Vulvovaginal Atrophy

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On completion of this article, you should be able to (1) recognize the common symptoms and signs of vulvovaginal atrophy, (2) evaluate the role of tests used in its identification, and (3) recommend effective treatment options.

Vulvovaginal atrophy (VVA) is a common and underreported condition associated with decreased estrogenization of the vaginal tissue. Symptoms include dryness, irritation, soreness, and dyspareunia with urinary frequency, urgency, and urge incontinence. It can occur at any time in a woman's life cycle, although more commonly in the postmenopausal phase, during which the prevalence is close to 50%. Clinical findings include the presence of pale and dry vulvovaginal mucosa with petechiae. Vaginal rugae disappear, and the cervix may become flush with the vaginal wall. A vaginal pH of 4.6 or more supports the diagnosis of VVA. Even while taking systemic estrogen, 10% to 20% of women may still have residual VVA symptoms. Breast cancer treatment increases the prevalence of VVA because the surgical, endocrine, and chemotherapeutic agents used in its treatment can cause or exacerbate VVA. Local estrogen treatment for this group of women remains controversial.

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AI = aromatase inhibitor; CI = confidence interval; ER = estrogen receptor; HT = hormone therapy; SERM = selective ER modulator; VMI = vaginal maturation index; VVA = vulvovaginal atrophy

Vulvovaginal atrophy (VVA) is a common condition, especially in postmenopausal women. Vaginal atrophy, atrophic vaginitis, and urogenital atrophy are other terms used to describe this constellation of symptoms associated with decreased estrogenization of the vulvovaginal tissue. Although treatment with topical estrogen is effective in alleviating symptoms, women frequently do not report symptoms and thus go untreated.[1,2]

Common symptoms include vaginal dryness, irritation, postcoital bleeding, and soreness. These symptoms may be associated with vaginal discharge and dyspareunia. Urinary symptoms associated with VVA include frequency, urgency, and urge incontinence.

PREVALENCE

Vulvovaginal atrophy can occur at any time in a woman's life cycle, although it is more common in the postmenopausal phase, a time of hypoestrogenism. Other causes of a hypoestrogenic state include lactation, various breast cancer treatments, and use of certain medications. In situations other than menopause, VVA may resolve spontaneously when estrogen levels are restored.

Numerous retrospective studies have evaluated the prevalence of symptoms of VVA (Table 1).[3-10] Although these studies differ in type of symptoms elicited, study design, and study population, they provide a range of estimates of VVA prevalence. They all used self-reported symptoms of vaginal dryness to determine the prevalence of VVA. In general, the prevalence ranged from about 4% in the early premenopausal groups to 47% in the late postmenopausal group.

The prevalence of VVA in some subgroups of women can be much higher. In a cohort of breast cancer survivors, vaginal dryness was present in 23.4% of the premenopausal patients and in 61.5% of the postmenopausal patients.[8]

PHYSIOLOGY

Vulvovaginal atrophy occurs under conditions of hypoestrogenism. In the premenopausal state, estradiol levels fluctuate from 10 to 800 pg/mL (to convert to pmol/L, multiply by 3.671),[11] depending on when measured during the cycle. In the postmenopausal state, estradiol levels are typically less than 30 pg/mL. After menopause, circulating estradiol derives from estrone, which is peripherally converted in adipose tissue from adrenal androstenedione.

The vaginal epithelium is a stratified squamous epithelium, which until menopause is moist and thick with rugae. At menopause, with declining levels of estrogen, the vaginal epithelium thins. Fewer epithelial cells result in less exfoliation of cells into the vagina. As epithelial cells exfoliate and die, they release glycogen, which is hydrolyzed to glucose. Glucose, in turn, is broken down into lactic acid by the action of lactobacillus, a normal vaginal commensal organism. Without this cascade, the pH in the vagina rises, resulting in a loss of lactobacilli and an overgrowth of other bacteria, including group B streptococcus, staphylococci, coliforms, and diphtheroids[12] (Figure 1). These bacteria can cause symptomatic vaginal infections and inflammation. After menopause, the elasticity of the vagina

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TABLE 1. **Studies Assessing Prevalence of Vaginal Dryness**

