

POSITION STATEMENT

Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society

Abstract

Objective: To update and expand the previous position statement of The North American Menopause Society (NAMS) on the management of symptomatic vulvovaginal atrophy (VVA) in postmenopausal women.

Methods: NAMS searched PubMed for medical literature on VVA published since their 2007 position statement on the role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women. A panel of acknowledged experts in the field of genitourinary health reviewed the literature to evaluate new evidence on local estrogen as well as on other management options available or in development for symptomatic VVA. The panel's conclusions and recommendations were reviewed and approved by the NAMS Board of Trustees.

Results: Symptomatic VVA can significantly impair the quality of life (QOL) of postmenopausal women and may be underdiagnosed. In most cases, it can be managed successfully. 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 VVA symptoms. These include vaginal lubricants and moisturizers, vaginal estrogen, hormone therapy, and the selective estrogen-receptor modulator ospemifene (indicated for dyspareunia). Long-term studies on the endometrial safety of local estrogen and ospemifene are lacking. Changes in the vaginal microbiome have various effects on symptoms.

Conclusions: Clinicians can improve the sexual health and QOL of postmenopausal women by educating women about, diagnosing, and appropriately managing symptomatic VVA. Choice of therapy depends on the severity of symptoms, the effectiveness and safety of therapy for the individual patient, and patient preference. Estrogen therapy is the most effective treatment for moderate to severe symptoms, although a direct comparison of estrogen and ospemifene is not available. Nonhormonal therapies available without a prescription provide sufficient relief for most women with mild symptoms. When low-dose estrogen is administered locally, a progestogen is not indicated for women without a uterus and generally is not indicated for women with an intact uterus. However, endometrial safety has not been studied in clinical trials beyond 1 year. There are insufficient data to confirm the safety of local estrogen in women with breast cancer; management of VVA should take the woman's needs and the recommendation of her oncologist into consideration. Research on the vaginal microbiome may lead to other therapies in the future.

Key Words: Menopause – Vulvovaginal atrophy – Vaginal dryness – Vaginal estrogen – Ospemifene – Dyspareunia.

Symptoms associated with vulvovaginal atrophy (VVA), such as lack of lubrication and pain with intercourse, affect 20% to 45% of midlife and older women,^{1,2} but

only a minority seek help or are offered help by their providers. In contrast to vasomotor symptoms that usually improve over time even without treatment, VVA can be progressive and less likely to resolve without intervention. It can have a significant effect on a woman's sexual health and quality of life (QOL).

A number of surveys of postmenopausal women (VIVA, REVEAL, HealthyWomen, CLOSER, REVIVE) have shown that VVA negatively affects sexual health and QOL. In an online survey conducted in 6 countries, an estimated 45% of postmenopausal women reported experiencing vaginal symptoms,³ but only 4% could identify these symptoms as VVA related to menopause. Seventy-six percent of women in Finland were satisfied with the available information about VVA; however, in the other 5 countries, including the United States and Canada, less than half (37%–42%) were

Received June 17, 2013; revised and accepted June 17, 2013.

This position statement was developed by The North American Menopause Society (NAMS) 2013 Symptomatic Vulvovaginal Atrophy Advisory Panel consisting of representatives of the NAMS Board of Trustees and other experts in women's health: Margery L.S. Gass, MD, NCMP, Chair; Gloria A. Bachman, MD; Steven R. Goldstein, MD, NCMP; Sheryl A. Kingsberg, PhD; James H. Liu, MD; Mark G. Martens, MD; Diane T. Pace, PhD, FNP, FAANP, NCMP; JoAnn V. Pinkerton, MD, NCMP; Jan L. Shifren, MD, NCMP. The Board of Trustees conducted independent review and revision and approved the position statement on June 7, 2013.

This position statement was made possible by donations to the NAMS Education & Research Fund.  There was no commercial support.

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satisfied. Among US women (n = 500), 63% associated vaginal symptoms with menopause, and only 41% of respondents believed that enough information about vaginal discomfort is available to them.⁴

The VIVA (Vaginal Health: Insights, Views & Attitudes) online survey asked women how vaginal discomfort affected their lives.⁴ Among the US women who responded

- 80% considered it to negatively affect their lives
- 75% reported negative consequences on sex life
- 68% reported that it makes them feel less sexual
- 36% reported that it makes them feel old
- 33% reported negative consequences on marriage/relationship
- 26% reported a negative effect on self-esteem
- 25% reported that it lowers QOL

The largest survey of US women, REVIVE (Real Women's Views of Treatment Options for Menopausal Vaginal Changes), included 3,046 women with symptoms of VVA.⁵ Only 7% reported that their healthcare practitioner initiated a conversation about VVA and yet

- 85% of partnered women had "some loss of intimacy"
- 59% indicated VVA symptoms detracted from enjoyment of sex
- 47% of partnered women indicated VVA interfered with their relationship
- 29% reported VVA had a negative effect on sleep
- 27% reported VVA had a negative effect on their general enjoyment of life

In contrast to surveys of women who were known to have symptomatic VVA, a study of 98,705 postmenopausal women aged 50 to 79 years who were not specifically recruited for a sexual function survey found lower rates of vaginal symptoms. Only 19% to 27% reported dryness, irritation, or itching.⁶

Responding to this unmet need, The North American Menopause Society (NAMS) has updated and expanded its 2007 position statement, *The Role of Local Vaginal Estrogen for Treatment of Vaginal Atrophy*.⁷ This updated position statement reviews the science of vulvovaginal aging and assesses the safety and effectiveness of products for the treatment of symptomatic VVA in postmenopausal women.

METHODS

NAMS searched the literature on VVA and "atrophic vaginitis" as well as on dyspareunia and vaginal lubrication in postmenopausal women. A 9-person Panel composed of expert clinicians and researchers in the field of vulvovaginal health reviewed the literature to evaluate new evidence on local estrogen as well as on other management options available or in development for symptomatic VVA. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established.

