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NAMS Position Statement

The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society

Abstract

Objective: To update and expand the 2013 position statement of The North American Menopause Society (NAMS) on the management of the genitourinary syndrome of menopause (GSM), of which symptomatic vulvovaginal atrophy (VVA) is a component.

Methods: A Panel of acknowledged experts in the field of genitourinary health reviewed the literature to evaluate new evidence on vaginal hormone therapies as well as on other management options available or in development for GSM. A search of PubMed was conducted identifying medical literature on VVA and GSM published since the 2013 position statement on the role of pharmacologic and nonpharmacologic treatments for VVA in postmenopausal women. The Panel revised and added recommendations on the basis of current evidence. The Panel's conclusions and recommendations were reviewed and approved by the NAMS Board of Trustees.

Results: Genitourinary syndrome of menopause affects approximately 27% to 84% of postmenopausal women and can significantly impair health, sexual function, and quality of life. Genitourinary syndrome of menopause is likely underdiagnosed and undertreated. In most cases, symptoms can be effectively managed. A number of over-the-counter and government-approved prescription therapies available in the United States and Canada demonstrate effectiveness, depending on the severity of symptoms. These include vaginal lubricants and moisturizers, vaginal estrogens and dehydroepiandrosterone (DHEA), systemic hormone therapy, and the estrogen agonist/antagonist ospemifene. Long-term studies on the endometrial safety of vaginal estrogen, vaginal DHEA, and ospemifene are lacking. There are insufficient placebo-controlled trials of energy-based therapies, including laser, to draw conclusions on efficacy and safety or to make treatment recommendations.

Conclusions: Clinicians can resolve many distressing genitourinary symptoms and improve sexual health and the quality of life of postmenopausal women by educating women about, diagnosing, and appropriately managing GSM. Choice of therapy depends on the severity of symptoms, the effectiveness and safety of treatments for the individual patient, and patient preference. Nonhormone therapies available without a prescription provide sufficient relief for most women with mild symptoms. Low-dose vaginal estrogens, vaginal DHEA, systemic estrogen therapy, and ospemifene are effective treatments for moderate to severe GSM. When low-dose vaginal estrogen or DHEA or ospemifene is administered, a progestogen is not indicated; however, endometrial safety has not been studied in clinical trials beyond 1 year. There are insufficient data at present to confirm the safety of vaginal estrogen or DHEA or ospemifene in women with breast cancer; management of GSM should consider the woman's needs and the recommendations of her oncologist.

Key Words: Dyspareunia – Genitourinary syndrome of menopause – Ospemifene – Vaginal dehydroepiandrosterone – Vaginal dryness – Vaginal estrogen – Vulvovaginal atrophy.

Genitourinary syndrome of menopause (GSM) describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract. Symptoms associated with GSM are highly prevalent, affecting approximately 27% to 84% of postmenopausal women.[1-4] In one report of more than

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900 women undergoing routine examinations, GSM was identified in 84% of women 6 years after menopause.[4] Principal symptoms included vaginal dryness, painful sex, burning, and dysuria. In contrast to vasomotor symptoms (VMS) that usually improve over time, GSM is generally progressive without effective therapy. Despite the high prevalence of GSM and lack of improvement without treatment, only a minority of affected women seek help or are offered treatment by their healthcare providers.[5,6]

In a survey of 1,858 US postmenopausal women with genitourinary symptoms, 50% had never used any therapy for this problem.[6] The reluctance of women as well as healthcare providers to initiate discussion of genitourinary symptoms and safety concerns about hormone therapies contribute to limited assessment and treatment of GSM.[7,8]

The genitourinary syndrome of menopause often has significant adverse effects on a woman's sexual health and quality of life (QOL).[9] Women who are not sexually active also experience bothersome symptoms of GSM, affecting activities of daily living.[10] In the *Vaginal Health: Insights, Views & Attitudes* (VIVA) online survey of 3,520 postmenopausal women in six countries, 45% reported experiencing vaginal symptoms, and 75% felt that their symptoms negatively affected their lives.[11] In 500 US women in the VIVA survey, of the 48% with vaginal discomfort, the most common symptoms were vaginal dryness and pain during intercourse.[5] Women in VIVA in the United States reported these adverse events (AEs) of vaginal discomfort:

- Negative effect on their lives (80%)
- Adverse effects on sexual intimacy (75%)
- Feeling less sexual (68%)
- Feeling old (36%)
- Negative consequences on marriage/relationship (33%)
- Negative effect on self-esteem (26%)
- Lower QOL (25%)

In a survey of 3,046 US women, *Real Women's Views of Treatment Options for Menopausal Vaginal Changes* (REVIVE),[7] women reported that their vulvovaginal atrophy (VVA) symptoms:

- Led to some loss of intimacy (85%)
- Detracted from enjoyment of sex (59%)
- Interfered with their relationship (47%)
- Negatively affected sleep (29%)
- Adversely affected general enjoyment of life (27%)

This updated position statement reviews the science of genitourinary aging and assesses the safety and effectiveness of available treatment options for postmenopausal women with GSM.

METHODS

A nine-member Panel composed of expert clinicians and researchers in the field of genitourinary health reviewed the literature to evaluate new evidence on management strategies, including vaginal estrogens, vaginal dehydroepiandrosterone (DHEA), ospemifene, and other management options available or in development for symptomatic GSM. A literature search was conducted using the terms ''genitourinary syndrome of menopause/GSM,'' ''vulvovaginal atrophy/VVA,'' ''atrophic vaginitis,'' ''dyspareunia,'' ''vaginal dryness,'' and ''vaginal lubrication.'' If evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established.

The Panel's completed draft of the updated Position Statement was submitted to the NAMS Board of Trustees for additional review, comments, and edits. The Board is composed of both clinicians and researchers from multiple specialties and disciplines. The Board approved the Position Statement with edits after final Panel review.

TERMINOLOGY

Genitourinary syndrome of menopause describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract, including the vagina, labia, urethra, and bladder.[12] This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness. Physical changes and signs are varied. Women may experience some or all of the symptoms and signs, which must be bothersome for a diagnosis of the syndrome. Other causes of similar signs and symptoms must be ruled out, including vulvovaginal dermatoses, infection, or cancer.

Vulvovaginal atrophy is a component of GSM.[13] Although VVA was the commonly used term in the past to describe the genitourinary changes of menopause, it has limitations. Vulvovaginal atrophy describes the appearance of the genital tissues but not the associated symptoms. It does not include urinary tract changes related to estrogen deficiency, and the term *atrophy* has negative associations for women. The term genitourinary syndrome of menopause was developed during a consensus conference of experts[12] and subsequently was accepted as the preferred term by many medical societies, including The North American Menopause Society and the American College of Obstetricians and Gynecologists.