Country, reference	Year(s) of accrual	Age range (y)	No. studied	Population studied	Patients reporting vaginal dryness (%)	
Sweden, Iosif & Bekassy[3]	1984	61	900	Community cross-sectional survey	38	
Australia, Dennerstein et al[4]	1991	45-55	438	Community longitudinal survey	4	Early perimenopausal
					47	Late postmenopausal
Sweden, Stadberg et al[5]	1992	46-62	4552	Community cross-sectional survey	21	
United States, "SWAN," Gold et al[6]	1995-1997	40-55	16,065	Community cross-sectional survey	8.6	Aged 40-43 y,
					19.8	Aged 52-55 y
United States, Wilbur et al[7]	Published 1997	35-69	153	Employment-based symptom survey	29	
United States, Crandall et al[8a]	Published 2004	30-62	476	Tumor registry cohort of breast cancer survivors	23	Premenopausal
					26	Perimenopausal
					61	Postmenopausal
United States, Williams et al[9]	2005	40-65	4402	Population-based cross-sectional survey	7.6	Perimenopausal
					7.3	Postmenopausal
10 countries, including United States, Cella et al[10b]	1996-2000	65	682	Clinical trial of adjuvant treatments for breast cancer survivors	18.5	Anastrazole
					9.1	Tamoxifen

[a] In this study, 38% of patients had taken tamoxifen in the past, 19% were currently taking tamoxifen, and 64% had taken tamoxifen and had received chemotherapy.
[b] This study compared quality of life in patient groups taking tamoxifen (n=347) and anastrazole (n=335).

is reduced and connective tissue increases.[13] A decline in estrogen level causes a decrease in vaginal blood flow and a decrease in vaginal lubrication. These changes can be reversed by the use of estrogens.[14,15]

The effects of endogenous estrogens on vulvovaginal tissues are mediated through estrogen receptors (ERs) α and β, found at sites throughout the urogenital area, including the vagina, vulva, labia, urethra, and bladder trigone. These sites, in turn, regulate transcription at specific areas on the DNA.[16]

SYMPTOMS

The initial symptom is often lack of lubrication during intercourse. Eventually, persistent vaginal dryness may occur. Thinning of the epithelial lining may also cause pruritus, soreness, and a stinging pain in the vaginal and vulvar area, which, in turn, may further contribute to dyspareunia. Vaginal spotting, due to small tears in the vaginal epithelium, may also occur. Women with VVA may report a thin yellow or grey watery discharge secondary to the rise in pH that accompanies VVA.[17]

Women with VVA often report symptoms such as urgency, frequency, nocturia, and urge incontinence. Urinalysis may show microscopic hematuria. Recurrent urinary tract infections can also result. Stress incontinence is commonly found in this age group of women, but current evidence suggests it is not directly attributable to VVA.[18]

Women do not always report their symptoms of VVA. They are more likely to report vaginal discharge and urinary urgency but are less likely to report vaginal itching, soreness, or dyspareunia. Women may not report symptoms because they are self-treating, feel the symptoms are not important enough, or are embarassed.[19]

CLINICAL FINDINGS

Clinical findings include atrophy of the labia majora and vaginal introitus. The labia minora may recede. Vulvar and

