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Genitourinary Syndrome of Menopause: What the Urologist Should Know About Its Evaluation and Management

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to perform a comprehensive history and physical examination, identify signs and symptoms associated with genitourinary syndrome of menopause, and offer treatment and counsel patients on nonpharmacological and pharmacological options for the management of symptoms of genitourinary syndrome of menopause.

This AUA Update aligns with the American Board of Urology Module on Neurogenic Bladder, Voiding Dysfunction, Female Urology, BPH, and Urethral Stricture. Additional information on this topic can be found in the AUA Core Curriculum sections on Female Pelvic Medicine and Urinary Incontinence and Overactive Bladder.

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Rena D. Malik, MD, FPMRS,[1] Yahir Santiago Lastra, MD, FPMRS,[2] and Rachel S. Rubin, MD[3]

[1]Division of Urology, Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland

[2]Department of Urology, UC San Diego School of Medicine, San Diego, California

[3]Department of Urology, Medstar Georgetown University, George Washington University, Washington, DC

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KEY WORDS: quality of life, postmenopause, sexual health, estrogens, female urogenital diseases

INTRODUCTION

Globally, urogenital health after menopause is fundamental and can significantly impact a woman's quality of life and sexual well-being. The term genitourinary syndrome of menopause (GSM) was proposed in 2014 to cohesively describe a "variety of bothersome genital, sexual, and urinary symptoms that can either be isolated or coexisting and not related to other medical conditions."[1] GSM is a chronic and progressive condition, and it is imperative that patients are recognized early and managed appropriately to preserve urogenital health at older ages. Despite the importance of early detection and treatment, the condition is consistently underdiagnosed and undertreated. In this Update, we summarize the critical knowledge needed to diagnose GSM in postmenopausal women and in women with low estrogen and low androgen states. Additionally, we summarize evidence-based treatments that can also be used, with a strong focus on prescription treatments and adjunctive therapies.

ANATOMY

Clinicians must be well versed in the evaluation of female anatomy to treat women with GSM. The functional anatomy of the urogenital tissues (vagina, vestibule, clitoris, bladder, urethra, and pelvic floor) are under the influence of sex steroids.[2] Female genital organs commonly affected by menopause include the vulva, external female genitalia made up of the labia majora and minora, vulvar vestibule, clitoris, vagina, cervix, and pelvic floor muscles (**Figure 1**).

- Labia minora are 2 flaps of skin on either side of the vaginal opening. They can vary considerably in width and length. They protect the vestibule from mechanical irritation, dryness, and infection. They also lubricate during intercourse to allow easy penetration. Menopause results in resorption and narrowing of the labia minora and thinning of the epithelium.[3]
- The vulvar vestibule is located between the labia minora and the hymen. This area is embryologically distinct to that of the vagina and arises from endodermal tissue. The external urethral meatus and the openings to the Bartholin's and Skene's glands are found within the vestibule.[4] The vestibule has shallow and dense sensory nerve endings, which are increased in density with loss of estrogen and can result in increased sensitivity and pain when provoked.[5,6]
- The clitoris arises from prepuce, glans, corona, corpora cavernosa, and crura, homologous to the male penis. It is often obscured by preputial skin or a "hood." Similar to penile foreskin, the clitoral hood can cause clitoral phimosis or balanitis, resulting in clitoral pain (clitorodynia) and/or anorgasmia.[6]
- The vagina is an elastic, muscular canal that extends from the vestibule to the cervix. It is highly responsive to hormonal changes and contains a high concentration of estrogen and androgen receptors. Estrogen plays a vital role in blood flow and lubrication. Activation of estrogen receptors releases nitric oxide, which increases capillary blood flow resulting in vasocongestion. This increases oncotic pressure within the vaginal submucosa, causing fluid transudation or lubrication.[7]

In GSM, the symptomatology is thought to be explained by a reduction in circulating estrogens and androgens and a reduction in the number of estrogen and androgen receptors of the genitourinary tract.[8] Subsequently, tissues