ANATOMY AND PHYSIOLOGY

The genital and lower urinary tract share a common embryologic origin in women, with the urethra, bladder trigone, vulvar vestibule, and the upper vagina all derived from the same estrogen receptor (ER)-rich primitive urogenital sinus tissue.[14] The vulva is also derived from the urogenital sinus, but the epithelium of the labia majora is of ectodermal origin. The vagina is composed of an inner stratified squamous epithelium, a middle muscular layer, and an outer fibrous layer. In the presence of endogenous estrogen after puberty and before menopause, the lining of the vagina is characterized by a thickened, rugated surface that is well vascularized and lubricated in most women.

Estrogen is a dominant regulator of vaginal and lower urinary tract physiology. Estrogen receptor-α is present in

the vaginal tissues of both premenopausal and postmenopausal women, whereas ER-β appears to have no or low expression in postmenopause vaginal tissue. Estrogen therapy (ET) does not appear to affect the presence of ER-β.[15,16] Estrogen receptor density is highest in the vagina, with decreasing density across the external genitalia to the skin. The density of the androgen receptor is the reverse. There are low levels in the vagina and higher levels in the external genitalia. Progesterone receptors are found in the vagina and the transitional epithelium of the vulvovaginal junction.[17]

Estrogen receptors have also been found on autonomic and sensory neurons in the vagina and vulva. Estrogen therapy has been reported to decrease the density of sensory nociceptor neurons in the vagina. This function may serve to decrease the discomfort associated with GSM.[18] With respect to the lower urinary tract, estrogen and progesterone receptors have been identified in the urethra, bladder, and pelvic floor muscles.[14]

The changing physiology of the vaginal epithelium after menopause is not completely understood. On the basis of a cell-culture model that used vaginal-cervical epithelial cells, diminished estrogen levels and aging were found to be independent factors in decreasing vaginal-cervical paracellular permeability, a change potentially related to vaginal dryness.[19] With atrophy, wet-mount microscopy shows more than one white blood cell per epithelial cell and immature vaginal epithelial cells with relatively large nuclei (parabasal cells). Cytology shows an increase in parabasal and intermediate cells, and superficial cells decrease or are absent.[20] Immune cell populations seem to be similar or slightly decreased in number, with similar cytolytic capacity as before menopause.[21-23] However, some studies show differences in inflammatory markers in the vaginal fluid of postmenopausal women compared with premenopausal women.[24]

Hormone changes throughout the life cycle influence the vaginal microbiome from birth through postmenopause.[25,26] During the reproductive years, the presence of a microbial community dominated by *Lactobacillus* species is associated with a lower pH and lower risk for bacterial vaginosis (BV), sexually transmitted infections, UTIs, and HIV infection.[27-35]

After menopause, women are less likely to have a *Lactobacillus*-dominant vaginal bacterial community and less likely to have a low vaginal pH.[26.36,37] Although cultivation-based studies show a significantly lower quantity of vaginal *Lactobacillus* in postmenopausal women,[37] several newer sequencing studies observe that close to half have a high proportion of lactobacilli.[38,39] In one study, a higher proportion of *Lactobacillus* correlated inversely with examiner-reported dryness in postmenopausal women,[38] but in another study, there was no association between *Lactobacillus* dominance and the severity of patient-reported symptoms.[40]

The vaginal bacteria community of postmenopausal women has many similarities with that of reproductive-aged women with BV: high pH,[36] higher diversity,[41] and an abnormal Nugent score.[42] In many women with GSM, however, these abnormalities reflect a decline in lactobacilli rather than an increase in the prevalence of pathogens.[42,43] Treatment with systemic or topical estrogen is associated with an increase in detection of vaginal lactobacilli.[44,45] This suggests that for many postmenopausal women, the best approach to promoting a healthy vaginal microbial community is not antibiotic therapy (as though treating BV) but rather vaginal estrogen therapy.

PRESENTATION

The diagnosis of GSM requires the presence of both characteristic examination findings and bothersome symptoms. The most commonly reported symptoms include irritation of the vulva, inadequate vaginal lubrication, burning, dysuria, dyspareunia, and vaginal discharge. Symptoms adversely affecting sexual function are often the most distressing.[12,46,47]

Signs of GSM include labial atrophy, vaginal dryness, introital stenosis, clitoral atrophy, and phimosis of the prepuce. Severe GSM can result in a vaginal surface that is friable and hypopigmented, with petechiae, ulcerations, and tears, as well as urethral findings such as caruncles, prolapse, or polyps. Bleeding may occur from minimal trauma, such as speculum insertion. Genitourinary atrophic changes increase the likelihood of trauma, pain, recurrent UTIs, bleeding with or after sex, and absence of sexual activity.[20,47]

The genitourinary syndrome of menopause most commonly develops in the setting of hypoestrogenism associated with natural menopause. Hypoestrogenic states also may occur in the setting of primary ovarian insufficiency (POI), surgical menopause (bilateral oophorectomy with or without hysterectomy), hypothalamic amenorrhea, the postpartum state and breastfeeding, use of gonadotropin-releasing hormone agonists or aromatase inhibitors (AIs), and cancer treatments such as surgery, pelvic radiation therapy, or chemotherapy that render ovaries inactive, either temporarily or permanently.

Several studies suggest that early estrogen deficiency caused by premature menopause or POI is associated with more severe sexual dysfunction compared with age-matched controls.[48,49] Younger women with vaginal atrophy and dyspareunia may be especially distressed by changes in sexual function.

Women with surgical menopause often present with a more severe GSM symptom profile than do women with natural menopause, likely because of the concomitant, abrupt, and persistent 50% decline in circulating androgen levels that occurs in addition to the loss of estradiol.[50,51] Genitourinary syndrome of menopause that develops in the setting of chemotherapy-induced menopause has been associated in some studies with greater sexual dysfunction and distress[52-54] and with poorer QOL outcomes.[55-58] Younger women with GSM related to induced menopause from cancer treatment may be especially distressed by changes in sexual function.[52,55] The stress, fatigue, and mood changes that accompany a cancer diagnosis and its treatment also contribute to sexual problems.