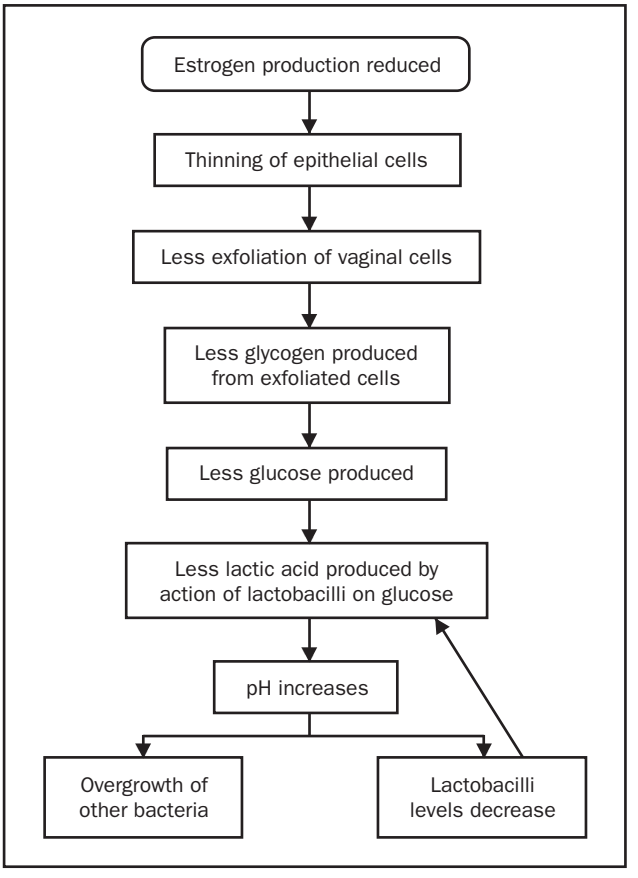

FIGURE 1. Proposed cascade-of-effects mechanism for vulvovaginal atrophy.

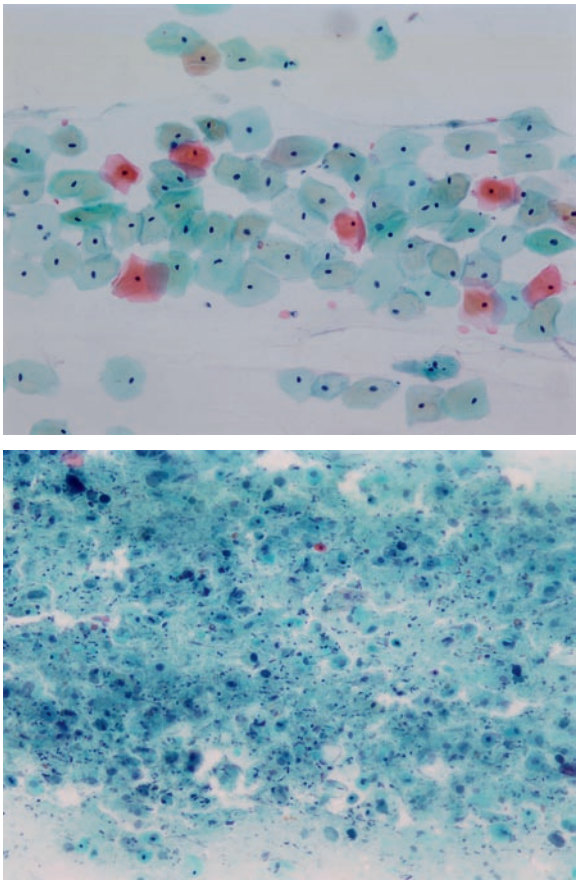

FIGURE 2. Photomicrographs of superficial and intermediate cells (top) and atrophic cells (bottom). (Papanicolaou stain; original magnification x20). Courtesy of the Mayo Cytopathology Laboratory.

vaginal mucosae may appear pale, shiny, and dry; if there is inflammation, they may appear reddened or pale with petechiae. Vaginal rugae disappear, and the cervix may become flush with the vaginal wall. Vaginal shortening and narrowing tend to occur.[20]

A thin watery yellow vaginal discharge may be observed. A urethral caruncle, a small, soft, smooth friable red outgrowth along the edge of the urethra, may develop.

CLINICAL TESTS

The diagnosis of VVA is a clinical one. However, 2 tests may be used to support the diagnosis: a vaginal pH and a vaginal maturation index (VMI). To assess pH, a piece of litmus paper is placed on the lateral vaginal wall until moistened. A pH of 4.6 or greater indicates VVA, assuming the patient does not have bacterial vaginosis. Premenopausal women without VVA typically have a pH of 4.5 or less.[12]

The VMI (Figure 2) is the criterion standard for VVA confirmation but is generally not used or needed in clinical practice. This test assesses the relative proportion of parabasal, intermediate, and superficial vaginal epithelial cell types. In premenopausal women, greater than 15% superficial cells would be considered normal; however, in postmenopausal women with VVA, the typical proportion would be less than 5%.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other conditions that cause chronic vaginal and vulvar itching, discharge, or pain (eg, vaginal infections, irritants, and vulvovaginal dermatoses). Vaginal infections can be caused by bacteria, viruses, protozoa, and fungi. The 3 most common vaginal infections are *Candida* vulvovaginitis, bacterial vaginosis, and trichomoniasis. Bacterial vaginosis may result from atrophic changes in the vagina. Irritants that can cause chronic vaginal itch include perfumes, any locally applied lubricant or moisturizer, and soaps. Vulvovaginal dermatoses, including lichen sclerosus, lichen planus, and lichen simplex chronicus, may cause similar symptoms.[21] Cancer and precancerous lesions, including vulvar intraepithelial neoplasm, vulvar cancer, and extramammary Paget disease, are in the differential diagnosis of any localized areas of redness, thickening, or ulceration (Table 2). Biopsy should be performed if a malignancy is suspected or if the diagnosis is unclear.