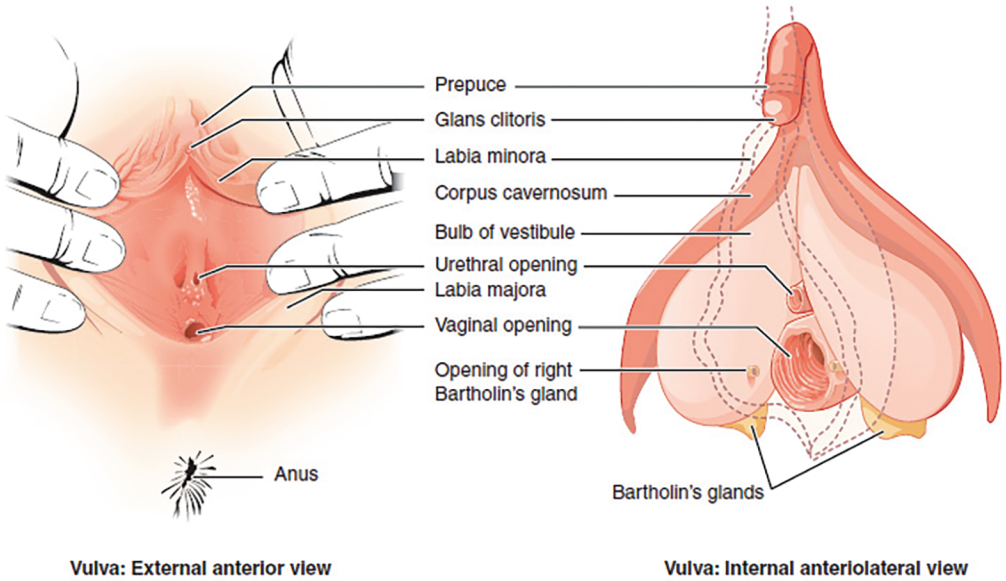

Figure 1. Internal and external vulvar anatomy. This figure, by OpenStax College, is reprinted under the terms of CC BY 3.0 (http://cnx.org/content/col11496/1.6/). Source: Anatomy & Physiology, Connexions website, June 19, 2013.

ABBREVIATIONS: dehydroepiandrosterone (DHEA), U.S. Food and Drug Administration (FDA), genitourinary syndrome of menopause (GSM), pelvic floor muscle training (PFMT), urinary tract infection (UTI), Vaginal Health Index (VHI), Vulvar Health Index (VVHI)

develop reduced collagen and elastin, loss of elasticity and flexibility, and diminished blood supply causing bothersome symptoms. The vagina, vestibule, and lower urinary tract share a common embryological origin and have analogous estrogen and androgen receptor characteristics.

Estrogen receptors are widespread within the epithelial, endothelial, and smooth muscle tissues of the female genital tract, and stimulation via estrogen is crucial for adequate functioning.[9] Estrogen regulates the proliferation, maturation, and stratification of the vaginal epithelium, maintaining vaginal wall integrity and normal blood flow to the urogenital tissues. In addition, estrogen influences neurotransmitter systems that regulate mood and desire.[10] Subsequently, estrogen deficiency can affect a multitude of sexual functions, including desire, arousal, orgasm, and sensitivity.

Estrogen also plays an essential role in the vaginal microbiome. Vaginal epithelial cells secrete glycogen in response to estrogen stimulation. This is broken down into lactic acid in the presence of lactobacilli, preserving the vaginal pH within a range of 3.5-4.5.[11] This acidic environment and presence of lactobacilli limit the overgrowth of pathogenic organisms associated with urinary tract infections (UTIs).[12,13] There is an inverse correlation between the presence of lactobacilli and vaginal dryness.[14] Similar to genital tissues, estrogen receptors in the urethra and bladder also respond to estrogen, maintaining healthy, mature urothelium required for the apoptosis and shedding of infected cells.[12]

A decline in estrogen reduces glycogen and lactic acid, causing a higher pH and decreased defense against colonization by Enterobacteriaceae.[13] In addition, it results in a decline in the collagen content of the bladder trigone, thinning of the urethral mucosa, decreased pelvic floor muscular tone, and decreased sensitivity of α-adrenergic receptors at the bladder neck and urethral sphincter.[15]

The microarchitecture of the genitourinary tract is supported by such androgens as testosterones, which are converted to estrogens intracellularly. In postmenopausal women, sex hormone production is reduced, leaving dehydroepiandrosterone (DHEA) as the exclusive source of intracellular androgens and estrogens.[16] Additionally, with age, DHEA production decreases by up to 60%, contributing to an overall deficit in bioavailable estrogen.[17]

