

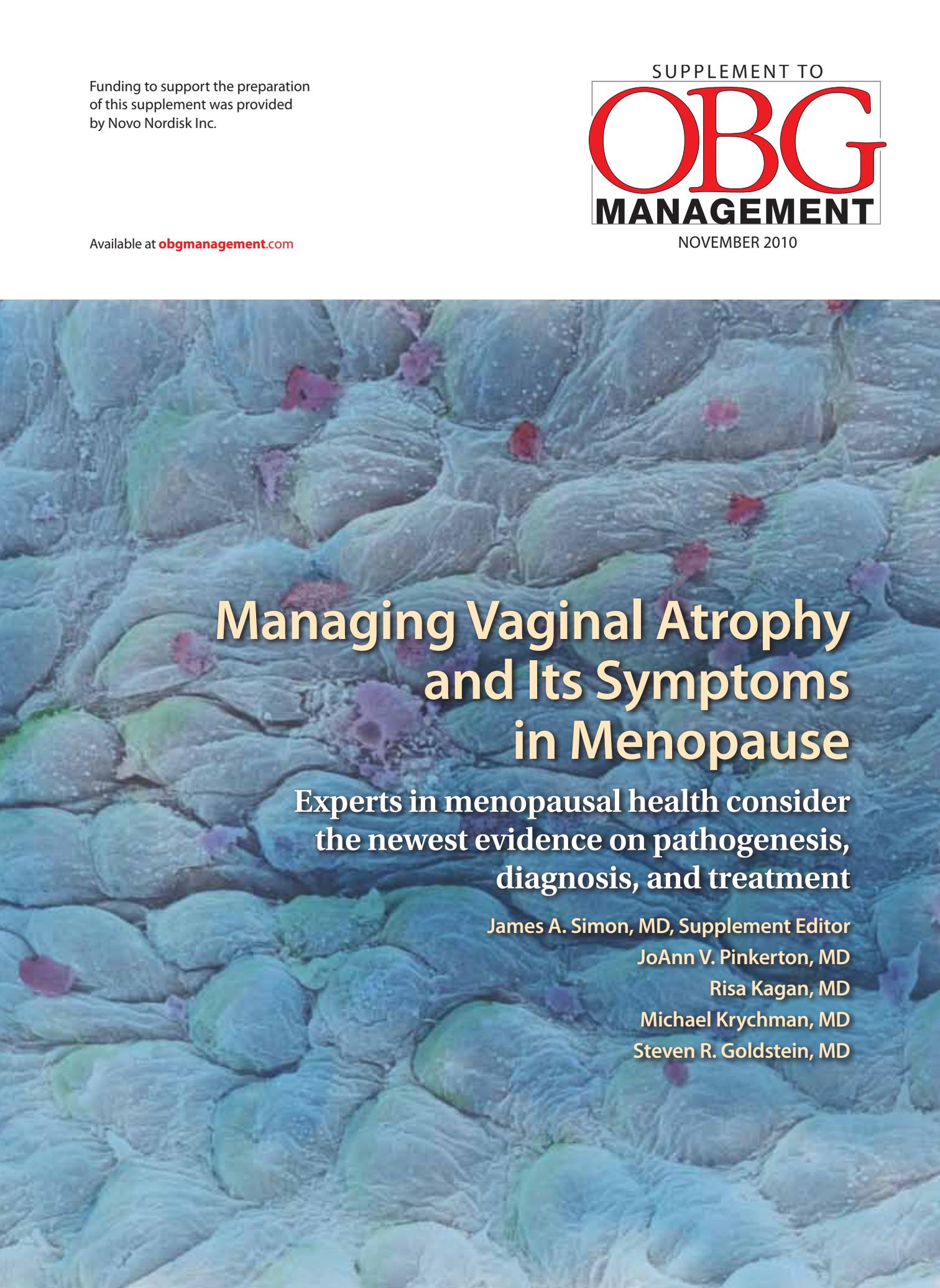
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Managing Vaginal Atrophy and Its Symptoms in Menopause

Experts in menopausal health consider the newest evidence on pathogenesis, diagnosis, and treatment

James A. Simon, MD, Supplement Editor

JoAnn V. Pinkerton, MD

Risa Kagan, MD

Michael Krychman, MD

Steven R. Goldstein, MD



Managing Vaginal Atrophy and its Symptoms in Menopause

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James A. Simon, MD, Supplement Editor