TREATMENT

Nonhormonal Treatments

Current over-the-counter treatments include nonhormonal vaginal moisturizers for VVA symptoms and lubricants for

TABLE 2. **Differential Diagnosis for Symptoms of Vulvovaginal Atrophy**

Lesion	Appearance
Lichen sclerosis	Hypopigmented, crinkled, waxy-appearing tissue, with coalescing ivory and pink plaques, often in butterfly or figure-of-eight pattern involving labia majora and minora and clitoral hood and extending around anus; may result in labial agglutination
Lichen planus	Painful, red plaques or erosions, variably with white lacy edges or violaceous borders; may extend into vagina
Lichen simplex chronicus (hyperkeratosis)	Thick, lichenified skin, often erythematous, caused by long-term rubbing or scratching
Contact dermatitis (irritant or allergic)	Redness, swelling, and itching, sometimes with blistering and painful, bright red swelling
Vulvar intraepithelial neoplasm	Red, white, or dark raised or eroded lesions, multifocal
Vulvar cancer	Commonly solitary ulcer with raised or indurated edge
Extramammary Paget disease	Brick red, scaly, eczematoid plaque with sharply demarcated border and sometimes a roughened surface

dyspareunia. Vaginal moisturizers, which are water based, are available as liquids, gels, or ovules inserted every few days. Vaginal moisturizers can be safely used long term, but they need to be used regularly for optimal effect.

Vaginal lubricants are shorter acting than moisturizers and are applied at the time of sexual activity to reduce dyspareunia. They can be either water or silicone based, with the water-based products being the most widely available. They are applied to the vaginal opening and/or to the penis and often require repeated application during sexual activity. Silicone-based lubricants require application of only a very small amount and last longer; however, they can interfere with erectile function in male partners. The choice of lubricant may depend on individual preferences and product availability.

Hormonal Treatments

On the basis of an evidence-based review of clinical trials examining available low-dose vaginal estrogen preparations for the treatment of VVA in postmenopausal women, The North American Menopause Society (NAMS) 2007 position statement noted that "the choice of therapy should be guided by clinical experience and patient preference."[22] NAMS also stated it is generally unnecessary to prescribe a progestogen in combination with low-dose vaginal estrogen to prevent endometrial hyperplasia or cancer.

On the basis of a meta-analysis of 19 randomized clinical trials involving 4162 postmenopausal women, the 2006 Cochrane Database of Systematic Reviews concluded that vaginal estrogen is an effective treatment for VVA[23] and that all forms, whether cream, ring, or tablet, appeared to relieve symptoms more effectively than nonhormonal gels and placebo. Differences observed between the treatments were in participant preferences.

Therefore, for symptomatic vaginal atrophy that does not respond to self-care measures, estrogen treatment is the standard of care, typically with vaginally administered local estrogens. Prescription vaginal estrogens are available as either estradiol or conjugated estrogens. In some countries outside the United States, vaginal estriol is also available.

SYSTEMIC ABSORPTION OF VAGINAL HORMONAL PREPARATIONS

An important concern about treatment safety relates to the extent of systemic absorption of vaginal estrogens. The conclusion from several studies comparing different doses of estradiol vaginal tablets[24,25] or different vaginal estrogen preparations (conjugated estrogens and estradiol vaginal tablets)[26] is that systemic absorption occurs, but to a limited extent. Labrie et al[26] showed that levels of estradiol increased on average from a baseline (pretreatment) level of 3 pg/mL to 17 pg/mL on day 7 of treatment for both estradiol vaginal tablets (25 μg) and conjugated estrogen cream (0.625 mg). Nilsson and Heimer[24] showed that, although plasma estradiol concentration diminished by the 14th day of daily treatment with 10 or 25 μg of vaginal estradiol, it was still statistically significantly higher than pretreatment levels. Some evidence shows that estradiol levels diminish over time when vaginal estrogens are used consistently.[24,25]