PRESENTATION

GSM, previously termed vulvovaginal atrophy/atrophic vaginitis, is characterized by genital symptoms (eg, dryness, burning, irritation); sexual symptoms (eg, lack of lubrication, discomfort or pain, decreased libido, difficulty with arousal and orgasm); and urinary symptoms (eg, frequency, urgency, dysuria, and recurrent UTIs). Risk factors for GSM include menopause; premature ovarian failure; surgically induced menopause (eg, bilateral oophorectomy); postpartum loss of placental estrogen; elevated prolactin secondary to lactation; absence of vaginal childbirth; decreased frequency and abstinence of sexual intercourse; history of radiation or chemotherapy; concomitant autoimmune disorders; smoking; alcohol abuse; and lack of exercise. GSM can also occur in hormone-depleted states, including breastfeeding, oral contraceptive use, adjuvant hormonal deprivation therapy for breast cancer treatment, gender-confirming hormone therapy, thyroid disorders, and pituitary tumors (**Figure 2**).[8] As estrogen and androgens decline, blood flow to the vagina and vulva also decreases, which can lead to impaired vaginal lubrication, vaginal burning, dryness, irritation, and an increased pH. Impaired lubrication can affect sexual function and cause pain with intercourse.

Approximately 50% of postmenopausal women experience GSM symptoms. Symptoms can occur several years after menopause and tend to increase with age.[18] Additionally, 15% of premenopausal women suffer from GSM.[8] Among women experiencing GSM symptoms, less than 10% utilize prescribed therapies[19]; this discrepancy between prevalence and treatment can be partly attributed to a lack of patient education and under-recognition of symptoms. To bridge this gap, clinicians must be cognizant of the varied symptomatology and effectiveness of treatments for GSM.

EVALUATION

The diagnosis of GSM is primarily a clinical diagnosis based upon history and physical examination.

History. A conversation centering around genitourinary symptoms and sexual function concerns should focus on several biopsychosocial aspects. **Due to the topic's sensitive nature, providers must be able to discuss the subject matter assuredly while making patients feel comfortable and safe. This is best done with the patient fully dressed.** A comprehensive history should then be performed, including a detailed characterization of the patient's symptoms; a focused sexual history, including sexual activity and behavior, which may include questions focused on decreased arousal, desire, and orgasm; and inquiry about what, if any, over-the-counter or at-home regimens they have tried to improve their symptoms. A targeted review of systems focusing on genitourinary symptoms, in addition to other systems and comorbidities, may rule out other possible organic

Systemic
Post-partum estrogen deficiency
Prolactinemia during breastfeeding
Hypoestrogenic states (eg, autoimmune disorders, thyroid conditions, pituitary tumors)

Pharmacological
Oral contraceptive use
Medroxyprogesterone
Danazol
Aromatase inhibtors
Selective estrogen receptor modulators (SERMs)
- Tamoxifen

Gonadotropin-releasing hormone agonist analogs
- Leuprolide
- Nafarelin

Gender affirming hormone therapy

Iatrogenic
Bilateral oophorectomy (i.e. surgical menopause)
Post-radiation ovarian failure

Figure 2. Causes of relative estrogen deficiency in premenopausal women.

Urinary
Frequency
Urgency
Post-void pain
Dysuria
Nocturia
Hematuria
Bacteriuria
Recurrent urinary tract infections
Prominence of urethral meatus

Genital
Dryness
Irritation / Burning / Itching of vagina and/or vulva
Leukorrhea
Erythema
Tissue fragility / fissures / petechiae
Decreased vaginal moisture / elasticity
Labial shrinkage / labial fusion
Loss of vaginal rugae
Clitoral hood retraction
Vaginal stenosis and shortening

Sexual
Decreased lubrication with sexual activity
Dyspareunia
Post-coital bleeding
Decreased arousal / orgasm / desire

Figure 3. Signs and symptoms of genitourinary syndrome of menopause.

causes, especially in premenopausal women (**Figure 2**). Symptom presentations vary widely and can occur with sexual activity or even randomly. **Figure 3** details the main GSM signs and symptoms that may be uncovered during the history and physical.[20] These should be used to guide the physical examination. Although GSM is a clinical diagnosis based on a thorough patient interview and detailed physical examination, some supportive tools can be helpful to providers. For example, rating scales of the most bothersome symptoms can be incredibly useful, especially when evaluating patient response to treatments. The Vaginal Health Index (VHI) and Vulvar Health Index (VVHI) are helpful tools to report findings from the pelvic examination in a standard fashion.[21] The VHI score is a clinical tool that evaluates 5 domains: vaginal elasticity, vaginal secretions, pH, epithelial mucous membrane, and vaginal hydration. This allows the clinician to assess severity on a numerical scale and track changes over time. Total score ranges from 5 to 25, with lower scores corresponding to greater severity of GSM (**Table 1**).