Once the Panel completed its draft, the 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, and the Panel reviewed it one final time.

ANATOMY AND PHYSIOLOGY OF VULVOVAGINAL ATROPHY

The upper three-fourths of the vagina is derived from embryonic mesoderm, and the lower, distal one-fourth is derived from endoderm, which also forms the urogenital sinus. 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 for most women. The vulva is also derived from the urogenital sinus, but the epithelium of the labia majora is of ectodermal origin.

Estrogen is a dominant regulator of vaginal physiology. Estrogen-receptor α is present in the vaginal tissues of premenopausal and postmenopausal women, whereas estrogen-receptor β appears to have no or low expression in postmenopausal vaginal tissue. Estrogen therapy does not appear to affect the presence of estrogen-receptor β .^{8,9} 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. The progesterone receptor is found only in the vagina and the transitional epithelium of the vulvovaginal junction.¹⁰

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 VVA.¹¹

The term *vulvovaginal atrophy* refers specifically to the changes in the vaginal and vulvar surfaces that on examination are thin, pale, and dry. The vagina can narrow and shorten, and the introitus may constrict, especially in the absence of penetrative sexual activity. The vaginal lining may exhibit petechiae and become thinner (often only a few cell layers thick), less elastic, and progressively smoother as rugal folds decrease. Vaginal blood flow diminishes. Although the sebaceous glands remain prominent, their secretions diminish, and lubrication during sexual stimulation is decreased and delayed.¹² The term *atrophic vaginitis* is commonly used when inflammation also is noted.

The physiology of the vaginal epithelium is not completely understood. Based on a cell-culture model that used vaginal-cervical epithelial cells, aging and diminished estrogen levels were found to be independent factors in decreasing vaginal-cervical paracellular permeability, a change potentially related to vaginal dryness.¹³ With atrophy, wet-mount microscopy

shows more than 1 white blood cell per epithelial cell, immature vaginal epithelial cells with relatively large nuclei (parabasal cells), and reduced or absent lactobacilli. Cytology shows changes in vaginal epithelial cell types. In premenopausal women, intermediate and superficial cells predominate, and few parabasal cells are noted. After menopause, parabasal cells and, at times, intermediate cells increase, and superficial cells decrease or are absent.¹²

Hormonal changes throughout the life cycle influence the vaginal microbiome from birth through postmenopause.¹⁴ During the reproductive years, production of lactic acid and hydrogen peroxide through the action of lactobacilli helps maintain a strong epithelial barrier with a pH in the range of 3.8 to 4.5.¹⁵ Lactobacilli play a key role in preventing a number of urogenital conditions such as bacterial vaginosis (BV), yeast infections, sexually transmitted infections, urinary tract infections (UTIs),¹⁶⁻²³ and HIV infection.^{24,25} A higher proportion of lactobacilli in the vagina correlates inversely with dryness in postmenopausal women.

During perimenopause, most women continue to be asymptomatic, even as the vaginal pH becomes more basic. Healthy women have communities of bacteria that produce various bacteriostatic and bacteriocidal compounds that reduce pathogen overgrowth through competitive exclusion.²⁶⁻²⁸ However, the continued decline in estrogen during perimenopause results in a continued decrease in acid-producing bacteria and a change in the resident flora.

The application of culture-independent molecular approaches based on the cloning and sequencing of 16S rRNA genes in the Human Microbiome Project has revealed significant differences in the vaginal microbiota between reproductive and postmenopausal women. These techniques have characterized bacterial species not previously identified by traditional culture methods.^{17,24,29}

The postmenopausal vagina has fewer species with less transitioning to and from BV-like organisms (2% of the time) than in the premenopausal women (17% transition).^{24,30} This stability appears to be protective because increased bacterial diversity in the postmenopausal vagina correlates with an increase in symptoms of vaginal dryness.

It was generally believed that lactobacilli are absent in the menopausal vagina, but the microbiome studies found that *Lactobacillus iners* and *L. crispatus* were the most common bacterial species in asymptomatic menopausal women.²⁴ A higher proportion of lactobacillus correlated inversely with dryness in postmenopausal women.

One species of lactic acid-producing bacteria previously classified as a lactobacillus species is now identified as *Atopobium vaginae* (*A. vaginae*). In the premenopausal woman, it appears to be associated with symptoms of BV. This species may actually represent “normal” postmenopausal flora in patients with reduced or absent lactobacillus species. Unfortunately, the newer diagnostic tests for BV often use *A. vaginae* as one of the markers of vaginal disease. This may lead to unnecessary antibiotic treatment of postmenopausal

women and the potential disturbance of their very fragile microbiome.²⁴

PRESENTATION OF SYMPTOMATIC VULVOVAGINAL ATROPHY

Commonly reported symptoms include dryness, irritation of vulva, burning, dysuria, dyspareunia, and vaginal discharge.^{2,6,31,32} Symptoms of VVA can be severe enough to interfere with a woman’s ability to have pain-free sexual activity.³³⁻³⁶ Dyspareunia has been shown to be strongly associated with female sexual dysfunction in postmenopausal women.³¹ Decreased genital arousal and vulvar pain disorders may occur as a consequence of VVA. Atrophy and phimosis of the prepuce of the clitoris may result in dyspareunia that leads to decreased interest in and avoidance of sexual activity.³⁷ In these scenarios, dyspareunia or avoidance of sexual activity may be a presentation of VVA.

Vulvar and vaginal atrophic changes increase the likelihood of trauma, infection, and pain. Left untreated, severe VVA can result in a vaginal surface that is friable, with petechiae, ulcerations, and tears, accompanied in some cases by stenosis. Bleeding may occur from minimal trauma, such as speculum insertion.¹² On questioning, patients may acknowledge bleeding with intercourse and/or wiping.