Aromatase inhibitors reduce breast cancer recurrence by blocking conversion of androgens to estrogens and

inducing a profound estrogen-deficiency state. The magnitude and duration of estrogen deficiency induced by AIs result in the development of severe GSM in most survivors, particularly given that extended duration therapy is now typical.[59-61] Compared with tamoxifen, AIs result in a greater incidence of vaginal dryness and dyspareunia, causing a large percentage of AI users to express dissatisfaction with their sex lives.[60,62-64]

EVALUATION AND DIAGNOSIS

The evaluation of GSM includes a history and pelvic examination. A medical history may identify contributing factors, alternative etiologies, and effective therapeutic interventions. The pelvic examination should identify signs consistent with GSM and eliminate other pathologic conditions that may cause similar symptoms.

History

Because women may not spontaneously report symptoms of GSM and related sexual concerns, providers should inquire about symptoms in all perimenopausal and postmenopausal women as part of a routine review of systems. The EMPOWER survey queried 1,858 menopausal US women with symptoms suggestive of GSM and found that in women who had never used any treatment, almost three-quarters had never discussed their symptoms with a healthcare provider.[6] The main reason for this reticence was the assumption that GSM was simply a natural part of aging with which women needed to live. Results of the *Women's Voices in the Menopause* survey revealed that in more than 1,000 US respondents, one-third of those with vaginal discomfort had not spoken with anyone regarding their condition and one-third preferred that discussion regarding vaginal discomfort be initiated by their healthcare providers.[65]

These survey results underscore the importance of clinicians being proactive in asking menopausal women whether symptoms suggestive of GSM are present. The goal of the history is to determine whether symptoms of GSM are present, whether they are bothersome, and how they affect the woman's sexual health and QOL. In the absence of symptoms, atrophic changes noted on examination do not necessarily require treatment, although women should be informed that these changes may worsen over time without proactive management.

Symptoms similar to GSM result from many other conditions. The differential diagnosis includes allergic or inflammatory conditions (eg, lichen sclerosus, erosive lichen planus, desquamative inflammatory vaginitis, contact dermatitis, and cicatricial pemphigoid), vulvovaginal candidiasis and other infections, trauma, foreign bodies, malignancy, vulvodynia, vestibulodynia, chronic pelvic pain, provoked pelvic floor hypertonia (previously known as vaginismus), and other medical conditions (eg, diabetes, lupus erythematosus) or psychological disorders. An alternate etiology is more likely in women with chronic or recurrent vulvovaginal symptoms that were present before menopause.

Documentation of GSM should include a description of symptoms, including time of onset, duration, level of associated distress, and effect on QOL. A sexual history that includes partner relationship(s), current level and types of sexual activity, and the effect of GSM symptoms on sex life and partner relationships is useful in determining management strategies. Previous interventions should be discussed, including their efficacy and adverse effects.

For a woman with a history of cancer, additional information is relevant, including cancer site, age at diagnosis, hormone receptor status, treatments (past, current), and type of menopause (spontaneous or induced). Cancer treatments, especially surgery and radiation therapy, can damage the vaginal epithelium, the vascular supply, and the anatomy of the vaginal canal. Some treated women experience a narrowed or foreshortened vagina. Genitourinary changes associated with cancer treatments can produce pain with pelvic examinations, dyspareunia, recurrent UTIs, and an increased risk of vaginal infections.[52,66]

Physical examination

The pelvic examination helps to exclude other vulvovaginal conditions that can cause similar symptoms. As GSM progresses, examination of the external genitalia often reveals reduced mons pubis and labia majora bulk, reduced labia minora tissue and pigmentation, and prominence (telescoping) and erythema of the urethral meatus. Urethral caruncle, a benign outgrowth of inflammatory tissue arising from the posterior urethral meatus, is common in postmenopausal women and likely related to hypoestrogenism. The clitoris may recede and in some cases become completely flush with the surrounding tissue. The vestibular tissue may become pale.

If the introitus is noted to be narrow, use of a narrow pediatric vaginal speculum with lubricant is appropriate. The vaginal mucosa may appear smooth (loss of rugation), shiny, and dry. Minimal blunt trauma from the speculum may result in petechiae (reflecting mucosal thinning) or bleeding (friability). With progression of GSM, attenuation of the vaginal fornices may be apparent, and the cervix may appear flush with the vaginal apex.

With atrophic vaginitis, brown or yellow (sometimes malodorous) discharge may be present. With severe GSM, there may be such shortening of the vaginal vault and narrowing of the introitus that speculum insertion and visual inspection of the vaginal vault as well as cervix may not be possible.

Although the vaginal maturation index (VMI) and vaginal pH are routinely assessed in clinical trials, they are not essential to make a diagnosis of GSM in clinical practice. With GSM, vaginal pH is typically greater than 5.0. Wet-mount microscopy shows more than one white blood cell per epithelial cell, immature vaginal epithelial cells with relatively large nuclei (parabasal cells), and reduced or absent lactobacilli. Repopulation with diverse flora can occur,

including enteric organisms commonly associated with UTIs.[67] The appearance of the wet mount in severe GSM may be difficult to distinguish from that of desquamative inflammatory vaginitis or vaginal erosive lichen planus.[68] A culture or vulvovaginal biopsy should be considered if there are atypical findings or if the vulvovaginal symptoms fail to resolve after a trial of vaginal estrogens or DHEA.

A woman's symptoms do not always correlate with physical findings. For example, a woman who is not sexually active may have few symptoms, despite signs of advanced genitourinary atrophy on examination. In contrast, a woman with an active sex life may complain of dryness and discomfort with sex, whereas the pelvic examination suggests only mild atrophy. Of note, women who are not sexually active also may be bothered by symptoms related to GSM, including discomfort with exercise or dysuria and benefit from treatment. Thus, both history and examination are essential to making a correct diagnosis.

TREATMENT

The primary goal of treating GSM is to alleviate symptoms. For the woman with GSM, after excluding other causes of her symptoms, treatment can be approached in a stepwise fashion based on symptom severity. First-line therapies for less-severe symptoms include nonhormone vulvar and vaginal lubricants with sexual activity and long-acting vaginal moisturizers used regularly (several times/wk). Although not supported by clinical trials, regular, gentle vaginal stretching exercises (eg, pain-free insertion of a finger or dilator) or sexual activity may reduce GSM symptoms. Prescription therapies include low-dose vaginal estrogens, vaginal DHEA inserts, and oral ospemifene. For women with moderate to severe dyspareunia associated with GSM with concurrent VMS, transdermal and oral HT are effective options. Symptom reduction may take 1 to 3 months, and continued therapy is generally required because symptoms are likely to recur on cessation of treatment. Outcomes data on the symptom recurrence rate are lacking.