Physical examination. The pelvic examination is the foundation for evaluating women with genitourinary and sexual health concerns. During a focused genital examination, one should evaluate for:

- Symmetry and size of genital tissues
- Evidence of vaginal atrophy, stenosis, or dermatological changes to the vestibule
- Areas of provoked pain, particularly in the vestibule and pelvic floor muscles
- Visible lesions, such as urethral caruncles, suburethral masses, excoriations secondary to itching, or scars from prior surgical interventions
- Presence of pelvic organ prolapse
- Pelvic floor muscle tone and voluntary control
- Presence and character of vaginal discharge
- Presence or absence of vaginal rugae

A thorough examination should include an external visual assessment, musculoskeletal and sensory evaluation, and a bimanual evaluation if the patient tolerates it. Visual inspection of the external genitalia, perineum, perianal areas, and mons pubis should be completed to assess signs of dermatological changes, trauma, atrophy, or infection. To assess possible pudendal neuropathy, evaluation of the distribution of the cutaneous branches of the pudendal nerve (perianal skin and labia) with light touch and pinprick using a neurological examination pin (Neurotip) can be helpful in patients with symptoms of pelvic pain. Prior to an internal exam, the vestibule should be inspected visually to evaluate for hyperemia, erythema, and abnormalities of the periurethral or perivaginal glands. Additionally, in patients with urinary complaints or pelvic pain, an external pelvic exam observing the function of the pelvic floor muscles while doing voluntary (eg, Kegel) and involuntary (eg, cough) contraction and relaxation can help identify pelvic floor dysfunction. A cotton swab test palpating the vestibule at 12, 1, 3, 5, 7, 9, and 11 o'clock can be performed to assess for vestibulodynia. Using a mirror during the examination may help patients better understand their anatomy and identify areas of concern.

The internal muscle examination should start with a single finger examination palpating the superficial pelvic floor bilaterally to assess for pelvic floor spasm or tenderness to evaluate for pelvic floor dysfunction. At this time, a bimanual examination to assess for uterine or adnexal abnormalities can be performed. Before removing the provider's finger, the patient can be asked to Valsalva to assess for apical prolapse. A warmed, small Graves or Penderson speculum should be used to assess the cervix and vaginal secretions. The top blade

Table 1. Vaginal Health Index[24]

Parameters	1	2	3
pH	>6.5	5-6.5	<5
Moisture/consistency	No moisture	Minimal moisture/superficial layer of scanty mucus	Normal moisture/flocculant fluid
Rugosity	None	Minimal	Good
Elasticity	Poor	Fair	Excellent
Length of vagina	<4 cm	4-6 cm	>6 cm
Epithelial integrity	Petechiae present	Petechiae after scraping	Normal, not friable
Vascularity	Minimal	Fair	Good

should then be removed and the posterior blade inserted in the vagina, compressing the posterior vaginal wall gently to evaluate the anterior vaginal wall, urethra, and vaginal tissues of the anterior vaginal wall. The patient should be asked to do a Valsalva maneuver and cough to assess for stress urinary incontinence and pelvic organ prolapse. The blade should be removed and then placed on the anterior aspect of the vaginal wall to assess the posterior vaginal wall. The patient should again be asked to repeat the Valsalva maneuver to evaluate posterior vaginal wall prolapse.

Notable anatomical changes that occur during GSM include thinning or absent pubic hair, thinning and regression of the labia minora, retraction or narrowing of the introitus, involution of the hymenal carunculae, and increased prominence of the urethral meatus relative to the introitus.[1] A urethral caruncle, prolapse, or polyps may also be seen. Examination of the vaginal tissue may reveal loss of vaginal rugae, vaginal caliber, pallor of vaginal tissues indicating atrophy, and even petechiae or bleeding after the examination.

GSM may also be diagnosed by other objective findings, such as an elevated vaginal pH > 5 assessed by the use of litmus paper placed on the lateral vaginal wall until moistened. A premenopausal woman would be expected to have a pH of 4.5 or less. Additionally, the vaginal maturation index, an assessment of tissue maturation, in a vaginal cytology sample can be utilized. It is measured in percentages of the 3 cell types of varying maturity, including superficial, intermediate, and parabasal cells. One would expect to find a decrease in superficial cells (<5%) or an elevated proportion of parabasal cells. This is most often used for research purposes. **A blood test does not confirm or disprove the diagnosis of GSM, as no set level of sex steroids has been established below to indicate that most women will develop GSM-related symptoms.**

Clinicians can offer treatment to women who report symptoms consistent with GSM after telemedicine evaluation, with plans for subsequent office evaluation to assess improvement in symptomatology and physical examination.