Symptomatic VVA may occur in hypoestrogenic states other than natural menopause. Examples include surgical menopause (bilateral oophorectomy, with or without hysterectomy); use of GnRH agonists to manage conditions such as endometriosis and uterine leiomyomata; hypothalamic amenorrhea caused by excessive exercise, disordered eating, or the postpartum state; and by cancer treatments, such as surgery, pelvic radiation therapy, chemotherapy, or endocrine therapy, that remove ovaries or render them inactive, either temporarily or permanently. Younger women with dyspareunia resulting from induced menopause may be especially distressed by changes in sexual function.^{38,39}

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 shortened vagina. These changes can produce pain with pelvic examinations, dyspareunia, and an increased risk of vaginal infections.⁴⁰

Vaginal symptoms related to an abrupt menopause induced by chemotherapy have been associated with greater sexual dysfunction and distress in some but not all studies^{39,41,42} and with poorer QOL outcomes.^{38,43-46} The stress, fatigue, and mood changes that accompany cancer diagnosis and treatment also contribute to reported sexual problems.

Aromatase inhibitors (AIs), however, are clearly associated with VVA.⁴⁷ They reduce breast cancer recurrence by inducing a profound estrogen-deficiency state and are becoming a more frequent component of the treatment of breast cancer in postmenopausal women. Compared with tamoxifen, AIs (anastrozole, letrozole, and exemestane) prevent conversion of androgens to estrogens and result in a greater

incidence of vaginal dryness and dyspareunia.⁴⁸⁻⁵¹ A pure estrogen-receptor antagonist, fulvestrant, has similar VVA-inducing effects.

EVALUATION AND DIAGNOSIS

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

History

Because women may not report symptoms of VVA and related sexual concerns, providers should address this issue for all perimenopausal and postmenopausal women as part of a routine review of systems. Results of the REVEAL (REvealing Vaginal Effects At mid-Life) survey found that about half of postmenopausal women surveyed agreed that it is still taboo to acknowledge symptoms such as VVA, and less than half had ever initiated a conversation with their healthcare provider about their symptoms.⁵² The goal of the history is to determine whether symptoms of VVA are present, whether they are bothersome, and how they affect the woman's sexual health and QOL. In the absence of symptoms, VVA does not necessarily require treatment, although women should be informed that it may worsen over time without proactive management.

The onset of VVA symptoms after menopause varies from one woman to another. Other hypoestrogenic states also result in VVA, and a careful history and targeted laboratory testing will identify primary ovarian insufficiency, medically induced menopause, surgically induced menopause, hypothalamic amenorrhea, and hyperprolactinemia. Endocrine therapies, including AIs, gonadotropin-releasing hormone agonists or antagonists, and certain selective estrogen-receptor modulators (SERMs) can induce an estrogen-deficient state and contribute to VVA.

Symptoms similar to VVA can be secondary to many other conditions. The differential diagnosis includes autoimmune disorders, allergic or inflammatory conditions (eg, desquamative inflammatory vaginitis, contact dermatitis, erosive lichen planus, lichen sclerosis, and cicatricial pemphigoid), chronic vaginitis, infections, trauma, foreign bodies, malignancy, vulvodynia, vestibulodynia, chronic pelvic pain, vaginismus, and other medical (eg, diabetes, lupus erythematosus) or psychological disorders. An alternate etiology is more likely in women with chronic or recurrent vulvovaginal symptoms that appear to predate their menopause.

Documentation of VVA 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 of sexual activity, and the effect of VVA symptoms on sex life and partner relationships is useful in determining management strategies.

Previous interventions should be discussed, including whether they were effective or had possible adverse effects.

For a woman with a history of cancer, additional information needs to be obtained, including cancer site, hormone dependence, treatments (past, current), age at diagnosis, and type of menopause (spontaneous or induced). Vaginal dryness is a common symptom among women treated for cancer, but it may not always be related solely to estrogen deficiency. For example, vaginal stenosis is a known complication of surgery and radiation therapy for gynecologic and colorectal malignancies.

Physical examination

The pelvic examination helps to exclude other vulvovaginal conditions that have similar symptoms. VVA can vary in degree of severity. In early stages, changes may be subtle. The epithelium of the vestibule can be thin and dry, and the vagina mildly erythematous. As atrophy progresses, there is loss of the labial fat pad, and the labia minora become less distinct.

In severe atrophy, there may be no clear definition between the labia minora and majora. The urethral meatus may be patulous and/or beef red secondary to eversion. The clitoris can recede and in some cases become completely flush with the surrounding tissue. Phimosis of the clitoris is not uncommon. The tissues of the vulva and vagina become progressively pale, thin, and dry. There is shortening and narrowing of the vagina as it loses elasticity and distensibility. The vaginal epithelium becomes very dry, with a glazed appearance and with areas of both erythema and pallor. Loss of vaginal rugae occurs. The fornices may become obliterated, making the cervix flush with the vault. Petechiae may be seen in the vestibule or vagina.

With atrophic vaginitis, brown or yellow secretions may be present. With severe VVA, there may be such shortening of the vaginal vault and narrowing of the introitus that speculum insertion and visual inspection of the vaginal vault may not be possible. Small pediatric speculums with lubrication may be helpful with severe atrophy.

Although assessment of the vaginal maturation index (VMI) and vaginal pH are routinely part of clinical trials, they are not essential to make a diagnosis of VVA in clinical practice. With VVA, vaginal pH is typically greater than 5.0. Wet-mount microscopy shows more than 1 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 occurs, including enteric organisms commonly associated with UTIs.⁵³ The appearance of the wet mount in severe VVA may be difficult to distinguish from that of desquamative inflammatory vaginitis or vaginal erosive lichen planus.⁵⁴ 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 low-dose vaginal estrogen therapy (ET).

