary care

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ABSTRACT

Females spend a third to half of their life in menopause, and the number of US females in menopause is growing. A high percentage of postmenopausal females experience bothersome, sometimes debilitating genitourinary symptoms, which can affect quality of life. The genitourinary syndrome of menopause (GSM) describes the condition previously referred to as vulvovaginal atrophy, atrophic vaginitis, or urogenital atrophy. Of concern, many patients with symptoms of GSM have never been asked about nor have they initiated conversations about these concerns with a healthcare provider. This article addresses the need to improve screening, identification, and patient-centered management in primary care of females with GSM.

Keywords: genitourinary syndrome, menopause, vulvovaginal atrophy, estrogen, atrophic vaginitis, dyspareunia

Learning objectives

- Describe an effective way to consistently identify patients experiencing GSM.
- Describe therapy options for patients experiencing mild GSM.
- Outline pharmacologic therapy for patients experiencing moderate to severe GSM.
- Recognize complex cases for which a referral is appropriate.

Genitourinary syndrome of menopause (GSM), formerly called vulvovaginal atrophy, atrophic vaginitis, or urogenital atrophy, describes the wide range of changes caused by the lack of estrogen during menopause. GSM also presents in a relatively small percentage of premenopausal females because of low estrogen states. The term GSM was adopted by the North American Menopause Society (NAMS) in 2014 to better characterize the wider effect of markedly diminished estrogen on reproductive tissues.[1] Although GSM is not a cause of increased mortality, it is a frequent cause of chronic morbidity. Up to 50% of postmenopausal females have reported symptoms consistent with GSM, and up to 15% of premenopausal females experience symptoms consistent with

GSM.[2] The prevalence of GSM-related symptoms (such as vaginal dryness, irritation, itching, and dyspareunia) varies widely from 13% to 87%. GSM is a highly prevalent condition, generally is progressive, and the incidence increases with age.[3] As the population ages and life expectancies increase, an estimated 90 million females in the United States will be postmenopausal by 2060.[4] Thus, the expected burden of GSM on the population is substantial and provides a compelling picture of the need for improved screening, diagnosis, and effective treatments.

In 2021, Mili and colleagues performed a systematic review on the prevalence and treatment of GSM, spanning 27 studies.[3] In 12 studies that explored the number of females who discussed GSM symptoms with a health professional, it was clear that many females experiencing GSM symptoms hesitated to initiate such a discussion. Discussions more commonly occurred in gynecology settings than other settings such as primary care. Commonly cited reasons for their silence were considering the symptoms to be a normal consequence of menopause and feeling embarrassment or not being comfortable discussing the symptoms.[3] Other factors that have been associated with a lower likelihood of females to discuss GSM symptoms

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Key points

- Postmenopausal patient care should include regular inquiry into symptoms of GSM and provide education on OTC options for relief of mild to moderate symptoms.
- Unlike vasomotor symptoms associated with menopause, genitourinary signs and symptoms are likely to progressively worsen over time and are unlikely to resolve without treatment.
- For females with moderate to severe symptoms of GSM without contraindications, pharmacologic therapy with vaginal estrogen is a first-line approach.
- For females with GSM and contraindications to hormonal therapy, ospemifene or a referral to a menopause-certified healthcare provider are options.

with a healthcare professional are lower socioeconomic status, lower education level, and advanced age.[3,5] Further, at least half of clinicians do not screen patients for GSM or ask them about symptoms of GSM.[3] Healthcare professionals, especially those in primary care, if educated on the prevalence, clinical manifestations, and initial treatments of GSM, are well positioned to help the many females who are suffering in silence with a syndrome that is likely to get worse with advancing age and unlikely to resolve spontaneously.

MANIFESTATIONS

Estrogen-dependent tissues of the genitourinary tract include the vagina, bladder, and external genitalia. Patients with GSM present with a progressive, individualized constellation of bothersome symptoms caused by the dramatically diminished levels of estrogen that are a natural product of menopause (**Table 1**).[2,6] Unlike vasomotor symptoms of menopause, which typically resolve over time, GSM does not resolve without intervention. Females who have experienced iatrogenic menopause—particularly surgical—report greater severity of symptoms because of the abrupt decrease in circulating androgens and estrogen.[7,8]