Clinical Professor, Department of Obstetrics and Gynecology
George Washington University
Medical Director, Women's Health & Research Consultants
Washington, DC

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JoAnn V. Pinkerton, MD

Professor, Department of Obstetrics and Gynecology
Director, The Women's Place Midlife Health Center
University of Virginia Health System
Charlottesville, Va

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Risa Kagan, MD

Clinical Professor, Department of Obstetrics and Gynecology
and Reproductive Sciences
University of California, San Francisco
East Bay Physicians Medical Group
Affiliated with Sutter East Bay Medical Foundation
Berkeley, Calif

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Michael Krychman, MD

Executive Director, the Southern California Center
for Sexual Health and Survivorship Medicine
Newport Beach, Calif

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Steven R. Goldstein, MD

Professor, Department of Obstetrics and Gynecology
New York University School of Medicine
Director, Gynecologic Ultrasound
Co-Director, Bone Densitometry
New York University Medical Center
New York, NY

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Introduction

James A. Simon, MD

Only 20% to 25% of women who experience symptoms of vaginal atrophy will seek treatment for them, despite the availability of safe and effective treatment options

The female vaginal tract relies on estrogen stimulation to maintain normal structure and function. After menopause, estrogen deficiency results in vaginal atrophy and its manifestations, including vaginal dryness, irritation, and burning; dyspareunia; and an increased risk of urinary tract infections. These symptoms and disorders are common, progressive, and unlikely to resolve without treatment. However, only 20% to 25% of women who experience these symptoms will ultimately seek treatment for them,^{1,2} despite the availability of safe and effective treatment options, including local low-dose vaginal estrogen therapy.

DISCLOSURE

The author is a consultant for Abbott, Allergan, Alliance for Better Bone Health, Amgen, Ascend Therapeutics, Azur Pharma, Bayer, BioSante, Boehringer Ingelheim, Concert Pharmaceuticals, Corcept Therapeutics, Depomed, Fabre-Kramer, GlaxoSmithKline, Graceway Pharmaceuticals, KV, Laboratoire HRA Pharma, Lipocine, Meditrina Pharmaceuticals, Merck, Merrion Pharmaceuticals, Nanma/Tripharma/Trinity, NDA Partners, Novo Nordisk, Novogyne, Pear Tree Pharmaceuticals, QuatRx Pharmaceuticals, Roche, Schering-Plough, Sciele, Solvay, Teva, Ther-Rx, Warner Chilcott, and Wyeth; receives grants/research support from Bio-Sante, Boehringer Ingelheim, FemmePharma, GlaxoSmithKline, Nanma/Tripharma/Trinity, Novartis, Procter and Gamble, QuatRx Pharmaceuticals, and Teva; and is a speaker for Amgen, Ascend, Bayer, Boehringer Ingelheim, GlaxoSmithKline, KV, Merck, Novartis, Novogyne, Novo Nordisk, Sciele, Teva, Ther-Rx, Warner Chilcott, and Wyeth.

In this supplement to OBG MANAGEMENT, four experts in menopausal health consider the latest evidence on the pathogenesis, diagnosis, and treatment of vaginal atrophy and its symptoms. In the first article, JoAnn Pinkerton, MD, considers the epidemiology, pathogenesis, evaluation, and diagnosis of vaginal atrophy, and in the second article, Risa Kagan, MD, reviews the therapeutic options used to treat vaginal atrophy and its symptoms. Michael Krychman, MD, evaluates its impact on postmenopausal quality of life and sexuality in the third article, and, in the final article of the supplement, Steven R. Goldstein, MD, considers the safety and tolerability of low-dosage local vaginal estrogen therapy.

We hope the information contained in the supplement will be useful and will assist you in your efforts to recognize, diagnose, and manage vaginal atrophy and its symptoms in your patients.