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 VVA on exam. In contrast, a woman with an active sex life may complain of dryness and discomfort with the pelvic exam but not with intercourse, suggesting only mild atrophy. Of note, women who are not sexually active may also be bothered by symptoms related to VVA. Thus, both history and examination are essential to making a correct diagnosis.

TREATMENT

The primary goal of treating symptomatic VVA is to alleviate symptoms. For the woman with symptomatic VVA unrelated to sexual activity and for whom all other causes of her symptoms have been eliminated, first-line therapies include nonhormonal, long-acting vaginal moisturizers and low-dose vaginal estrogen, assuming no contraindications. She may need only a short course (1-3 mo) of therapy to become symptom-free, although symptoms may recur on cessation of treatment. Outcomes data on the symptom recurrence rate are lacking. Because long-term endometrial safety data are not available for vaginal estrogen use, treatment on an as-needed basis may be preferred.

Treatment of the woman with symptomatic VVA related to sexual activity can be approached in a stepwise fashion based on the severity of symptoms. Options include nonhormonal vaginal lubricants to be used with intercourse/vaginal sexual activity, long-acting vaginal moisturizers used regularly (several times per week), and regular sexual activity. For symptomatic VVA that does not respond to these initial management approaches, low-dose vaginal ET is an option. For women with moderate to severe dyspareunia associated with VVA who prefer a nonvaginal therapy, transdermal and oral hormone therapy (HT) as well as ospemifene are options. Some women may already have vaginal constriction or vaginismus limiting vaginal penetration. Gentle stretching of the vagina with the use of lubricated vaginal dilators of graduated sizes can play an important role in restoring and then maintaining vaginal function. Reinitiating regular sexual activity once vaginal penetration is again comfortable will help to maintain vaginal health. Many women with this condition benefit from referral to pelvic floor physical therapy.⁵⁵ Starting vaginal estrogen before initiating vaginal dilatation and/or pelvic floor therapy may facilitate progress.

Nonprescription therapies
Lubricants and moisturizers

First-line therapies to alleviate symptoms of VVA include nonhormonal vaginal lubricants and moisturizers as well as regular sexual activity with partner, device, or solo. Regular use of nonhormonal, long-acting vaginal moisturizing agents can decrease vaginal pH to premenopausal levels, although they do not improve VMI. Use of lubricants during vaginal intercourse may also reduce friction-related irritation of atrophic tissue.

A number of over-the-counter (OTC) vaginal lubricants and moisturizers are available (Table 1). However, few

TABLE 1. Examples of nonhormonal therapeutic options for dyspareunia secondary to VVA

Lubricants	Moisturizers
<i>Water based</i>	
Astroglide Liquid	Replens
Astroglide Gel Liquid	Me Again
Astroglide	Vagisil
Just Like Me	Feminease
K-Y Jelly	K-Y SILK-E
Pre-Seed	Luvena
Slippery Stuff	Silken Secret
Liquid Silk	
<i>Silicone based</i>	
Astroglide X	
ID Millennium	
K-Y Intrigue	
Pink	
Pjur Eros	
<i>Oil based</i>	
Elégance Women’s Lubricants	
Olive oil	

Abbreviation: VVA, vulvovaginal atrophy.

clinical studies have been conducted on the efficacy of these products. 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.⁵⁶ Other studies have shown that, although vaginal moisturizers are not as effective in resolving vaginal dryness as hormonal treatments, they can significantly decrease or even eliminate symptoms for many women.^{57,58}

In a study that examined the safety of personal moisturizers and lubricants, investigators found that a number of water-based gels are hyperosmolar.⁵⁹ 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. One jelly and one moisturizer were also 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 with use of petroleum jelly compared with controls (95% confidence interval [CI], 1.3-3.9) and colonization with candida species with use of oils compared with nonusers (44.4% vs 5%, respectively; $P < 0.01$).⁶⁰

Because there are no published reports on the irritation potential of different 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, they can switch products to the iso-osmolar (eg, Good Clean Love, PRÉ), propylene glycol-free (eg, Sliquid H₂O, Pjur Woman Bodyglide, Slippery Stuff, Good Clean Love), or silicone-based lubricants (Table 1). Note that oil-based lubricants can erode condoms; however, most brands of

water-based and silicone-based lubricants are latex safe and condom compatible.

Herbal products

The Herbal Alternatives for Menopause (HALT) study, a randomized, double-blind, placebo-controlled trial of 1-year duration evaluating 351 women, reported the effect of herbal products on VVA.⁶¹ The trial investigators concluded that dietary supplements such as black cohosh, other herbs, and soy have no beneficial effect on VVA as evaluated by the VMI. There was no significant change in follicle-stimulating hormone or estradiol levels in the herbal groups. The trial had a high retention and compliance rate for all regimens.

Prescription therapies

The benefits and risks of systemic HT have been reviewed previously and have shown that for symptomatic women who are younger than 60 years or who are within the first 10 years of menopause, benefits may outweigh the risks.⁶² When systemic HT is needed to treat other menopausal symptoms, the woman will generally derive satisfactory resolution of her vaginal symptoms as well. However, 10% to 15% of women on systemic HT may not derive adequate relief of vaginal symptoms,⁶³ and additional low-dose vaginal ET may be added if needed.