Although vaginal estrogens applied as a cream, vaginal tablets, or a low-dose vaginal ring are systemically absorbed, the rise in serum estrogen levels appears to remain well below premenopausal levels. Nonetheless, this may be of concern to women with a history of breast or other hormonally sensitive cancers

PRACTICAL ISSUES

Because all low-dose vaginal estrogens appear comparable in efficacy for the treatment of VVA, the choice of estrogen formulation is determined by the clinician and by each woman's preferences. Estrogen creams are currently the least costly and most widely used but require commitment to regular use for sustained effect. Dosing vaginal creams can be confusing because the dose of active estrogen cream is specified in milligrams, the dose of base cream in grams, and applicator volume in proportions. A simplified approach to dosing is provided in Table 3. The estradiol tablet is preferred by some to avoid the messiness of cream. The estradiol ring is long acting and requires less sustained effort to use; however, it requires dexterity to insert and remove and needs to be replaced every 3 months. The presence of a cystocele or rectocele may cause ring displacement.

SYSTEMIC ESTROGEN AGENTS AND VVA

Systemic estrogen therapy, in the form of patches, oral agents, or a higher-dose vaginal ring, is sometimes used for VVA, especially when the patient also has hot flashes. However, 10% to 20% of women may have residual VVA symptoms even while taking systemic estrogen.[27] These women will require administration of local vaginal estrogens alone or along with systemic therapy for relief of VVA symptoms.

Two studies have shown that oral hormone therapy (HT) may worsen symptoms of urinary incontinence. The Heart and Estrogen-Progestin Replacement Study found a higher risk of both urge (odds ratio, 1.5; 95% confidence interval [CI], 1.2-1.8; $P<.001$) and stress incontinence (odds ratio, 1.7; 95% CI, 1.5-2.1; $P<.001$) in the hormone-treated group vs the placebo group throughout the treatment period.[28]

It has been suggested that urge incontinence worsened with HT because progesterone was a component. How-

TABLE 3. **Vaginal Estrogen Products**

Product type	Generic name of active component	Strength	Treatment[a]	Advantages	Disadvantages
Vaginal cream	Estradiol	0.1 mg (100 μg)/g of cream; 1 g = ¼ applicator	¼ to ½ applicator twice weekly	Lower in cost, flexible in dosing	Managing and cleaning applicator frequently
Vaginal cream	Conjugated estrogens	0.625 mg (625 μg)/g of cream; 1 g = ½ applicator	¼ to ½ applicator twice weekly	Lower in cost, flexible in dosing	Managing and cleaning applicator frequently
Vaginal tablets/ ovules	Estradiol	25 μg	Insert twice weekly	Less messy	Higher in cost, requires regular applications
Vaginal ring	Estradiol	7.5 μg/24 h	Replace every 90 d	Convenience (lasts 90 d)	Cost and acceptance of intravaginal device

[a] Cream or tablet can be administered daily for the first 2 wk.

ever, in the Women's Health Initiative, 3 treatment groups were evaluated for urge incontinence (conjugated estrogens alone, conjugated estrogens with progesterone, and placebo). Women given conjugated estrogens alone were at increased risk of developing urge incontinence compared with those receiving placebo (relative risk, 1.32; 95% CI, 1.10-1.58), whereas the women given combination conjugated estrogens with progesterone were not (relative risk, 1.15; 95% CI, 0.99-1.34).[29] Thus, whether oral HT adversely affects urge urinary incontinence remains unclear.

BREAST CANCER AND VVA

Currently, more than 2 million women in the United States have a history of breast cancer. In breast cancer survivors, the estimated prevalence of vaginal atrophy, by symptom report, ranges from 23% to 61%.[8] Prescribing even very low-dose localized estrogen treatments for these patients can cause concern because of the potential for systemic absorption.

Concern about the provision of any form of estrogen, either systemic or local, to breast cancer survivors contributes to the high incidence of VVA in women with breast cancer. Discontinuation of HT may trigger the onset of VVA symptoms.