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Vaginal impact of menopause-related estrogen deficiency

JoAnn V. Pinkerton, MD

KEY POINTS

- Vaginal atrophy associated with postmenopausal estrogen deficiency is a common, but under-recognized and undertreated disorder affecting 7% to 57% of postmenopausal women
- Although symptoms for an individual patient may vary, the most commonly reported symptoms include: vaginal dryness, itching, burning, inadequate lubrication during sexual activity, and pain with intercourse (dyspareunia)
- Vaginal atrophy symptoms can have an adverse effect on sexual functioning and quality of life
- Decreased estrogen stimulation following menopause reduces the glycogen content of vaginal epithelial cells leading to a fall in vaginal lactic acid. The resulting increased pH can undermine the patient's defense against vaginal and urinary tract pathogens
- Other disorders that can cause symptoms similar to those of vaginal atrophy include: infection, trauma, the presence of a foreign body, lichen sclerosis, benign and malignant tumors, other medical disorders (e.g., diabetes and lupus), and, potentially, psychological problems

Vaginal atrophy associated with postmenopausal estrogen deficiency is a common but under-recognized and undertreated disorder. Because the vagina and surrounding tissues require estrogen stimulation to maintain normal structure and function,¹ declines in estrogen levels—regardless of the cause—can result in vaginal atrophy and its associated symptoms, such as vaginal dry-

ness, itching, burning, and inadequate lubrication during sexual activity. Together, these symptoms can lead to dyspareunia, vaginitis, and vaginismus. Urinary symptoms associated with vaginal atrophy include increased frequency, urgency, and recurrent urinary tract infections, as well as urinary incontinence resulting from pelvic floor relaxation.

The urogenital system is exquisitely sensitive to estrogen loss because of the presence of estrogen receptors in the vagina, vulva, musculature of the pelvic floor, endopelvic fascia, urethra, and bladder.² Declines in estrogen concentrations associated with menopause can result in significant cytologic and structural changes in the vulva, vagina, and lower urinary tract; can prompt the development of vulvovaginal and urinary symptoms; and may contribute to symptoms of sexual dysfunction.^{3,4}

Other causes of vaginal atrophy related to estrogen deficiency include lactation, various treatments for breast cancer (e.g., aromatase inhibitors) and other gynecologic cancers, and the use of certain medications. However, vaginal atrophy and its symptoms may resolve with use of systemic or topical estrogen.

Symptoms of vaginal atrophy—which can range from annoying to very bothersome—can cause significant emotional distress, sexual dysfunction, and reductions in quality of life.⁵⁻⁸ Because these symptoms are often progressive and do not typically resolve without treatment, and women are living longer, untreated women may experience these symptoms for more than one third of their lives.⁵ Therefore, there is a clear need to reevaluate the symptoms of vaginal atrophy and its causes, and for a greater clinical focus on this disorder.

DISCLOSURE

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PREVALENCE OF VAGINAL ATROPHY AND ITS SYMPTOMS

VAGINAL ATROPHY. The prevalence of vaginal atrophy has been evaluated in numerous studies with varying results.⁹ Generally, the prevalence of vaginal atrophy has been reported to range from 7% to 57% in healthy peri- and postmenopausal women.⁹⁻¹¹ In observational studies, 27% to 55% of postmenopausal women reported vaginal dryness,^{5,11-13} and 19% reported irritation or itching.¹⁴

The prevalence of vaginal atrophy in certain populations, such as breast cancer survivors, is even higher. For example, in a 2004 study, 62% of postmenopausal breast cancer survivors reported vaginal dryness.¹⁵ More recent studies have demonstrated that current endocrine therapy for breast cancer has an even more profound impact on vaginal dryness during intercourse (73%).¹⁶ More than 20% of premenopausal breast cancer survivors also experienced these symptoms. Nearly one half of women who have breast cancer and are receiving endocrine therapy experience vaginal dryness, and one half of these patients have moderate or severe symptoms.¹⁶

SEXUAL DYSFUNCTION. According to a recent study, as many as 55% of sexually active postmenopausal women experience sexual dysfunction.¹⁰ Symptoms associated with vaginal atrophy have an adverse effect on sexual function and interest in sexual activity. For example, vaginal dryness has been associated with reduced sexual enjoyment in midlife women.¹⁷ Another study found that 39% of postmenopausal women experience difficulty with vaginal lubrication during sex.¹⁸

In women who have vaginal atrophy and who are sexually active, dyspareunia is frequently reported.¹⁸ Recent population-based prevalence studies of postmenopausal women not using hormone therapy have estimated that approximately 22% to 29% suffer from dyspareunia.¹⁹⁻²¹ In a 2009 study of women receiving endocrine therapy for breast cancer, 56% of sexually active women reported dyspareunia, and a very high percentage of patients

also have vaginal dryness during intercourse, as stated earlier.¹⁶

URINARY SYMPTOMS. Urinary symptoms associated with vaginal atrophy include urinary tract infection and urinary urgency and incontinence.^{22,23} About 20% of elderly women not institutionalized show evidence of bacteriuria and up to 17% experience recurrent urinary tract infection (UTI).^{24,25} Among women aged 60 years or older still living in the community, urinary incontinence affects approximately 15% to 35%.^{24,26} In women receiving endocrine therapy for breast cancer, 41% reported urinary urgency, 36% reported urinary incontinence, and 11% reported an increased frequency of urinary tract infection.¹⁶