Vaginal estrogen

Effectiveness. For symptomatic VVA that does not respond to the patient's satisfaction with nonhormonal interventions, low-dose vaginal ET is likely to provide greater benefit. For decades, systemic and vaginal estrogen have been the gold standard for treatment of symptomatic VVA. Estrogen delivered locally is now the preferred mode of delivery when vaginal symptoms are the only complaint. Low-dose vaginal ET can provide sufficient estrogen to relieve symptoms with minimal systemic absorption. Vaginal ET has been shown to be more effective than systemic oral ET in the relief of VVA symptoms, with 80% to 90% of women reporting a favorable response compared with 75% of women using oral ET.^{64,65}

Studies of the effectiveness of vaginal ET have used subjective and objective outcome measures, including improvements in atrophic symptoms (including dyspareunia when that indication was sought), lower urinary tract symptoms, gross vaginal mucosal appearance, decreases in vaginal pH, increases in the number of vaginal lactobacilli, favorable shifts in the vaginal and/or urethral cytology or changes in urine culture results, and patient preference.

Many trials demonstrating the effectiveness of vaginal ET have been reported in the literature.^{7,57,66-78} Government regulatory bodies confirm the efficacy of vaginal ET for the treatment of vaginal atrophy. A 2006 Cochrane review comparing 19 efficacy trials reported that all products tested alleviated symptoms with similar efficacy.⁷⁹ This conclusion was reaffirmed in 2010. Comparative analyses of these trials are limited by variations in methods and outcome measures, small sample sizes, and substantial heterogeneity in 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. Several trials were not blinded. Nevertheless, no newer effectiveness trials have since been reported.

The therapeutic benefit of vaginal ET has been observed in conditions other than VVA, such as in reducing the risk of recurrent UTIs^{80,81} and in overactive bladder.^{82,83} The low-dose estradiol ring has been approved for the treatment of dysuria and urinary urgency. However, systemic HT has been associated with an increase in stress incontinence⁸⁴⁻⁸⁷ and renal stones.⁸⁸

Adverse effects and safety. Low-dose vaginal estrogen is considered to have a lower risk profile compared with commonly used doses of systemic ET because it produces very low serum levels. In general, serum estrogen levels reported with use of low-dose vaginal estrogen are below the average level for postmenopausal women.⁸⁹ Reported estradiol levels with use of the vaginal ring (releasing approximately 7.5 µg/d) ranged from 5 pg/mL to 10 pg/mL.^{74,90,91} Serum levels with use of the 10-µg vaginal tablet were in the 3 pg/mL to 11 pg/mL range.⁹²⁻⁹⁴ Use of 0.2 mg of estradiol cream (200 µg) resulted in serum levels of 80 pg/mL.⁹⁵ A dose of 0.3 mg conjugated estrogens (CE) cream produced no change in serum levels.⁹⁶ Hormone assays have become more sensitive to lower levels over the years, and older studies may not have detected small changes.⁹⁷ In addition, CE contain a significant number of compounds, some estrogenic and some antiestrogenic. The plasma estradiol level after use of CE may not reflect actual estrogenic activity.

All government-approved, low-dose vaginal ET products in the United States and Canada differ slightly in their adverse event profiles. However, the dosing and the symptoms captured differed among the products tested. Vulvovaginal candidiasis, vaginal bleeding, and breast pain have been reported. The incidence of vulvovaginal candidiasis in postmenopausal women is largely unstudied, but studies suggest that women who experience spontaneous menopause and use vaginal ET may be at higher risk.^{98,99}

The 2006 Cochrane review found no report of increased risk of venous thromboembolism (VTE),⁷⁹ but data for women at high risk of VTE are lacking. Vaginal bleeding, breast pain, and nausea have been reported in some vaginal estrogen trials. These symptoms are dose related and suggest that the dose was large enough to result in noteworthy systemic absorption.

The primary concern regarding use of any ET in women who have an intact uterus is the risk of endometrial carcinoma associated with unopposed estrogen. Although available evidence suggests that low doses of vaginal estrogen are generally safe for the endometrium, the long-term data are limited.

A study of the endometrial safety of the 10-µg estradiol vaginal tablet was evaluated in 336 nonhysterectomized postmenopausal women for 52 weeks of treatment.¹⁰⁰ At study's end, there was no evidence of increased endometrial proliferation or hyperplasia.

In another clinical study of 52 weeks evaluating the 10- μ g estradiol dose, there was 1 case of endometrial adenocarcinoma stage II in a participant with no baseline endometrial biopsy. The authors considered it unlikely to have developed and progressed to that degree in that time span.¹⁰¹ The 2006 Cochrane review, reaffirmed in 2010, reported no significant differences among the delivery methods in terms of endometrial thickness or hyperplasia or the proportion of women with adverse events.⁷⁹ Thus, although endometrial hyperplasia has been seen with low-dose vaginal estrogens, it is rare, and the concomitant use of a progestogen has not been indicated.⁹²

The concern for women at risk of VTE or breast cancer is systemic absorption of estrogen. Most studies measuring systemic estradiol in vaginal estrogen users were done before 2007.⁷ Studies of circulating estradiol since that time also have reported an increase in circulating estrogen, but the clinical relevance of the small increases remains unclear. There could be a growth-promoting effect or an apoptotic effect on breast cancer, depending on the circumstances, and there could even be a small beneficial effect on bone.¹⁰²⁻¹⁰⁴

Small studies have suggested that vaginal administration of estradiol or progesterone, particularly in the upper third of the vagina, may result in a uterine first-pass effect.¹⁰⁵⁻¹⁰⁹ The studies indicate that vaginal administration of hormones resulted in a preferential effect in the uterus.