Many surgical, endocrine, and chemotherapeutic treatments for breast cancer can cause or exacerbate VVA.[10,30-37] Tamoxifen acts as an estrogen antagonist or agonist depending on the target organ and menopausal status. In premenopausal women, tamoxifen may cause VVA by acting as an estrogen antagonist and blocking the naturally high levels of endogenous estrogen. In postmenopausal women, however, it acts as an estrogen agonist on the urogenital tract.[38]

Raloxifene does not appear to have an effect on the urogenital area in either premenopausal or postmenopausal women. Davies et al[35] found no significant differences in incidence of VVA when comparing databases of postmenopausal women treated with raloxifene vs placebo.

Aromatase inhibitors (AIs) are prescribed as adjuvant systemic therapy to women with ER^+ breast cancer. In the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study, designed to compare outcomes in postmenopausal breast cancer survivors taking tamoxifen, anastrozole (an AI), or a combination of both, Cella et al[10] demonstrated that vaginal dryness was more common in the group taking anastrozole than in the group taking tamoxifen (18.5% vs 9.1%). Dyspareunia was also more common in the anastrozole group (17.3% vs 8.1%).[10]

Chemotherapy itself can result in vaginal dryness and dyspareunia. In a randomized clinical trial comparing high-dose chemotherapy with standard-dose chemotherapy for breast cancer survivors, followed by radiotherapy and tamoxifen in all patients, more patients in the high-dose chemotherapy group experienced persistent vaginal dryness.[37]

Chemotherapeutic agents used in the treatment of breast cancer can also cause VVA because of chemotherapy-induced ovarian failure. Premenopausal women account for 25% of all diagnosed breast cancer cases and are more likely to need systemic chemotherapy. The risk of permanent chemotherapy-induced ovarian failure is more common in women older than 40 years (49%-100%) than in those younger than 40 years (21%-71%).[39]

Premenopausal women with hormone-sensitive (ER^+) advanced breast cancer may be offered gonadotropin-releasing hormone agonists to induce a temporary menopause through suppression of ovarian function, with VVA as a potential adverse effect.[40] High-risk premenopausal women who are *BRCA1*/2^+ sometimes choose bilateral oophorectomy, which in turn increases their likelihood of developing VVA.

Whether breast cancer survivors with VVA can be safely treated with low-dose vaginal estrogens remains controversial. Kendall et al[41] addressed this question when they followed up 7 breast cancer survivors taking AIs to suppress estrogen levels. These women took 25-μg vaginal tablets of estradiol daily for 2 weeks and then twice weekly for severe symptoms of VVA. After 2 weeks of treatment, mean serum estradiol levels increased from a pretreatment value of 1.4 pg/mL or less to 19.6 pg/mL. The estrogen levels had decreased to less than 9.5 pg/mL by 4 weeks of therapy in

most women, but only 2 women had pretreatment estradiol levels at week 7. If third-generation AIs decrease the levels of circulating estrogens more than earlier-generation AIs and at the same time improve survival, Kendall et al[41] hypothesized that a small increase in circulating estradiol could worsen survival outcomes.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medicine products have been extensively studied in the treatment of hot flashes, but less information is available on their use in VVA. One study found that Vitamin E and phytoestrogen applied locally as a gel improved the symptoms of VVA.[42] An evaluation of VVA was undertaken in a cross-sectional study of 60 women, half of whom had taken 1,25-dihydroxyvitamin D (0.5 μg/d of calcitriol) orally for at least 1 year and half of whom had not. The prevalence of vaginal atrophy was significantly higher in the group who did not use vitamin D, as measured by VMI and symptoms.[43]

In a separate study, soy supplementation for the treatment of VVA was investigated. Phytoestrogens such as soy bind to ERs in the vagina and bladder. A randomized controlled trial evaluating dietary supplementation with 12 to 20 mg/d of soy showed no improvement in VMI.[44]

Currently, well-established effective complementary and alternative medicine treatments for VVA are lacking.