MANAGEMENT

The primary goal for treatment is to alleviate symptoms, restore vaginal pH, and prevent recurrent UTIs. Narrow-banded pH paper can be used easily in the clinic during an exam to show progress in GSM therapy and vaginal estrogen supplementation. The goal pH is 4.5. Multimodal treatment may benefit women with vulvovaginal symptoms related to sexual activity. The mainstay of treatment is lifetime low-dose vaginal hormone therapy, which can be administered in the form of vaginal creams, intravaginal tablets, or intravaginal rings. **Table 2** lists the different formulations and associated considerations with their route of administration. These have been shown to maintain tissue integrity, elasticity, and pliability. Other available treatments include nonhormonal vaginal lubricants for use as needed prior to intercourse, long-acting vaginal moisturizers for symptom control, laser therapy, and pelvic floor physical therapy. Although these options can offer significant symptom relief, the gold standard treatment is vaginal estrogen therapy

Nonprescription treatments. Topical Lubricants and Moisturizers: Women who have vulvovaginal symptoms often use a variety of over-the-counter lubricants to relieve vulvovaginal

Table 2. Summary of Available Vaginal Hormone Therapy Preparations

Brand name	Preparation	Dosing	Administration	Considerations
Estring	Estradiol vaginal ring	2 mg estradiol reservoir	Releases 7.5 µg/d for 90 d	<2% risk of vaginal ulcers[14]
Vagifem, Yuvafem, Imvexxy	Estradiol vaginal suppository	4, 10 µg estradiol	1 vaginal tablet daily for 2 wk followed by 1 tablet twice weekly	
Estrace	Estradiol vaginal cream	0.1 mg estradiol per g cream	2-4 g daily for 1-2 wk followed by 1-2 g daily for 1-2 wk Maintenance: 1 g 1-3 times weekly A pea size amount on urethra is insufficient; may be used in addition to maintenance 1 g dosing	No randomized controlled trials in the past 10 y[14]
Premarin	Estradiol vaginal cream	0.625 mg conjugated equine estrogens per g cream	Cyclically: 0.5-2 g daily for 21 d/mo Continuously: 0.5 g twice weekly	There was a small and transient increase in circulating estradiol seen[14]
Intrarosa	DHEA vaginal suppository	6.5 mg prasterone	1 insert daily at bedtime using the applicator	Contraindicated in women with undiagnosed abnormal vaginal/uterine bleeding

Abbreviation: DHEA, dehydroepiandrosterone.

symptoms (water-, silicone-, and oil-based products). **Although they offer symptomatic relief, they do not improve hormonal imbalance and can treat mild-to-moderate symptoms. Many women who opt out of vaginal estrogen therapy may find symptomatic relief using over-the-counter lubricants or moisturizers**.

Lubricants are used as needed, typically prior to intercourse.[22] They effectively relieve discomfort experienced during intercourse and are easily obtained over the counter. They work by relieving friction and, therefore, trauma to the tissues. Choosing a product physiologically similar to the vaginal environment in terms of vaginal osmolality and pH is recommended.[23] Water-based lubricants can be beneficial for women who are sensitive or prone to yeast infections as they are typically the least irritating. However, they evaporate quickly, require reapplication, and may exacerbate symptoms of chafing in many women. Silicone-based lubricants are longer-lasting, but attention should be paid to the main ingredients in the lubricant itself because there are often ambiguous safety concerns associated with components, such as parabens and glycol. Glycol and its metabolite glycerin, broken down into sugar, can predispose to candidal growth. Antibacterial agents in the lubricants used to extend shelf life may also have unwanted effects on the vaginal biome. Additionally, caution should be used with oil-based lubricants because use with condoms can lead to breakage. Unprocessed virgin olive oil or coconut oil free of any additives or preservatives can be used as lubricants. However, these and other oil-based lubricants can result in changes in the vaginal pH making some individuals more prone to yeast infections.

Moisturizers are typically used regularly (irrespective of sexual activity) to ameliorate the symptoms of vaginal dryness as they are easily accessible over the counter. They act as an emollient by locking in moisture and adhering to the vaginal epithelium. They typically have a more extended period of effectiveness than vaginal lubricants and closely mimic naturally occurring vaginal secretions. Often, women who are not offered treatment with vaginal estrogen supplementation will use vaginal moisturizers in lieu of topical estrogen placement to the vagina. However, the greatest effect is seen in women who use vaginal moisturizers as an adjunctive treatment to vaginal estrogen supplementation. It is important to be aware of the ingredients in the vaginal moisturizer, as these can also prove irritating to the vaginal epithelium. Hyaluronic acid is considered beneficial as an active ingredient. Glycol, alcohol, and parabens are common irritants that should be avoided. Petroleum jelly can be beneficial for vulvar irritation but should not be placed within the vagina. Additionally, some can have bactericidal properties that disrupt the vaginal microbiome.[22]