The one nearly universal complaint of females with GSM is unremitting vaginal dryness. For most, this leads to painful intercourse, though GSM is not limited to sexually active females. The mucosal dryness typically is visible to the naked eye on pelvic examination. Thinning of the vaginal rugae makes the tissue look shiny and smooth internally with extension to the external genitalia. Pallor of the mucosa and petechiae also may be observed. Females may experience itching, burning, and coital bleeding from the fragile, friable mucosa. The loss of tissue elasticity also may lead to stenosis of the introitus, atrophy or fusion of the labia, pelvic support defects, or prolapse.[8] Hypoestrogenic changes to the vaginal microbiome also are evident microscopically and are caused by reduced glycogen in the tissue and an increased pH (5 or greater).[2,7] These conditions lead to a loss in the *Lactobacillus* species closely associated with vaginal health and an increase of parabasal cells (small, immature epithelial cells with large nuclei) and inflammatory cells, making females with GSM more susceptible to vaginitis.[9] Females experiencing GSM also may report chronic urinary symptoms including urgency, frequency, dysuria, and nocturia as well as experience recurrent urinary tract infections.[3]

The physical changes associated with GSM can significantly affect sexual function. Diminished or absent vaginal lubrication associated with sexual arousal often is one of the earliest symptoms that females recognize with menopausal changes. Other common findings include varying degrees of dyspareunia, decreased libido, decreased arousal sensation, and decreased orgasm. The effect of altered sexual function on a female's quality of life varies based on multiple factors, including relationship status, partner's sexual function, and desired sexual activities.[8]

DURING THE PATIENT VISIT

Because GSM is a high-prevalence condition among postmenopausal females, routine screening and recognition of GSM-related symptoms are key. NAMS has developed

TABLE 1. Diagnostic criteria and common findings in patients with GSM[6]

The clinical diagnosis is based on patient history and physical examination, and must include bothersome symptoms.

Patient history

- Vulvovaginal dryness
- Dyspareunia
- Vulvovaginal itching, burning, or irritation
- Urinary frequency, dysuria, nocturia, urinary urgency, recurrent urinary tract infections
- Postcoital bleeding
- Delayed or decreased orgasm

Physical examination

- Vulvovaginal atrophy—pallor, loss of rugae, introital retraction, excoriations
- Vulvar thinning, fusion of labia, clitoral hood retraction
- Vaginal discharge—pH greater than 5 with parabasal cells
- Prominent urethral meatus

TABLE 2. Differential diagnosis

- Use of bladder stimulants such as caffeine or alcohol
- Cervical neoplasia
- Isolated pelvic support defects
- Sexual dysfunction
- Sexually transmitted infection
- Urinary tract infection (acute, chronic, or recurrent)
- Vulvovaginitis, such as bacterial vaginosis or trichomoniasis
- Vulvar dermatoses, including lichen sclerosus, lichen simplex chronicus, lichen planus, localized vulvodynia, and allergic or irritative dermatitis
- Vulvar neoplasia

TABLE 3. Prescription pharmacologic therapies for GSM[32-39]

Therapy	Product	Dosing	Indication(s)	Contraindications
Low-dose vaginal estrogen cream	Conjugated estrogens (Premarin)—0.625 mg/g	0.5 to 1 g intravaginally daily for 2 weeks, then 0.5 to 1 g intravaginally twice/week	GSM, dyspareunia	Current diagnosis of, history of, or high risk for estrogen-sensitive neoplasia
	17-beta estradiol (Estrace)—0.1 mg/g	• Initial: 2 to 4 g intravaginally daily for 1 to 2 weeks • Reduce dose by 50% for 1 to 2 weeks • Maintenance: 1 g 1 to 3 times/week		
Low-dose vaginal estrogen insert	17-beta estradiol (Imvexxy)	• Initial: 4 or 10 mcg intravaginally daily for 2 weeks • Maintenance: 4 or 10 mcg twice weekly		
	17-beta estradiol (Vagifem, Yuvafem)—10-mcg tablet/insert	• Initial: insert 1 intravaginally daily for 2 weeks • Maintenance: insert 1 intravaginally twice weekly		
Low-dose vaginal estrogen ring	17-beta estradiol acetate (Estring)—2-mg ring, releases about 7.5 mcg/day	Place ring as deeply in the vagina as possible; replace every 90 days		
SERM	Ospemifene (Osphena)—60 mg	Oral, once daily	Moderate to severe dyspareunia and vaginal symptoms	Current treatment for breast cancer or on another SERM
Prasterone (DHEA) inserts	Intrarosa—6.5 mg	Insert once intravaginally daily at bedtime	Moderate to severe dyspareunia	Same as vaginal estrogens

a comprehensive menopause health questionnaire that is a useful point-of-care resource.[10] Another validated questionnaire is the 21-question Vaginal Symptom Questionnaire.[11] Its significant limitation is that it does not explore urinary symptoms associated with GSM.[2] Alternatively, simply ask all peri- and postmenopausal females about vulvovaginal discomfort, urinary symptoms, and sexual function as a component of regular wellness. Pertinent history findings for GSM should be confirmed with a physical examination and effort to rule out other pathology with overlapping symptoms (**Table 2**). Atrophic changes that do not cause bothersome symptoms do not need to be treated and do not meet the criteria for a diagnosis of GSM.[7]