Symptoms of VVA are a common complaint among sexually active women with breast cancer, particularly those on endocrine treatments such as AIs or tamoxifen. It should be noted that in premenopausal women, tamoxifen exerts antiestrogenic effects on the vagina. In postmenopausal women, it exerts weak estrogenic effects on the vagina, but some women treated with tamoxifen still experience symptoms of urogenital atrophy.¹¹⁰

Aromatase inhibitors act by blocking 95% of estrogen synthesis, typically resulting in circulating estradiol levels of less than 1 pg/mL.¹¹¹ As might be expected from studies in otherwise healthy women, vaginal administration of estradiol 25- μ g tablets resulted in small increases in serum estradiol in a study involving women receiving AI therapy.¹¹² At day 14, the median serum estradiol level had increased from 0.82 pg/mL to 19.6 pg/mL. Although the increase is small, and levels decreased to less than 10 pg/mL (median, <5 pg/mL) by day 28, any rise above baseline serum estradiol levels may have an effect on AI efficacy.

The safety of the use of HT in women with breast cancer has been an ongoing concern. One meta-analysis of systemic HT reported a striking difference in the risk of breast cancer recurrence found in 2 randomized, controlled trials (relative risk [RR], 3.41; 95% CI, 1.59-7.33) compared with the risk found in 8 observational studies (RR, 0.64; 95% CI, 0.50-0.82).¹¹³ There are even fewer reports regarding the safety of vaginal ET in women with breast cancer. In a case-control study, patients receiving endocrine treatment such as tamoxifen and AIs for breast cancer did not show increase of recurrence with local estrogen use compared with nonuse.¹¹⁴ Vaginal estrogen treatment by ring or tablet, however, did result in ele-

vated circulating estrogen levels initially in this population of breast cancer survivors, although elevated levels did not appear to be sustained.¹¹⁵ An initial increase in systemic estrogen levels during the first weeks of vaginal ET use, with levels decreasing after 1 month, has been noted.⁹⁵ Because the efficacy of AIs is based on their ability to reduce estrogen levels below those typically seen in postmenopausal women, even the small increases in circulating estrogen levels seen with low-dose vaginal estrogen therapies may render AI therapy less effective.

Breast cancer survivors using adjuvant therapy with the AIs and, to a lesser degree, tamoxifen have been reported to have increased complaints of dyspareunia.^{47,48,51} Because of the effect of moderate or severe symptomatic VVA on QOL, patients with breast cancer who do not respond to nonhormonal therapies may want to discuss the risks and benefits of low-dose vaginal ET in consultation with their oncologist. In some cases, a short course of low-dose vaginal ET may be all that is required to allow resumption of sexual activity. Regular sexual activity or vaginal stimulation then may prevent recurrence of symptoms and signs of atrophy.

Management of VVA in women who have been treated for nonhormone-dependent cancers is similar to that for women without a cancer history. For women treated with pelvic irradiation, low-dose vaginal ET may be indicated after treatment to stimulate epithelial regeneration, promote healing, and improve vaginal elasticity and lubrication. Use of vaginal dilators with or without referral for pelvic floor physical therapy may be useful in this setting.

Types of vaginal estrogen. Vaginal estrogen products have been government approved for use in the United States and Canada for the treatment of symptomatic VVA and atrophic vaginitis (Table 2). The lower doses of those studied and approved are preferred for most cases of VVA. One vaginal estrogen product is an estradiol acetate ring (Femring) that delivers a *systemic* dose of estrogen. This product is approved for the treatment of vasomotor symptoms in addition to VVA. Femring should not be confused with Estring, which delivers a low dose of estrogen and is indicated only for VVA.

Therapy with estrogen creams or tablets can be individualized. When a therapeutic response is attained, typically after 2 weeks of daily use, the frequency of use can often be reduced. A maintenance schedule of 2 to 3 doses per week is common, but dosing should be titrated to the lowest dose and frequency of vaginal estrogen that provides the desired effect. No randomized, controlled trial data are available for the vaginal cream containing estradiol. Although efficacy is similar for the available products, creams may offer more immediately soothing comfort to the vulva, although some users consider them messy.

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. Dosing at least 12 hours before coital activity is recommended to prevent estrogen absorption by a sexual partner.

TABLE 2. Vaginal ET products for postmenopausal use in the United States and Canada

Composition	Product name	FDA-approved dosage
<i>Vaginal creams</i>		
17 β -estradiol	Estrace Vaginal Cream ^a	Initial: 2-4 g/d for 1-2 wk Maintenance: 1 g/1-3 times/wk ^c (0.1 mg active ingredient/g)
Conjugated estrogens	Premarin Vaginal Cream	For VVA: 0.5-2 g/d for 21 d then off 7 d ^c For dyspareunia: 0.5 g/d for 21 d then off 7 d, or twice/wk ^c (0.625 mg active ingredient/g)
Estrone	Estragyn Vaginal Cream ^b	2-4 g/d (1 mg active ingredient/g) Intended for short-term use; progestogen recommended
<i>Vaginal rings</i>		
17 β -estradiol	Estring	Device containing 2 mg releases approximately 7.5 μ g/d for 90 d (for VVA)
Estradiol acetate	Femring ^a	Device containing 12.4 mg or 24.8 mg estradiol acetate releases 0.05 mg/d or 0.10 mg/d estradiol for 90 days (both doses release systemic levels for treatment of VVA and vasomotor symptoms)
<i>Vaginal tablet</i>		
Estradiol hemihydrate	Vagifem	Initial: 1 tablet/d for 2 wk Maintenance: 1 tablet twice/wk (tablet containing 10.3 μ g of estradiol hemihydrates, equivalent to 10 μ g of estradiol; for VVA)

Abbreviations: ET, estrogen therapy; FDA, US Food and Drug Administration; VVA, vulvovaginal atrophy.

Products not marked are available in both the United States and Canada.

^aAvailable in the United States but not Canada.

^bAvailable in Canada but not the United States.

^cSome FDA-approved dosages of conjugated estrogen and estradiol creams are greater than those currently used in clinical practice that are proven to be effective.

Doses of 0.5-1 g of estrogen vaginal cream, used 1-2 times weekly may be adequate for many women.