FUTURE STUDIES

Future studies will continue to explore the use of even lower doses of vaginal estrogens. The efficacy and safety of 10-μg vaginal tablets of low-dose estradiol for the treatment of VVA were evaluated in a 2009 study; after 12 weeks of therapy, significant improvements in symptoms, pH, and VMI were observed, with no adverse effects.[45] In a recent study comparing treatment with 25 μg of estradiol, 10 μg of estradiol, and placebo, Bachmann et al[46] found that both active groups experienced improvement in vaginal atrophy symptoms, vaginal pH, and VMI, with greater improvements seen for the higher dose.

Interest in vaginal estriol products is strong because of the inverse relationship with breast cancer risk at a population level. Studies have shown that estriol improves symptoms of VVA and reduces the incidence of urinary tract infection. Exogenous estriol administration does not alter serum estradiol or follicle-stimulating hormone levels.[47-50]

Studies are currently under way to evaluate newer selective ER modulators (SERMs), which specifically target urovaginal health without compromising breast health.[51]

Because moisturizers and lubricants also play a role in the treatment of VVA, better delivery systems for these nonhormonal vaginal treatments will likely be developed in the future.

CONCLUSION

Vulvovaginal atrophy, a common and often underreported condition, occurs in women who experience hypoestrogenic states. Systemic treatment, when prescribed for menopausal symptoms, may not be sufficient to control VVA. Local estrogens include creams, tablets, and rings, all of which are equally effective. Thus, patient preference will guide the choice. A growing number of women are at risk of developing VVA because of decreased use of systemic HT and increased use of SERMs, AIs, and chemotherapy in women with a history of breast cancer, for whom the safety of even low-dose vaginal estrogens has not been established.

Future research on VVA will likely explore the use of much lower doses of vaginal estrogens, seek to develop newer delivery systems for nonhormonal therapy, and develop SERMs that preferentially target urogenital tissues.

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CME Questions About Vulvovaginal Atrophy

1. A 58-year-old woman, who has been taking oral hormone therapy (HT) for successful control of hot flashes and night sweats, reports vaginal itching, burning, and dyspareunia. Clinical examination reveals a pale shiny vulva and petechiae in the vagina, consistent with vulvovaginal atrophy (VVA).

   Which <u>one</u> of the following treatments would be <u>*most effective*</u> for managing this patient's symptoms?

   a. Increase her current dose of oral HT
   b. Decrease her current dose of oral HT, and recommend initiation of vaginal estrogen applied twice weekly and vaginal lubricant applied at time of intercourse
   c. Continue current dose of oral HT, and recommend initiation of vaginal estrogen applied twice weekly and vaginal lubricant applied at time of intercourse
   d. Substitute transdermal patch estrogen for oral estrogen and recommend initiation of vaginal lubricant applied at time of intercourse
   e. Continue current dose of oral HT and advise use of vaginal lubricant at time of intercourse

2. A 65-year-old postmenopausal woman who is not taking HT therapy reports new-onset vaginal itching, burning, and dyspareunia. Clinical examination reveals a generalized pale shiny vulva and a white raised area on the vulva.
   Which *one* of the following would be the *best* recommendation for this patient?
   a. Apply low-dose estrogen cream to the vulvovaginal area
   b. Apply low-dose estrogen cream to the vulvovaginal area and hydrocortisone cream to the whitened area
   c. Apply hydrocortisone cream to the whitened area
   d. Perform biopsy of the whitened area
   e. Administer 1 dose of fluconazole (150 mg) orally, followed by application of low-dose estrogen cream to the vulvovaginal area

3. A 58-year-old woman, who has been taking oral HT for successful control of hot flashes and night sweats, reports vaginal itching, burning, and dyspareunia. Clinical examination reveals a pale shiny vulva and petechiae in the vagina, consistent with VVA.
   Which *one* of the following tests is *necessary* to make the diagnosis?
   a. pH of the vaginal mucosa
   b. No test required
   c. Urinalysis
   d. Vaginal maturation index (VMI)
   e. Vaginal culture

4. Which *one* of the following is *not* associated with VVA?
   a. Lactation
   b. Premenopausal use of tamoxifen
   c. Postmenopausal use of tamoxifen
   d. Premenopausal use of chemotherapeutic agents
   e. Postmenopausal use of chemotherapeutic agents

5. Which *one* of the following medications would be *most likely* to cause VVA in a postmenopausal woman?
   a. Raloxifene
   b. Tamoxifen
   c. Exemestane
   d. Systemic estradiol
   e. Medroxyprogesterone

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