THERAPEUTIC OPTIONS

Shared decision-making is an important facet of effective care for females with GSM. The goal of treatment is to minimize the effect of symptoms on the patient's needs and sexual health, maximizing genitourinary function and comfort. Options for treating GSM include over-the-counter (OTC) lubricants and moisturizers, locally applied hormonal therapies, an oral selective estrogen receptor modulator (SERM), adjuvant lifestyle modifications, and laser or radiofrequency-based vaginal devices.[2]

Treatment benefits can be seen within several weeks of therapy; however, maximal improvement may take up to 12 weeks.[6] Because symptoms generally recur with discontinuation of treatment, treatment can continue as long as the patient does not develop a condition for which the treatment is contraindicated (**Tables 3** and **4**).[2]

OTC THERAPIES

Lubricants and vaginal moisturizers OTC lubricants are designed to reduce friction and tissue trauma during sexual activity. Vaginal moisturizers rehydrate by being absorbed into the tissue. The two are the first-line agents and the most-used products for females experiencing vaginal dryness associated with GSM, including among those patients who have consulted with a clinician. Lubricants and moisturizers can be used in conjunction with each other and as an adjuvant to other therapies, and both may be used without reservation in females who have contraindications to hormonal therapy. Both have been shown to be effective in reducing dyspareunia associated with mild to moderate vaginal dryness. Moisturizers may have additional, potential benefits of relieving vaginal itching and discomfort. Unfortunately, neither treats the underlying cause of GSM nor changes the trajectory of the progressive process.

Lubricants are available in a variety of preparations including water-, silicone-, mineral oil-, and plant oil-based. For maximal effect, lubricants may need to be reapplied during intercourse. Patients may start treatment of GSM

TABLE 4. OTC pharmacologic therapies for GSM[12,27,30]

Therapy	Product examples	Dosing	Indication(s)
Vaginal lubricant	Water-based options at recommended pH and osmolality include Yes Baby and Good Clean Love; silicone-based options include überlube and Pjur	As needed	Dyspareunia
Vaginal moisturizer	Option at recommended pH: YES VM vaginal moisturizer	Apply intravaginally two or three times/week	Vaginal symptoms
Hyaluronic acid	Bonafide Revaree vaginal insert and Good Clean Love BioNourish ultra moisturizing vaginal gel with hyaluronic acid	Apply intravaginally two or three times/week	Vaginal symptoms
Vitamin E	Multiple unregulated brands of vaginal suppositories and inserts	In studies: intravaginally daily for 2 weeks, then every other day	Vaginal symptoms
Pelvic floor muscle training/therapy		Designed by physical therapist based on patient symptoms	Dyspareunia, urinary symptoms, genital prolapse
At-home devices	iTouch, Kegelmaster	Varies by product	
Laser therapy	MonaLisa Touch, FemTouch	Three or more sessions 4 to 6 weeks apart, with annual maintenance therapy	Vaginal symptoms

with a lubricant and add a moisturizer if sufficient relief is not achieved. Vaginal moisturizers can provide symptomatic relief for 2 to 3 days and have a longer effect than lubricants. Moisturizers should be applied to the vaginal mucosa regularly, several times each week with no temporal relationship to sexual activity, for best absorption and results.[12]

When selecting from the wide array of these topical products, patients should choose one with a pH and osmolality that is most body-similar to limit additional irritation and potential tissue damage. With water-based products, a pH level between 3.5 and 5 and an osmolality in the range of 200 to 600 mOsm/kg are recommended. Avoid products with parabens, chlorhexidine, or polyquaternium-15, which may worsen symptoms and may make patients more susceptible to urinary tract and vaginal infections.[13] Advise patients using condoms to protect against sexually transmitted infections to avoid oil-based lubricants, which can deteriorate latex.[14]