Some women may already have vaginal narrowing or provoked pelvic floor hypertonia limiting vaginal penetration. Gentle stretching of the vagina with the use of lubricated vaginal dilators of graduated sizes (or an expandable dilator) can play an important role in restoring and maintaining vaginal function for penetration. Reinitiating regular sexual activity once vaginal penetration is again comfortable, if desired, may help to maintain vaginal pliability. Many women with this condition benefit from referral for pelvic floor physical therapy (PFPT).[69,70] Starting pharmacologic treatment to restore tissue integrity before initiating vaginal dilatation and/or PFPT may facilitate progress.

Nonprescription therapies

Lubricants and moisturizers

First-line therapies to alleviate symptoms of GSM include over-the-counter (OTC) nonhormone vaginal lubricants and moisturizers, a number of which are available (Table 1), but few clinical studies have been conducted on the efficacy of these products.

TABLE 1. *Examples of nonhormone therapeutic options for dyspareunia secondary to GSM*

Lubricants	Moisturizers
Water based	Replens
Astroglide Liquid	Me Again
Astroglide Gel Liquid	Feminease
Astroglide	K-Y SILK-E
Good Clean Love	Luvena
Just Like Me	Revaree
K-Y Jelly	Silken Secret
Pre-Seed	Hyalo-gyn
Slippery Stuff	
Liquid Silk	
YES WB	
SYLK	
Sliquid	
Silicone based	
Astroglide X	
ID Millennium	
K-Y Intrigue	
Pink	
Pjur Eros	
Uberlube	
Sliquid	
Oil based	
Elégance Women's Lubricants	
Olive oil	
YES OB	

A vaginal moisturizer is a bioadhesive product used regularly, most often two to three times a week, irrespective of the timing of sexual activity. The goal of use is to reduce daily symptoms of GSM as well as to facilitate comfortable sexual activity. Data suggesting improvement in genitourinary symptoms with nonhormone treatments are sparse, and to date, there are no adequately powered, randomized, double-blind, placebo controlled studies directly comparing low-dose vaginal estrogen therapies or vaginal DHEA with commonly used nonhormone treatments. One randomized, controlled, but short-term study demonstrated effectiveness of a pH-balanced gel compared with placebo in women treated for breast cancer. Mild irritation with administration was noted.[71] In a randomized, controlled trial (RCT; N = 302), a significant improvement in most bothersome symptom severity was seen in all three arms: the vaginal estradiol tablet (plus placebo gel), vaginal moisturizer (plus placebo tablet), and dual placebo arms.[72] In that trial, the placebo gel likely had lubricating properties.

Vaginal lubricants are used by both (or all) partners to decrease discomfort caused by friction during sex. Regular use has also been associated with increase in pleasure and ease of orgasm.[73] In a review and meta-analysis, the effect of lubricant use on symptom severity could not be compared in studies because of heterogeneity. However, the meta-analysis of sexual function outcomes showed a small advantage to hormone-based therapies over lubricants in restoring sexual function.[74] One small crossover study in survivors of breast cancer demonstrated greater benefit with silicone-based lubricants compared with water based.[75]

In studies examining the safety of personal moisturizers and lubricants, investigators found that a number of water-based products are hyperosmolar.[76,77] This characteristic is associated with epithelial cellular toxicity and damage in cultures of epithelial cells and ectocervical explants. Near iso-osmolar and silicone-based lubricants did not have this effect. The World Health Organization recommends an osmolarity of less than 1,200 mOsm/kg.[78] One jelly and one moisturizer also were found to be toxic to lactobacilli. There are very few data on the health and safety effects of lubricants that contain flavors (sugar), warming properties, or solvents and preservatives such as propylene glycol and parabens. One study on the use of vaginal products in women aged 18 to 65 years reported a 2.2-fold risk of BV in women using petroleum jelly compared with controls and increased colonization with candida species with users of oils compared with nonusers.[79]

Because there are no published reports on the irritation potential of OTC vaginal lubricants and moisturizers, women can test these on a small patch of skin for 24 hours before using them intravaginally. If the product they test successfully on the skin still causes irritation in the vagina, a woman can switch to an iso-osmolar, propylene glycol-free, or silicone-based product (Table 1). It is noteworthy that oil-based lubricants can erode condoms; however, most brands of water-based and silicone-based lubricants are latex safe and condom compatible.

Hyaluronic acid

Hyaluronic acid is a polymer found in cartilage and other soft tissues in the body that is added to many commercial skincare and wound-healing products because of its purported effect of drawing moisture to any area to which it is applied. In four small RCTs comparing hyaluronic acid to placebo or vaginal ET, the former was associated with a similar decrease in severity of dryness and dyspareunia.[80-83] To date, there is no evidence that products with hyaluronic acid have a greater benefit than nonhyaluronic acid lubricants or moisturizers.

Herbal products

Herbal products appear ineffective for GSM. The Herbal Alternatives for Menopause study, a double-blind RCT in 351 women, identified no change in vaginal dryness, vaginal cytology, follicle-stimulating hormone or estradiol levels following treatment for 1 year with black cohosh, a multibotanical supplement, or soy.[84]

Prescription therapies

For women with persistent GSM symptoms after nonhormone interventions, prescription therapies may provide greater benefit.

Vaginal estrogen

Estrogen delivered vaginally provides sufficient estrogen to relieve genitourinary symptoms with minimal absorption and is preferred over systemic therapy when only genitourinary symptoms are present.[85,86] When systemic HT is needed to treat other menopause symptoms, a woman also will generally derive satisfactory resolution of her genitourinary symptoms, although additional low-dose vaginal estrogen may be added if needed.

Efficacy studies of low-dose vaginal ET use both subjective and objective outcome measures. Subjective effects are often assessed using patient-reported outcome measures that include improvements in symptoms such as dyspareunia, vaginal dryness, and lower urinary tract symptoms and clinician-reported outcomes such as the appearance of the vulvovaginal tissues. Objective outcomes include decreases in vaginal pH, increases in the number of vaginal lactobacilli, and favorable shifts in the vaginal and/or urethral cytology (greater numbers and percentages of superficial cells and fewer numbers and percentages of parabasal cells).[87,88]

Efficacy

Low-dose vaginal ET is available in several forms, including cream (estradiol, estrone, and conjugated estrogens), a slow-release estradiol intravaginal ring, and an estradiol vaginal tablet and insert. Products vary in dosage and formulation (Table 2).[89-97] All approved products have proven efficacy in placebo-controlled RCTs.[86,98-111] In the United States, FDA requires efficacy data for treatment of a specific, most bothersome symptom, which includes dyspareunia, vaginal dryness, vaginal/vulvar irritation, vaginal soreness, dysuria, or bleeding associated with sexual activity. Dyspareunia and vaginal dryness are the most common indications for low-dose vaginal ET.