From Estrace¹¹⁶; Premarin¹¹⁷; Estragyn¹¹⁸; Estring¹¹⁹; Femring¹²⁰; Vagifem¹²¹; Bachmann G, et al.¹²²

Although 2 doses of the vaginal tablet were shown to be effective when used as recommended, the lower dose (10 μ g) is preferred and is currently the only dose available in the United States and Canada.^{68,69,74-76,78,101} After 2 weeks of daily dosing, the woman can use the standard maintenance dose twice a week or less frequently if she prefers.

The sustained-release estradiol vaginal ring provides up to 90 days of continuous therapy, a feature that appeals to many women. Effective relief of atrophic urogenital symptoms, including dyspareunia, dysuria, and urge incontinence, has been consistently documented in randomized, controlled trials with this estrogen delivery system.^{66,67,70-74}

The estradiol ring may change position or dislodge with bowel movements, Valsalva maneuvers, douching, or vaginal sexual intercourse. 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 coital activity, although opinions are mixed about tampon use with the ring. There are no data to suggest an allergic reaction to the silicone product.

If there is significant stenosis of the vagina, regular use of vaginal dilators in a graduated approach after initiation of an estrogen cream or tablet may be necessary before an estrogen ring can be inserted. There are no data to suggest any advantage for initial use of both systemic and local vaginal estrogen in cases of severe atrophy.

In VVA cases complicated by other conditions, including relationship issues, referral of the individual/couple to a sex therapist can be very beneficial.¹²³

Therapy duration and monitoring. Improvement in VVA symptoms typically occurs within a few weeks of starting

vaginal ET¹²⁴; however, some women may need to use vaginal estrogen for 12 weeks to obtain maximal benefit.

Symptoms of VVA unresponsive to estrogen may be because of undiagnosed dermatitis/dermatosis, vulvodynia, or vaginismus, so treatment failure warrants further evaluation. A thorough repeat vaginal examination, including Q-tip test for vestibulodynia if not already done, is indicated to determine the source of discomfort.

For women with VVA, low-dose vaginal ET may be continued for as long as they are distressed by their symptoms without estrogen intervention. There are no clinical trial safety data extending beyond 12 months, but no time limits for duration of therapy have been established.

A progestogen is generally not indicated when low-dose vaginal estrogen is used for VVA for 1 year or less. The 2006 Cochrane review concluded that available data cannot answer the question of whether women need progestogen to counter possible adverse effects on the endometrium from vaginal absorption of estrogen.⁷⁹ Others have concluded that the concomitant use of a progestogen is not indicated.⁹² If a woman is at high risk for endometrial cancer (eg, obese) or is using a higher dose of vaginal ET than typically recommended, surveillance using annual transvaginal ultrasound or progestogen withdrawal may be considered. Because uterine bleeding is generally a sign of endometrial proliferation, any spotting or bleeding from the uterus requires a thorough evaluation, which may include a transvaginal ultrasound and/or endometrial biopsy. Data are insufficient to recommend annual endometrial surveillance in asymptomatic women using vaginal ET.^{79,125,126}

Potential contraindications to vaginal ET. Although most symptomatic women are candidates for vaginal ET, potential

contraindications exist. Vaginal ET is inappropriate for postmenopausal women with undiagnosed vaginal/uterine bleeding and controversial in women with estrogen-dependent neoplasia (eg, breast, endometrial). Comanagement with the woman's oncologist may be considered in the case of estrogen-dependent neoplasia. The role of low-dose vaginal ET in women at increased risk of thrombosis has not been studied.

Ospemifene

Ospemifene is the only SERM approved in the United States for treatment of moderate to severe dyspareunia (Table 3). It is a SERM with unique vaginal effects. Two studies of 12 weeks' duration showed improvement in VMI, vaginal pH, and most bothersome symptom of vaginal dryness with daily use of ospemifene 60 mg orally.^{127,128} A 52-week efficacy and safety extension study showed sustained improvements on visual examination of the vagina with no cases of VTE, endometrial hyperplasia, or carcinoma in this small group of women (n = 180) aged 46 to 79 years.¹²⁹ Vasomotor symptoms were the most common adverse event, with rates of 2% in the placebo group and 7.2% in the group taking 60 mg of ospemifene.

The prescribing information for ospemifene contains precautions similar to those listed for estrogens and other SERMs, such as class labeling for risk of VTE.¹³⁰ With regard to breast cancer, it is stated that ospemifene should not be used in women with breast cancer or at high risk for breast cancer because the drug has not been adequately studied in that group. Ospemifene has, however, demonstrated antiestrogenic activity in preclinical models of breast cancer.¹³¹ Data in women with or at risk for breast cancer are lacking.

Investigational and off-label therapies

Raloxifene is a SERM that appears to have no estrogen-agonist effect on the vagina.¹³²⁻¹³⁵ Two randomized, controlled trials demonstrated safe use with vaginal estrogen^{135,136} but not with systemic estrogen because of small increases in endometrial hyperplasia.¹³⁷ Tamoxifen exerts an estrogen-agonist effect in the uterus and vagina, but it is not under consideration as a therapy for VVA.^{124,128} One adverse effect of tamoxifen related to QOL is bothersome or worse vaginal discharge.¹³⁸

Lasofoxifene

In postmenopausal women with osteoporosis, lasofoxifene produced significant improvements in vaginal pH and VMI

at 6 months compared with placebo, whereas raloxifene was not found to improve vaginal pH or VMI.¹⁴⁰ In a separate trial, lasofoxifene was found to reduce substantially the incidence of breast cancer (hazard ratio, 0.21; 95% CI, 0.08-0.55).¹⁴¹

A 6-month randomized, controlled trial of 387 postmenopausal women with VVA reported reduced symptoms associated with sexual intercourse.¹⁴² Despite several trials suggesting that lasofoxifene improved VVA, clinical development in the United States is on hold.