Hyaluronic acid A systemic review of five small studies investigated the use of vaginal hyaluronic acid for vaginal atrophy associated with GSM, and found it had similar efficacy to local estrogen, as measured by vaginal pH, cell maturation on biopsy, and patients' perception of improvement of vaginal dryness and dyspareunia.[15] Hyaluronic acid releases water molecules into vaginal tissue, maintaining tissue integrity and hydration and increasing blood supply.[2,8,15] No adverse reactions were reported with vaginal use of hyaluronic acid either alone or in combination with other topical moisturizers, and it was well-tolerated among study participants.[15] Because it is nonhormonal, hyaluronic acid may be a good alternative for patients who are not good candidates for estrogen therapy and whose symptoms are not resolved by vaginal lubricants and moisturizers. Hyaluronic acid can be purchased under several different brand names in the form of suppositories or creams to be used every 2 to 3 days before bedtime. However, rigorous studies on the benefits of hyaluronic acid compared with other vaginal moisturizers are lacking.[15]

Vitamin E Menopause societies in the United States and Europe do not recommend isolated, vaginal vitamin E use in their guidelines, but patients may ask about using it.[16] Vitamin E, an antioxidant, protects tissues from oxidation and cell damage. Several small studies have evaluated vitamin E vaginal suppositories as an alternative, nonhormonal therapy for patients experiencing GSM.[16] Vitamin E may be particularly appealing for patients who are unable or unwilling to use hormones or who desire a more natural approach. A recent systematic review of randomized controlled trials found that vitamin E was superior to placebo in alleviating GSM symptoms—irritation, itching, vaginal dryness, and dyspareunia.[16] Compared with vaginal estrogen, vitamin E was not inferior at 8 and 12 weeks and was inferior compared with vaginal hyaluronic acid.[16] Because of concerns about study design and rigor, more studies need to be done before vitamin E can be recommended.

PHARMACOLOGIC THERAPIES

Estrogen Topical estrogen is the most effective treatment for GSM because it restores vaginal pH, improves microflora, and promotes epithelial thickening and increased vaginal secretions.[3] Local, low-dose estrogen applied vaginally in the form of creams, a sustained-release ring, soft-gel inserts, or tablets is the mainstay of therapy and is safer because of the lack of systemic estrogen effects. All vaginal preparations appear to be equally efficacious.[17] Because these products have minimal systemic absorption, they do not appear to increase patient risk for cardiovas-

cular disease, gynecologic cancers, or hip fractures; however, local estrogen should always be used at the lowest effective dose.[18,19] Current recommendations advise that endometrial surveillance is not needed unless the patient experiences postmenopausal bleeding and that a progestogen (any natural or synthetic form of progesterone) is not indicated with low-dose, local estrogen preparations.[20] Estrogen treatment is contraindicated in patients who are experiencing uterine or vaginal bleeding and for those who have or have had estrogen-dependent cancers such as some types of endometrial and breast cancer.[21] Although women who have a history of estrogen-dependent neoplasia should be offered a nonhormonal first-line treatment for GSM, several observational studies have suggested that local estrogen therapy may not pose an elevated risk of breast cancer recurrence. Any shared decision-making about estrogen use in patients with a history of these cancers should be made in consultation with an oncologist.[2]

On a practical note, although serum levels of estradiol in postmenopausal patients on low-dose vaginal estrogen are comparable to those who are not, product labeling includes the same boxed warning as for other systemic estrogens. Educating patients on the difference between the two is important for both reassurance and treatment adherence.[2] Patients also should be advised to wait at least 1 hour after estrogen application before using vaginal lubricants or moisturizers for best efficacy of all topical products.[12]

Oral estrogen or combined estrogen and progestogen treatment is not indicated for vulvovaginal symptoms alone.[22] Systemic estrogens may be used for a limited time if patients experience other bothersome effects of menopause, such as vasomotor symptoms.[20]

Ospemifene This oral SERM is FDA-approved for moderate to severe dyspareunia and vulvovaginal atrophy due to menopause. Taken as a daily 60-mg oral dose, ospemifene acts as an estrogen agonist in the vagina and appears to have no estrogenic effects on the endometrium or breast. Ospemifene treats the underlying condition by promoting estrogenic effects, such as lowering pH and decreasing parabasal cells in vaginal tissue, without harming the endometrium.[23,24] The drug should not be prescribed concurrently with any other SERM or estrogen product but can be used in patients with a history of breast cancer.[23] Ospemifene is the only approved oral option, and the ease of dosing may make it particularly attractive for some patients. The most common adverse reactions are hot flashes, increased vaginal discharge, and headaches; however, in multiple studies, fewer than 1% of patients discontinued treatment because of adverse reactions.[23,24]