The comparative efficacy of the various forms of vaginal ET was evaluated in a 2016 Cochrane review comparing 19 trials.[112] This review concluded that all tested products alleviated symptoms of vaginal dryness and dyspareunia with similar efficacy. Comparative analyses of these trials are limited by variations in methods and outcome measures, small sample sizes, lack of blinding, and substantial heterogeneity of results. Some trials of the same estrogen preparation used different doses or dosing schedules. Some trials included preparations not approved for use in the United States or in Canada.

Vaginal estrogen and urinary symptoms

In a 2014 systematic review that included 44 RCTs, assessment of urinary symptoms was variable, leading to a lower quality of evidence for the effectiveness of vaginal estrogen for urinary symptoms compared with vulvovaginal symptoms.[113] This review reported moderate-quality evidence supporting vaginal ET in the treatment of urge incontinence and recurrent UTIs and low or very-low quality evidence supporting the use of vaginal ET for improvement of dysuria, urinary frequency and urgency, nocturia, and stress incontinence.

A Cochrane review of vaginal ET for urinary incontinence determined that vaginal ET improves incontinence (relative risk [RR], 0.74; 95% confidence interval [CI], 0.64-0.86) but

TABLE 2. *Government-approved therapies for genitourinary syndrome of menopause in the United States and Canada*

Type	Composition	Product name	Commonly used starting dose	Commonly used maintenance dose	Typical serum estradiol level (pg/mL)
Vaginal creams	17B-estradiol 0.01% (0.1 mg active ingredient/g)	Estrace vaginal cream[a]	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Conjugated estrogens (0.625 mg active ingredient/g)	Premarin vaginal cream	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Estrone 0.1% (1 mg active ingredient/g)	Estragyn vaginal cream[b]		0.5-4 g/d, intended for short-term use; progestogen recommended	Variable
Vaginal inserts	17B estradiol inserts	Imvexxy[a]	4 or 10 μg/d for 2 wk	1 insert twice/wk	3.6 (4 μg) 4.6 (10 μg)
	Estradiol hemihydrate tablets	Vagifem Yuvafem	10 μg/d for 2 wk	1 tablet twice/wk	5.5
	Prasterone (DHEA) inserts	Intrarosa	6.5 mg/d	1 insert/d	5
Vaginal ring	17β estradiol	Estring	2 mg ring releases approx 7.5 μg/d	Replace ring every 90 days	8
Oral tablet	Ospemifene	Osphena[a]	60 mg/d	1 tablet by mouth/d	N/A

DHEA, dehydroepiandrosterone.
Products not marked are available in both the United States and Canada.
[a]Available in the United States but not Canada.
[b]Available in Canada but not the United States.
Estrace[89]; Premarin[90]; Estragyn[91]; Imvexxy[92]; Vagifem[93]; Yuvafem[94]; Intrarosa[95]; Estring[96]; Osphena.[97]

that systemic estrogen alone and in combination with a progestogen worsens incontinence (RR, 1.32; 95% CI, 1.17-1.48 and RR, 1.11; 95% CI, 1.04-1.18, respectively).[114] Most of these studies were conducted for reasons other than urinary symptoms, failed to use validated tools to assess symptom severity and QOL, and showed statistically significant but not clinically relevant changes. For example, in the Heart and Estrogen/Progestin Replacement Study, women randomized to systemic oral estrogen plus progestogen therapy experienced 0.7 more leak episodes per week compared with 0.1 fewer episodes in the placebo group, but both changes met the a priori definition of ''no change in incontinence severity.''[115]

Few trials have been conducted comparing vaginal ET to other treatments for postmenopausal urinary tract symptoms. Two small trials comparing vaginal ET (conjugated equine estrogens) to pelvic floor muscle therapy (PFMT) for urinary incontinence favored PFMT over vaginal estrogen,[114] but a trial that compared estriol alone to estriol combined with pelvic floor rehabilitation favored combined therapy.[69] A comparison of the estradiol ring to oral oxybutynin showed similar efficacy for treatment of overactive bladder but with different AEs; oxybutynin resulted in more dry mouth, constipation, and blurry vision, whereas the estradiol ring resulted in more vaginal discharge.[116] When women present with both vulvovaginal and urinary symptoms, an initial trial of vaginal ET is prudent. If urinary symptoms are not sufficiently improved or resolved after 3 months of vaginal ET, the use of other evidence-based therapies for urinary tract symptoms is warranted.[117]

Recurrent UTI, defined as the occurrence of two culture-proven UTIs in 6 months or three culture-proven UTIs in 1 year, commonly affects postmenopausal women and is a component of GSM.[118] Treatment of GSM with vaginal ET (conjugated equine estrogen cream or low-dose estradiol vaginal ring) in a small RCT reduced the frequency of recurrent UTIs in postmenopausal women.[119] An RCT of vaginal estriol cream (0.5 mg) in postmenopausal women with recurrent UTIs led to a significant decrease in number of UTI episodes per year (0.5 compared with 5.9).[120] In another randomized trial, the low-dose estradiol ring was found to prolong the time to next recurrence in postmenopausal women with recurrent UTIs and to decrease the number of recurrences per year (RR, 0.64).[121]

Women who use a vaginal pessary for treatment of uterovaginal prolapse are often advised to use vaginal ET to facilitate pessary use and to limit potential complications such as vaginal discharge and vaginal wall erosions. Prospective data are lacking, but observational studies show lower discontinuation rates and less vaginal discharge when pessary users are treated with vaginal ET.[122]

Safety

Low-dose vaginal ET has a more favorable risk profile than systemic ET because estrogen doses are significantly lower (Table 2).[89-97] Estrogens are systemically absorbed from the vagina in a dose-dependent manner, and in general, serum estrogen levels reported with use of low-dose vaginal ET remain within the postmenopause range.[123] A review of systemic estradiol measurements reported baseline levels in normal, untreated postmenopausal women of 3.1 pg/mL to 4.9 pg/mL using highly sensitive assays such as liquid or gas chromatography/mass spectroscopy and levels that were undetectable to 10.5 pg/mL using the less-sensitive radioimmunoassay.[85] Serum estradiol levels with use of the low-dose vaginal ring (releasing approximately 7.5 μg/d) ranged from 5 pg/mL to 10 pg/mL.[107,124,125] Serum estradiol levels with use of the 10-μg vaginal tablet ranged from 3 pg/mL

to 11 pg/mL.[126-128] Serum estradiol levels after daily use of the 4-μg and 10-μg vaginal insert for 14 days were 3.6 pg/mL and 4.6 pg/mL, respectively, which was not statistically different from placebo (4.3 pg/mL). After twice weekly use for 84 days, there was no difference in serum estradiol levels compared with baseline or placebo.