Pelvic Floor Physical Therapy: To date, few studies have described the mechanism of action of pelvic floor muscle training (PFMT) to improve the signs and symptoms of GSM in postmenopausal women. One small study of 29 women demonstrated that PFMT significantly improved vaginal blood flow parameters, increased pelvic floor muscle strength, and improved vaginal atrophy index.[24] PFMT is ideally suited for women with high-tone pelvic floor dysfunction that arises from painful sexual activity due to GSM.

Vaginal Dilators and Vibrators: Consistent use of vaginal dilators can increase vaginal elasticity, decreasing dyspareunia with deep penetration. Passive dilation with vaginal vibrators should be considered in women with painful vaginismus. The vibrators stimulate blood flow and preserve vaginal function in women with or without a sexual partner.

Prescription treatments. Estrogen: Estrogen has a direct action on urogenital cells and can improve both genital and urological symptoms related to GSM. Multiple systematic reviews of vaginal estrogen therapy in patients with GSM have found significant improvements in symptoms of vaginal dryness, dyspareunia, and urogenital symptoms, as well as anatomical improvements in vaginal tissues, increased *Lactobacillus*, and reduction of vaginal pH.[25] Hormonal therapy can reduce autonomic and sensory vaginal innervation density, which may, in part, contribute to relief from vaginal discomfort. Topical therapy causes more dramatic reductions in innervation than systemic hormone replacement therapy.[26] Systemic hormone replacement therapy with oral or transdermal options is not recommended and is often insufficient for GSM treatment. Currently available vaginal estradiol preparations, dosing, and treatment regimens are noted in Table 2. In a 2014 Cochrane review, no difference in efficacy was noted based on the topical hormonal preparation utilized.[27] When determining preparation type, convenience, cost, and ease of use must be considered. It is important to note that when using cream-based preparations, a full 1-g dose is required for adequate treatment of the vaginal tissue,[28] and some patients may find this administration difficult or "messy" and note increased vaginal discharge with use. Also, notably, patients may experience a burning sensation and breast pain during the first few weeks of application, which should resolve with time. Additionally, initial treatment with vaginal estrogen may also uncover vaginal yeast infections, and therapy should be continued while the yeast infection is treated. Patients undergoing counseling should also be aware that symptom relief or reduction of recurrent UTIs can take up to 12 weeks, and all patients should be assessed for compliance and improvement at this time. Anatomical changes on examination correlate with symptom improvement.[29] Hence, women without symptom relief, despite anatomical improvement, should be considered for alternative diagnoses causing symptomatology, like pelvic floor dysfunction such as vestibulodynia, lichen sclerosus, pudendal neuralgia, and interstitial cystitis. The assessment of compliance, symptom relief, and anatomical improvement should be evaluated consistently to assure long-term treatment compliance as GSM is a chronic and progressive condition.

Recurrent UTI Prevention: **Vaginal estrogen therapy has been proven effective for preventing recurrent UTI through multiple randomized clinical trials.** Specifically, the use of local estrogen acidifies the vagina, allowing for population with lactobacilli and prevention of uropathogenic bacterial colonization.[30] Postmenopausal women receiving vaginal estradiol have been shown to experience a greater abundance of lactobacilli and lower vaginal pH after 12 weeks of use.[31] The AUA guidelines encourage treatment with vaginal estrogen therapies for peri- and postmenopausal women with recurrent UTIs. In a randomized, double-blinded, placebo-controlled trial of a topical intravaginal estriol cream in postmenopausal women, the experimental group noted a significant reduction in the incidence of UTIs, increased colonization of lactobacilli, decreased vaginal pH, and decreased colonization by Enterobacteriaceae.[30] These results were also

seen in another multicenter randomized, open parallel-group study using an estradiol vaginal ring.[32]

Lower Urinary Tract Symptoms: While less robust, data support that there may be an improvement in urinary symptoms, specifically, nocturia, urinary frequency, and urinary urgency incontinence, with vaginal estrogen therapy.[33] Vaginal estrogen was shown to improve urinary incontinence with an RR of 0.74 (95% CI, 0.64-0.86) in a 2012 Cochrane review.[34] This has been corroborated in subsequent, open-label, prospective cohort studies with significant improvements in the Overactive Bladder Symptom Score after a 12-week treatment period.[35]