Prasterone A synthetic, intravaginal dehydroepiandrosterone (DHEA) gel is indicated for moderate to severe dyspareunia caused by menopause and has been shown to improve other vaginal symptoms of GSM without harming the endometrium.[2] DHEA is an endogenous steroid that is converted intracellularly by aromatase activity into androgens and estrogens.[3] Prasterone improves tissue function, reduces vaginal pH, and increases collagen fiber and nerve density.[20,25] The gel is inserted into the vagina with a single-use applicator once daily at bedtime and can be administered indefinitely.[20] Although patients' serum estrogen and testosterone typically remain within normal limits, prasterone has not been studied in females with a history or current diagnosis of breast cancer and should not be used in these patients.[21]

Testosterone Compounded intravaginal testosterone cream also has been used to treat GSM, but data on safety and efficacy are limited, and as a result, the use of testosterone is not recommended.[2]

NONPHARMACOLOGIC THERAPIES

Pelvic floor muscle training and physical therapy Females experiencing sexual dysfunction, urinary incontinence, or genital prolapse associated with GSM may benefit from pelvic floor muscle training and physical therapy. Physical therapists who specialize in women's health can design a personalized plan to reduce discomfort with penetration secondary to shortened, painful pelvic floor muscles. This may include training in ongoing use of graduated vaginal dilators, exercise of pelvic floor muscles with repeated contractions to increase blood flow and reduce guarding, and education on modifications of sexual positions.

For patients with urinary symptoms, therapy can focus on the levator ani muscle for modification of the blood flow, tone, endurance, and strength needed to improve function. Although published studies about these therapies typically are small and less rigorous, they have nonetheless demonstrated statistically significant improvement in symptoms, sexual function, and patient quality of life.[26,27] Another advantage of pelvic floor muscle training is that it can be used in conjunction with any of the pharmacologic therapies without concerns about safety or adverse reactions. Commercially available at-home pelvic floor training devices include devices that use intravaginal resistance, biofeedback, electrostimulation, mechanical stimulation, magnets, and combination modalities. A recent meta-analysis showed a large positive effect of these devices on both incontinence and urogenital distress.[28] The analysis did not evaluate the effect on sexual dysfunction.[28]

Vaginal laser therapy This emerging, energy-based treatment may stimulate *Lactobacillus* and other premenopausal flora and regenerate connective tissue in the vagina, improving vaginal health and restoring a normal vaginal pH.[20] However, in 2018, the FDA issued a warning asserting that these devices had not been adequately evaluated for use in vaginal rejuvenation procedures and may pose a risk for patient injury.[29] Since then, several small, multicenter randomized controlled trials have been published; a systematic review and meta-analysis suggested that the

therapy may be effective for GSM, but larger studies lasting more than 1 year are needed to confirm the benefit.[30]

Treatment with vaginal laser therapy consists of three or more sessions 4 to 6 weeks apart with a maintenance therapy annually. Each treatment takes about 5 minutes, and no recovery time is needed. Most participants reported only minor adverse reactions.[30] As with other nonhormonal therapies, vaginal laser therapy is of particular interest for patients who have a history of estrogen-responsive cancers such as breast cancer and who are not candidates for hormonal therapy. These patients often have more severe symptoms of GSM because of therapy with aromatase inhibitors.[30] Until more robust data are available, energy-based treatment should not be routinely recommended, and clinicians should be aware that patients must pay for this treatment as an elective, out-of-pocket expense.[31]

REFERRALS

Patients who likely would benefit from a referral for more specialized care include those who remain dissatisfied after treatment and those with more complex presentations, such as patients with a high risk for or history of estrogen-sensitive neoplasia, those with iatrogenic menopause, and transgender men. One reliable source for referrals is NAMS, which publishes a list of certified menopause clinicians. A patient's oncology team is another prudent source of collaboration.[21]

CONCLUSION

Despite a high prevalence among postmenopausal patients, GSM is underdiagnosed. Patients often are reticent to initiate discussion on this topic, and many clinicians (especially in the primary care setting) fail to inquire about symptoms. To support improved screening and better diagnosis of GSM, start by asking all perimenopausal and postmenopausal patients about genitourinary symptoms including vaginal discomfort, urinary symptoms, and sexual health. Provide proactive general education for every patient, beginning in the perimenopausal years, about vaginal lubricants and moisturizers to normalize the conversation and build a bridge of trust about what may be a sensitive topic for the patient. Topical estrogen therapy is the most effective treatment option for females suffering from GSM and should be considered in patients experiencing moderate to severe symptoms that are not responsive to OTC topicals and who do not have contraindications. Other pharmaceutical alternatives include ospemifene and prasterone. Refer patients to a menopause specialist if they have contraindications to pharmacologic therapies and their symptoms do not respond to OTC therapies. Finally, patients with persistent dyspareunia and/or urinary symptoms may benefit from pelvic floor muscle training or physical therapy to augment the efficacy of other therapies. **JAAPA**

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