Serum estradiol levels associated with use of vaginal estradiol cream are derived from older data using higher doses and less-sensitive assays that lack accuracy for lower estrogen levels.[129] Use of estradiol cream 0.5 mg (500 μg) daily for 3 weeks resulted in no change in serum estradiol levels.[130] In contrast, another study showed that daily use of estradiol cream 0.2 mg (200 μg) daily resulted in serum estradiol levels that rose from a baseline of 16.6 pg/mL to 37.2 pg/mL after 3 weeks of use.[131] Use of 0.3 mg conjugated estrogens (CE) cream 3 times weekly for 6 months produced no change in serum estradiol or estrone levels.[132] Of note, CE contains a significant number of compounds, some estrogenic and some antiestrogenic, so serum estradiol and estrone levels after use of CE may not reflect actual estrogenic activity. Vaginal bleeding, breast pain, and nausea have been reported in some trials of vaginal estrogen cream. These symptoms are dose related and suggest that the dose was large enough to result in significant systemic absorption.

Adverse events associated with use of vaginal ET include vaginal discharge, vulvovaginal candidiasis, vaginal bleeding, and breast pain. Differing AE profiles may reflect variations in product formulation and dose.[133,134]

The risks typically associated with systemic ET, including breast and endometrial cancer and cardiovascular disease (CVD), have been evaluated in several trials of vaginal ET. Clinical trial data beyond 1 year are lacking, however, because the longest duration of any RCT was 52 weeks.[135] Endometrial safety was assessed in two systematic reviews that included RCTs and large observational studies.[136,137] In 20 RCTs, 2,983 women were exposed to vaginal ET for up to 1 year. There was one case of endometrial cancer (0.03%) and 12 cases of endometrial hyperplasia (0.4%). The cases were sporadic and their incidence similar to the baseline rate in the general population. A 2016 Cochrane review of RCTs reported no significant differences among vaginal estrogen formulations in terms of endometrial thickness or hyperplasia or the proportion of women with AEs.[112] Large observational studies evaluating longer exposures to vaginal ET identified no increase in endometrial cancer. In the Women's Health Initiative-Observational Study, the rate of endometrial cancer was not statistically different in users of vaginal ET compared with nonusers (1.3 vs 1 case per 1,000 woman-years, respectively). Thus, occurrence of endometrial cancer and hyperplasia with low-dose vaginal ET use is rare and consistent with rates in the general population.

The risk of venous thromboembolism (VTE) was not increased with vaginal ET use in a 2016 Cochrane review, a 2020 systematic review of RCTs, and three large observational studies.[112,135,137-139] Of note, systematic, prospective data for women at high risk of VTE are lacking.

A prospective cohort study of approximately 45,000 women in the Women's Health Initiative Observational Study examined risks associated with vaginal ET use. Outcomes assessed included coronary heart disease (CHD), invasive breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, and death. The findings were very reassuring, with no increased risk of CVD or cancer in postmenopausal women using vaginal estrogens.[135] Another prospective cohort study of approximately 54,000 postmenopausal women in the Nurses' Health Study also was very reassuring regarding the safety of vaginal ET. There was no increase in health outcomes assessed with vaginal ET use, including CVD (total myocardial infarction, stroke, pulmonary embolism/VTE), hip fracture, and cancer (total invasive, breast, endometrial, ovarian, and colorectal).[138] In a 2019 meta-analysis, investigators used individual participant data from 58 observational studies reported between 1992 and 2018 to assess associations between hormone therapy and breast cancer.[140] Use of vaginal estrogen was not found to be associated with risk of breast cancer.

Potential contraindications to vaginal estrogen therapy

Although most women with GSM are candidates for low-dose vaginal ET, use is contraindicated in women with undiagnosed vaginal/uterine bleeding and should be used with caution in women with estrogen-dependent neoplasia. Management of GSM in women with nonhormone-dependent cancers is similar to that for women without a cancer history. Low-dose vaginal ET has not been studied in women at increased risk of thrombosis, but may be used with caution given minimal systemic absorption, the absence of a hepatic first-pass effect, and minimal, if any, effect on prothrombotic factors. Of note, in large observational studies, neither vaginal estrogen nor systemic transdermal formulations of ET have been associated with an increased risk of VTE.[139]

Although circulating estrogen concentrations generally remain within the menopause range with low-dose vaginal ET, the package insert for these products includes the same boxed warning regarding risk of endometrial cancer, breast cancer, cardiovascular disorders, and probable dementia that accompanies systemic HT products. Women must be educated about the differences between low-dose vaginal and systemic ET and be prepared for the boxed warning, or else they may not initiate prescribed treatment.

Vaginal estrogen products

Several low-dose vaginal estrogen products have been government approved for use in the United States and Canada, including cream (estradiol, estrone, and conjugated estrogens), a slow-release estradiol intravaginal ring, and an estradiol vaginal tablet and insert (Table 2).[89-97] Vaginal estrogen creams are generally used two to three times weekly, estradiol tablets and inserts used twice weekly, and the estradiol ring changed every 3 months. Estrogen creams, tablets and inserts are used daily for 2 weeks at the initiation of treatment for more rapid improvement in symptoms (Table 2).[89-97] One vaginal ET

product (Femring) delivers a *systemic* dose of estradiol and is approved for the treatment of VMS in addition to GSM.[141] Femring should not be confused with Estring, which delivers a low dose of estradiol and is indicated only for GSM. There are no data to suggest an advantage for initial use of combined systemic and vaginal estrogen in cases of severe GSM.

Therapy with low-dose vaginal estrogen can be individualized to identify the lowest dose and frequency of use that provides the desired effect. Although efficacy is similar among the available products, estrogen creams dispensed with an applicator may offer more immediate soothing relief of symptoms, possibly because of the emollient nature of the carrier. Another potential advantage of the creams is that they can be digitally applied directly to the vulvar and vestibular tissues. However, some women consider the creams messy, and some report sensitivity to the vehicle used in the creams. With estrogen cream delivery, the user has the responsibility of preparing the dose because the amount of cream inserted is not in a prepackaged dosing unit—potentially leading to use of higher-than-recommended doses. The clinical implications of potential male partner estrogen absorption remain unknown.