Safety: **The use of vaginal estrogen therapy causes minimal systemic absorption, and studies have identified serum estrogen levels that remain in the postmenopausal range after treatment with topical/local therapies.[36]** Adverse events with vaginal estrogen are minimal, including headache (4%-13%), vulvovaginal pruritus (8%), genital candidiasis (6% to 8%), leukorrhea (7%), vaginitis (5%), vaginal discomfort (≤5%), vaginal pain (≤5%), bacterial vaginosis (4%; asymptomatic), vaginal hemorrhage (4%), and UTI (2%).[28] Treatment with vaginal estrogen therapy has not been found to be associated with the risk of development of endometrial carcinoma or increase in endometrial thickness in systematic reviews and long-duration observational studies. Similarly, in multiple systematic reviews and large observational studies, there was no identified risk of venous thromboembolism related to treatment with local estrogen therapy.[27,37] A 2019 meta-analysis also found no evidence of vaginal estrogen use correlated with risk of breast cancer development.[38] Contraindications to low-dose vaginal estrogen are few but include unexplained postmenopausal vaginal bleeding and caution in use with active, hormonally sensitive gynecologic cancers.[28]

Use in Breast Cancer Patients: A randomized controlled trial of 61 postmenopausal women with hormone receptor–positive early breast cancer and GSM symptoms receiving nonsteroidal aromatase inhibitors was conducted to assess the safety of topical estrogen in breast cancer. The experimental group was treated with ultralow-dose vaginal estrogen (0.005% vaginal gel, 50 µg of estradiol in 1-g gel). Levels of circulating follicle-stimulating hormone, luteinizing hormone, estriol, estradiol, and estrone remained unchanged after a 12-week treatment, improving Female Sexual Function Index scores, vaginal pH, vaginal maturation scores, and vaginal dryness symptoms.[39] The American College of Gynecology and the British Society for Sexual Medicine released a position statement in 2021, which reads, **"Women with a history of any type of cancer, including estrogen-receptor-positive cancer, should use vaginal estrogen if required and if beneficial; they should continue using this in the long term."[40]**

Ospemifene is a third-generation selective estrogen receptor modulator that can exert variable effects on estrogen receptors. It is formulated as a 60-mg tablet to be taken once daily and significantly improves the structure and pH levels of the vagina and reduces dyspareunia, overactive bladder symptoms, stress incontinence, and sexual function.[41] Symptoms improve after 4 weeks of use, and it has a minimal effect on the endometrium. It is the only oral option available for treatment of GSM and is best used for patients who need local therapy and are averse to or unable to place something in the vaginal canal or those who are not candidates for intravaginal treatments. Vulvoscopic photographs at 20 weeks identified improvements in anatomical changes due to GSM, including vaginal stenosis and rugae, meatal prominence, and vestibular changes.[42] Ospemifene is contraindicated in patients with active arterial thromboembolic disease, abnormal postmenopausal vaginal bleeding, and hormonally dependent neoplasias.[43] Side effects include hot flashes, vaginal candidiasis, discharge, bleeding, rash, and headaches.[42]

Vaginal DHEA: Prasterone is a plant-derived version of endogenous DHEA. It can be used interchangeably with vaginal estrogen but may have enhanced properties due to its androgen receptor activity. Intravaginal DHEA is an inactive steroid converted into biologically active estrogens and androgens.[16] It is the only U.S. Food and Drug Administration (FDA)–approved option for GSM with an androgen. Its dosing daily makes it easy for patients to remember and its palm oil base is quite moisturizing. It is an excellent first choice therapy for GSM; however, it is not always well covered by first-line insurance without a prior authorization. We recommend requesting a prior authorization if a patient is not responding to or does not want to try vaginal estrogen. Prasterone compared to placebo has been shown to be effective in the reduction of vaginal pruritis, dryness, burning, and symptoms of sexual dysfunction, particularly libido and dyspareunia. A recent retrospective cohort study found that vaginal prasterone reduced UTI recurrence in women over a period of 12 months; however, further randomized controlled trials are needed.[44] Additionally, improvements were noted in vaginal pH, vaginal maturation index, and tissue structure.[17] Emerging data show DHEA is useful to treat urinary urgency and may help alleviate GSM treatments when estradiol has not been effective enough.[45] Treatment with prasterone does not impact serum levels of estradiol, testosterone, or endometrial thickness.[17,46] Prasterone is inserted vaginally once nightly.