Bazedoxifene and conjugated estrogens

The combination of bazedoxifene (BZA) and CE has been designated a tissue-selective estrogen complex (TSEC). Vaginal effects of BZA/CE were evaluated in 2 large clinical trials in which BZA 20 mg/CE (0.45 mg or 0.625 mg) demonstrated significantly improved measures of VVA, with rates of endometrial hyperplasia similar to placebo.

In the first trial, 2 doses of BZA (10 mg/d or 20 mg/d) combined with 2 doses of CE (0.45 mg/d or 0.625 mg/d) were found to improve VMI compared with placebo.¹⁴³ In the second 12-week trial of postmenopausal women with moderate to severe VVA, BZA 20 mg with CE (0.625 mg/d and 0.45 mg/d) significantly improved VMI. BZA combined with the higher dose of CE (0.625 mg/d) improved vaginal pH and most bothersome symptoms. Both doses of CE (0.625 mg/d and 0.45 mg/d) combined with BZA improved vaginal dryness. BZA alone does not have positive vaginal effects.¹⁴⁴

Intravaginal DHEA

Dehydroepiandrosterone (DHEA) is an androgen derivative that is available in Canada by prescription only and available in the United States without a prescription as a "dietary supplement." It has been evaluated intravaginally for effectiveness in treating VVA and is thought to exert an effect through the androgen and estrogen receptors.¹⁴⁵ The 12-week trials showed improvements in VMI and vaginal pH at 2 doses—3.25 mg and 13 mg, once daily. It also significantly improved the most bothersome symptoms.¹⁴⁶ Further research is ongoing.

Testosterone

Testosterone cream was used in the past for treatment of vulvar lichen sclerosus, but a Cochrane review found it to be no better than placebo.¹⁴⁷ Testosterone has been used with estrogen cream by some clinicians in the treatment of provoked vestibulodynia, but clinical trial data are lacking. 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 vaginal maturation index without increasing estradiol; median testosterone level increased from 15.5 ng/dL to 21.5 ng/dL (P = 0.02).¹⁴⁸ Existing clinical trial data are insufficient to recommend the use of vaginal testosterone for VVA at this time. Longer and larger studies are needed to assess safety and efficacy of topical testosterone.¹⁴⁹

TABLE 3. Other medical therapies considered for VVA or dyspareunia

Name	Category	Route	Clinical phase
Lasofoxifene	SERM	Oral	Approved in EU, not US
BZA/CE	TSEC	Oral	Phase 3
DHEA	Prohormone	Vaginal	Phase 3
Testosterone	Hormone	Vaginal	None

Abbreviations: BZA/CE, bazedoxifene/conjugated estrogens; DHEA, dehydroepiandrosterone; SERM, selective estrogen-receptor modulator; TSEC, tissue-selective estrogen complex; VVA, vulvovaginal atrophy. Adapted from Chollet JA.¹³⁹

PROACTIVE EDUCATION

Data are lacking about the value of proactively educating women about potential vaginal changes that can occur in a low-estrogen state. Many sexually active women are unaware of the effect these changes can have on the vagina in the absence of sexual activity. Because the changes occur gradually and often without symptoms in the sexually abstinent, women may be very distressed when later attempts at sexual intercourse are very uncomfortable or even impossible because of progressive VVA and vaginal stenosis.

Clinicians should discuss the concept of preserving sexual function for postmenopausal women. Women with a sexual partner should be informed that regular sexual activity/intercourse or other vaginal stimulation helps to maintain vaginal health and increase the likelihood that sexual activity will remain comfortable in the future. For women without a sexual partner, information can be given on the use of vaginal dilators and vibrators as a means of maintaining vaginal function. Postmenopausal women may benefit from the use of lubricants with sexual activity and regular use of vaginal moisturizers. Although it is likely that regular use of low-dose vaginal ET will prevent the signs and symptoms of VVA, clinical trial data are available for treatment, not prevention.

CONCLUSIONS AND RECOMMENDATIONS

- First-line therapies for women with symptomatic VVA include nonhormonal lubricants with intercourse and, if indicated, regular use of long-acting vaginal moisturizers. [Level A]
- For symptomatic women with moderate to severe VVA and for those with milder VVA who do not respond to lubricants and moisturizers, estrogen therapy either vaginally at low dose or systemically remains the therapeutic standard. Low-dose vaginal estrogen is preferred when VVA is the only menopausal symptom. [Level A]
- Ospemifene is another option for dyspareunia. [Level A]
- For women with a history of breast or endometrial cancer, management depends on a woman’s preference, need, understanding of potential risks, and consultation with her oncologist. [Level C]
- Estrogen therapy carries a class effect risk of VTE. Low-dose vaginal estrogen may carry a very low risk, but there has been no report of an increased risk in the vaginal estrogen clinical trials. Data in high-risk women are lacking. [Level C]
- A progestogen is generally not indicated when low-dose vaginal estrogen is administered for symptomatic VVA. Endometrial safety data are not available for use longer than 1 year. [Level B]
- If a woman is at high risk of endometrial cancer or is using a higher dose of vaginal ET, transvaginal ultrasound or intermittent progestogen therapy may be considered. There

are insufficient data to recommend routine annual endometrial surveillance in asymptomatic women using vaginal ET. [Level C]

- Spotting or bleeding in a postmenopausal woman who has an intact uterus requires a thorough evaluation that may include transvaginal ultrasound and/or endometrial biopsy. [Level A]

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

- For women treated for non-hormone-dependent cancer, management of VVA is similar to that for women without a cancer history. [Level B]
- Vaginal ET or ospemifene, with appropriate clinical surveillance, can be continued as long as bothersome symptoms are present. [Level C]
- Proactive education on vaginal health is recommended for postmenopausal women. [Level C]

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