Low-dose estradiol tablets and inserts are convenient, fixed-dose vaginal estrogen formulations. Although two doses of the vaginal tablet (25 μg and 10 μg) were shown to be effective, only the lower dose (10 μg) is available in the United States and Canada.[101,102,107-109,111,142] There are two approved doses of the vaginal insert (4 μg and 10 μg), with the 4-μg dose providing the lowest available formulation of vaginal ET.[143-145]

The sustained-release, low-dose estradiol vaginal ring provides 90 days of continuous estradiol. Effective relief of genitourinary symptoms, including dyspareunia, dysuria, and urge incontinence, has been consistently documented in RCTs with this estrogen delivery system.[99,100,103-107] The estradiol ring may change position or dislodge with bowel movements, Valsalva maneuvers, douching, or vaginal sexual penetration, particularly in women with uterovaginal prolapse or hysterectomy. Vaginal ring users are encouraged to remove and replace their own vaginal rings unless discomfort or limited dexterity makes such self-care difficult. The ring can remain in the vagina during sexual activity. There are no data to suggest an allergic reaction to the silicone product. If there is significant stenosis of the vagina, regular use of graduated vaginal dilators after initiation of estrogen cream, tablet, or insert may be necessary before an estrogen ring can be inserted.

Given similar efficacy among vaginal estrogen formulations, women should be provided with information on all options, with personal preference guiding choice. Although some women prefer estrogen creams to allow for vulvar and vestibular as well as vaginal application, others find creams messy and dislike cleaning the applicator after use. Because creams do not provide a specific, fixed dose of estrogen, other options may be preferred if careful dosing and predictable results of serum estrogen levels are desired. Vaginal estradiol tablets and inserts are convenient, requiring only twice weekly application after 2 weeks of daily use. The tablet is placed in the vagina with a plastic applicator, whereas the insert is placed with a finger. Preference for insertion method may determine product choice. For women who are comfortable using a vaginal ring, this formulation is convenient, requiring placing a new ring only four times yearly. Vaginal estrogen formulations are often costly, and variation in price, depending on a woman's particular insurance coverage, also may be a factor in product choice.

Vaginal dehydroepiandrosterone

Dehydroepiandrosterone (also known as prasterone) is a steroid hormone that is an intermediate in the biosynthesis of androgens and estrogens. A low-dose DHEA vaginal insert used daily with an applicator is approved in the United States and Canada for the treatment of moderate to severe dyspareunia in menopausal women (Table 2).[89-97] Dehydroepiandrosterone is transformed by vaginal mucosal cells to estrogens, including estradiol, and to androgens, including testosterone.[146] Twelve-week RCTs have demonstrated the efficacy of DHEA 6.5 mg daily in improving the VMI, vaginal pH, dyspareunia, and vaginal dryness in menopausal women with GSM. Vaginal discharge was the most common AE, reported by 6% of study participants. In 422 women receiving DHEA for 52 weeks, endometrial sampling demonstrated inactive or atrophic endometrium in all participants.[147]

Ospemifene

Ospemifene is an estrogen agonist/antagonist and the only orally available product approved for treatment of vaginal dryness and moderate to severe dyspareunia. It is available in the United States, but not in Canada.[97,148] Twelve-week RCTs have demonstrated the efficacy of ospemifene 60 mg daily in improving VMI, vaginal pH, dyspareunia, vaginal dryness, and genital exam findings.[149-151] A 52-week efficacy and safety extension study in 180 women showed sustained improvements on visual examination of the vagina, with no cases of VTE, endometrial hyperplasia, or cancer.[152] Vasomotor symptoms were the most common AE, with rates of 2% in the placebo group and 7.2% in the group taking 60 mg of ospemifene. Ospemifene was shown to reduce recurrent UTIs in a 6-month retrospective observational study.[153]

The prescribing information for ospemifene contains precautions similar to those for estrogens and other estrogen agonist/antagonists, including an increased risk of endometrial cancer and CVD.[97] With regard to breast cancer, labeling states that ospemifene should not be used in women with known or suspected breast cancer because the drug has not been adequately studied in this group. Ospemifene has, however, demonstrated antiestrogenic activity in preclinical models of breast cancer.[154] In ex vivo human breast tissue, ospemifene inhibited proliferation and opposed stimulation caused by estradiol similar to but not as potently as the estrogen agonist/antagonists tamoxifen and raloxifene.[155] Ospemifene 60 mg has been associated with decreased risk

for breast cancer and breast cancer recurrence in preliminary studies.[156]

Duration of therapy and monitoring

Improvement in GSM symptoms typically occurs within a few weeks of starting therapy[157]; however, treatment for 12 weeks may be needed for maximum benefit. In the absence of contraindications, therapy should be continued as long as needed for symptom management as symptoms will recur upon discontinuation. Clinical trial safety data are limited to 1 year, but observational studies demonstrate safety with long-term use.

Based on available limited safety data, use of a progestogen[112,126] and routine endometrial surveillance[112,158,159] are not recommended in low-risk women using low-dose vaginal ET. Women at increased risk of endometrial cancer because of obesity or diabetes may warrant endometrial surveillance. Because uterine bleeding is generally a sign of endometrial proliferation, any spotting or bleeding requires a thorough evaluation that may include transvaginal ultrasound (TVU) and/or endometrial biopsy.

Testosterone

Topical testosterone cream has been used for the treatment of vulvovaginal conditions, including lichen sclerosus and vestibulodynia, despite limited efficacy data.[160,161] Although not government approved for this indication, there are limited data supporting the use of vaginal testosterone cream for the treatment for GSM. A 4-week pilot trial of 20 postmenopausal women with breast cancer found that vaginal testosterone (150 μg and 300 μg) improved dyspareunia, vaginal dryness, and VMI without increasing estradiol; median testosterone level increased from 15.5 ng/dL to 21.5 ng/dL ($P = .02$).[162] A 12-week RCT in 76 menopausal women taking AIs after treatment for early stage breast cancer who reported vaginal dryness, dyspareunia, or reduced libido compared the low-dose estradiol vaginal ring with compounded vaginal testosterone cream. Symptoms of GSM and sexual desire improved in both treatment arms. The observation that levels of serum estradiol were increased in trial participants at baseline complicates interpretation of these findings.[163] Existing clinical trial data are insufficient to recommend the use of vaginal testosterone for GSM.[164] Longer and larger studies are needed to assess safety and efficacy.