Laser Technologies Using Fractional CO_2 Laser or Erbium:YAG Laser: Laser, or light amplification by stimulated emission of radiation, leads to collagen synthesis, elastin production, vasodilation, and angiogenesis of vaginal tissues.[47] Limited investigations have found laser technologies to be effective in restoring vaginal architecture and improvement in symptoms related to GSM. In a 12-week, double-blind, randomized, sham-controlled trial, 58 women were recruited to receive fractional CO_2 laser or sham treatments. The experimental group noted significant improvements in dryness, dyspareunia, Female Sexual Function Index, itching, burning dysuria, and scores in the Urogenital Distress Inventory short form (UDI-6).[48] In breast cancer survivors, a retrospective study of 135 postmenopausal women (45 breast cancer survivors and 90 healthy women) noted that there was a significant improvement in both groups for objective (VHI and VVHI) and subjective outcomes (Visual Analogue Scale for dyspareunia and vaginal dryness, and a pain questionnaire). Improvement was progressive and long lasting, up to 12 months after the end of the treatment. There were no severe adverse events. The laser induced significant long-lasting improvement in GSM symptoms in breast cancer survivors, but the improvement was slower than in healthy women.[48]

The FDA has not yet approved the use of laser technologies to treat GSM, urinary incontinence, or sexual dysfunction. At this time, laser therapy should be used in an experimental setting.

Vaginal Testosterone: Small studies have shown some potential benefits with vaginal testosterone use, but intravaginal testosterone is not yet FDA approved due to the lack of high-quality data. In postmenopausal women with breast cancer on aromatase inhibitors, vaginal testosterone has been shown to improve vaginal maturation index, dyspareunia, and dryness symptoms without affecting serum estradiol levels.[49,50] Further high-quality studies are needed to evaluate the safety and efficacy of testosterone on GSM symptoms.

Duration of treatment and monitoring. Patients with symptoms of GSM should receive life-long treatment as GSM is a chronic and progressive condition. Providers should regularly evaluate patients for symptom resolution for nonhormonal treatment options and offer hormonal options when symptom resolution is not adequate or UTIs persist. For hormonal options, patients should be examined at 3 months after beginning treatment to assess for anatomical changes and patient compliance and to assess for any side effects or challenges with dosing. Alternative preparations can be offered to those who may have difficulty with specific routes of administration.

DID YOU KNOW?

- GSM is a chronic disease with pervasive and bothersome genitourinary symptoms that can worsen with age or arise years after the onset of menopause.
- Diagnosis of GSM is made with a thorough history and examination, ruling out alternative diagnoses and identifying hallmark physical examination findings.
- Several nonpharmacological and pharmacological treatments are available, but local vaginal hormone therapy is the most effective in reducing symptomatology and preventing recurrent UTIs.
- Local vaginal estradiol therapy is safe to use in women with a history of hormonally sensitive gynecologic cancers.

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Study Questions Volume 42 Lesson 14

1. Which of the following anatomical changes is most likely seen in GSM?
   a. Prominence of the urethral meatus
   b. Thin, hypopigmented, ivory-white, porcelain-like, and sclerotic plaques on the periclitoral hood
   c. White interlacing linear papules/plaque(s) on the labia minora
   d. Erythema of the vulva and vaginal mucosa, and vulvar edema

2. Which of the following is a risk associated with vaginal estradiol use?
   a. Venous thromboembolism
   b. Breast cancer
   c. Endometrial cancer
   d. Breast pain

3. Which of the following describes the change in the vaginal microflora during menopause?
   a. Low glycogen content of the thinned epithelium leads to an increase in lactic acid production by lactobacilli, resulting in a decrease in vaginal pH
   b. High glycogen content of the thinned epithelium leads to an increase in lactic acid production by lactobacilli, resulting in a decrease in vaginal pH
   c. Low glycogen content of the thinned epithelium leads to a reduction in lactic acid production by lactobacilli, resulting in an increase in vaginal pH
   d. High glycogen content of the thinned epithelium leads to a reduction in lactic acid production by lactobacilli, resulting in an increase in vaginal pH

4. Which of the following treatments for GSM has been shown to significantly reduce the recurrence of urinary tract infections for women in hypoestrogenic states?
   a. Vaginal laser therapy
   b. Vaginal estrogen preparations
   c. Systemic estrogen therapy
   d. Vaginal moisturizers

5. Which of the following acts as a selective estrogen receptor modulator functioning as an estrogen agonist improving sexual function and symptoms of dyspareunia?
   a. Vaginal testosterone
   b. Vaginal DHEA
   c. Ospemifene
   d. Intravaginal laser