Energy-based therapies

Vulvovaginal energy-based devices including lasers (fractional CO_2, Erbium:YAG) and radio-frequency devices are under investigation as treatments for GSM, but none have FDA approval for this indication. In a 2018 Safety Communication, FDA issued a public warning about the use of these devices for vaginal cosmetic purposes, stating that the effectiveness and safety of the devices have not yet been established.[165]

Vulvovaginal energy-based devices are thought to improve vaginal health by causing microtrauma, which induces collagen formation, angiogenesis, and epithelial thickening. The fractional CO_2 laser has demonstrated safety and efficacy in tissues of the skin, face, and neck.[166-169] Using a probe adapted to the vagina, fractional CO_2 vaginal laser therapy induces similar morphologic changes in the vagina, and data from small studies support improvement in GSM symptoms of vaginal dryness and dyspareunia.[170-178] Several RCTs have compared laser therapy to vaginal ET. Overall, no treatment was superior to another, and the studies were not designed to assess noninferiority.[179-182] Radiofrequency devices are nonablative and emit focused electromagnetic waves that heat the superficial layers of the tissue. Several RCTs evaluating the efficacy of energy-based devices in the treatment of GSM are in progress.

Safety

Adverse events associated with energy-based therapies include discomfort during treatments, vaginal scarring, vaginal lacerations on resumption of intercourse, and persistent and/or worsening dyspareunia.[183] These treatments are costly and generally not covered by insurers.

Consensus statements regarding the use of energy-based therapies for GSM treatment have been published by several professional societies summarizing the small but growing body of evidence as well as concerns about safety.[184-187] Additional randomized, prospective, sham-controlled trials of adequate size and scope are necessary before these therapies can be routinely recommended for treatment of GSM.

Treatment considerations in women with breast cancer

Treatment of GSM in women with breast cancer can be complicated by 1) adjuvant treatment (AIs or tamoxifen), which lower estrogen concentrations or antagonize estrogen effects; 2) product labeling; 3) limited clinical trial data in patients with breast cancer or survivors; and 4) absence of agreement between the oncology community and other practitioners involved in genitourinary and sexual healthcare. Many women with breast cancer and GSM will benefit from the regular use of vaginal moisturizers, lubricants for sexual activity, and PFPT. For persistent symptoms, other therapies may be beneficial, including topical lidocaine, low-dose vaginal ET, vaginal DHEA, ospemifene, and vaginal energy-based therapies.[188-191]

For women with breast cancer, low-dose vaginal ET is contraindicated according to FDA class labeling. However, off-label use of several products may be acceptable because of their very low systemic absorption.[192] Low-dose vaginal ET formulations, including the estradiol tablet, insert, and ring, result in serum estradiol within the postmenopausal range and similar to placebo.[145,146] Several organizations, including the American College of Obstetricians and Gynecologists, have endorsed the use of low-dose vaginal estrogens in women with breast cancer, including ER-positive disease. A systematic review and meta-analysis also suggests safety, based on the use of low-dose vaginal ET in survivors of breast cancer using concomitant AIs.[193] Many oncologists allow the use of low-dose vaginal ET or vaginal DHEA in their patients with

breast cancer when GSM symptoms persist after trials of nonhormone interventions and QOL is adversely affected.

Use of vaginal DHEA for GSM in women with breast cancer is not contraindicated, but US labeling advises caution because estrogen is a metabolite of DHEA.[95] Although vaginal DHEA has not been studied in women with a history of breast cancer, levels of estradiol and testosterone remain within the postmenopause range.[194]

Ospemifene is not recommended for treatment of GSM in women with known or suspected breast cancer because the drug has not been adequately studied in this group. Preliminary data on ospemifene suggest both a decreased risk of incident breast cancer and a reduced risk of breast cancer recurrence with this therapy.[156]

Clinical trials of laser therapy for GSM in survivors of breast cancer provide limited evidence for safety and efficacy in this patient population.[195-197] These studies generally do not have either a positive or sham control, a shortcoming of many of the studies on these devices.

Education

Healthcare providers should educate women about GSM and the urogenital changes that often occur with menopause. Many women are unaware that vaginal dryness, recurrent UTIs, discomfort with sexual activity, and other GSM symptoms are a consequence of estrogen deficiency. Unlike VMS that typically improve with time, GSM symptoms often worsen in the absence of treatment. Women also may not know that effective and safe OTC and prescription therapies are available. Women who are sexually active are more likely to notice GSM symptoms and seek care, but sexually inactive women also will benefit from education about GSM. Women who are concerned about future urogenital function may consider *preventive* use of lubricants, moisturizers, vaginal dilators, or prescription therapies, but there is no evidence to support this approach. It is unknown whether treatment to preserve sexual function or prevent the future occurrence of GSM is indicated in the absence of urogenital symptoms.

CONCLUSIONS AND RECOMMENDATIONS

- Education about and screening for GSM is recommended for perimenopausal and postmenopausal women. [Level C]
- First-line therapies for women with GSM include nonhormone lubricants with sexual activity and regular use of long-acting vaginal moisturizers. [Level A]
- For women with moderate to severe GSM and those who do not respond to lubricants and moisturizers, several safe and effective options are available:
  - Low-dose vaginal ET [Level A]
  - Vaginal DHEA [Level A]
  - Ospemifene [Level A]
  - Systemic ET (when VMS are also present) [Level A]
- For women with a history of breast or endometrial cancer, management depends on a woman's preferences, symptom severity, and understanding of potential risks after consultation with her oncologist. [Level C]
- Although product labeling for low-dose vaginal ET notes risks associated with systemic HT (including CHD, stroke, VTE, breast and endometrial cancer), these risks are highly unlikely given minimal systemic absorption and reassuring findings from clinical trials and observational studies. [Level B]
- Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance. Endometrial safety clinical trial data are not available for use longer than 1 year, although observational studies are reassuring regarding longer-term use. [Level B]
- Routine endometrial surveillance is not recommended for asymptomatic women using low dose vaginal ET. Transvaginal ultrasound or intermittent progestogen therapy may be considered for women at increased risk of endometrial cancer. [Level C]
- Spotting or bleeding in a postmenopausal woman requires a thorough evaluation that may include TVU and/or endometrial biopsy. [Level A]
- Energy-based therapies, including vaginal laser and radiofrequency devices, require long-term, sham-controlled safety and efficacy studies before their routine use can be recommended. [Level C]
- Therapy for GSM should be continued, with appropriate clinical follow up, for as long as bothersome symptoms are present. [Level C]

Strength of Recommendation

- Level A Supported by sufficient, consistent scientific evidence
- Level B Supported by limited or inconsistent evidence
- Level C Based primarily on expert opinion

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The 2020 Genitourinary Syndrome of Menopause Position Statement of The North American Menopause Society has been designated a CME activity for all NAMS members. NAMS members should log-in to the NAMS website www.menopause.org and then select Online CME in the Member Center. CME credit will be available from September 1, 2020, to September 1, 2021.