ROLE OF ESTROGEN IN UROGENITAL HEALTH

Estrogen has numerous effects on urogenital tissues. In a recent study of RNA profiling of vaginal biopsies in women with postmenopausal vaginal atrophy after estrogen treatment, investigators reported that more than 3,000 genes are regulated by estrogen, including those involved in regulating cell growth, proliferation, and defense against infection.²⁷ Estrogen receptors are found not only in the vagina and vulva but also in the urethra and neck of the bladder.

In the vagina, estrogen causes a thickening of the vaginal epithelium, creating a redundant tissue layer. During sexual arousal, this redundancy allows the vaginal surface area to expand. The thickened vaginal epithelium, along with cervical mucous secretions and local bacterial flora, also act as physical barriers, preventing infection.

In addition, estrogen stimulation increases the glycogen content of vaginal epithelial cells. Glycogen is metabolized by organisms in the vagina to lactic acid, which acts to maintain the vaginal pH at about 3.5 to 4.5.^{28,29} This acidic pH is an important component of a woman's nonspecific defense against pathogens.²⁸⁻³⁰

In premenopausal women, estradiol levels typically fluctuate from 10 to 800 pg/mL, whereas circulating estradiol levels after

TABLE 1

Genital and urethral signs of vaginal atrophy^{34,35}

Genital signs	Urethral signs
Pale, smooth, or shiny vaginal epithelium	Urethral caruncle
Friable, unrugated epithelium	Eversion of urethral mucosa
Reduced elasticity or turgor of skin	Cystocele
Paucity of pubic hair	Urethral polyps
Dryness of labia	Ecchymoses
Fusion of labia minora	Minor lacerations at peri-introital and posterior fourchette
Introital stenosis	
Vulvar dermatoses	
Vulvar lesions	
Vulvar patch erythema	
Petechiae of epithelium	

Source: Adapted from Bachmann.³⁵

menopause are typically less than 30 pg/mL.³¹

Evidence suggests that the incidence of symptoms related to vaginal atrophy is associated with estrogen levels.³² In one study, women with lower serum estradiol levels (<50 pg/mL) had higher rates of vaginal dryness and dyspareunia compared with those with higher levels (>50 pg/mL).³²

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF VAGINAL ATROPHY

VAGINAL ATROPHY. In premenopausal women, intermediate and superficial cells predominate and few parabasal cells are observed in the vaginal epithelium.^{28,33} After menopause, cytologic changes in the vagina associated with estrogen deficiency are readily observed, including an increase in parabasal and intermediate cells and a large decrease in superficial cells.²⁸

Clinically, vaginal atrophy is characterized by thin, pale, dry, and possibly inflamed vaginal walls (TABLE 1).^{28,34,35} The vaginal walls

may exhibit petechiae, or non-raised, round, purple or red spots caused by intradermal or submucous hemorrhage.

Vaginal walls may become thinner, less elastic, and progressively smoother as vaginal rugation decreases. In addition, the vagina may shorten and narrow and become paler in color. If untreated, vaginal atrophy can result in a friable, ulcerated surface that may tear and bleed, often after the minimal trauma associated with intercourse or speculum insertion.

Similar changes in the vulva are observed. Losses in vulvar collagen, adipose tissue, and the ability to retain water are common and may cause the epithelial surface of the vulva to thin.^{5,36} In addition, the clitoral glans may lose its protective covering and be easily irritated from contact. Clitoral blood flow has been shown to be reduced in the presence of estrogen deficiency. Estrogen and androgen deficiency have been shown to be associated with reduced expression of sex steroid receptors and, most importantly, with attenuated genital blood flow and lubrication in response to stimulation.³⁷

SEXUAL DYSFUNCTION. Estrogen deficiency can impair vaginal function and impede the physiologic responses that characterize sexual arousal, such as smooth muscle relaxation, vasocongestion, and vaginal lubrication.^{1,5} Decreased blood flow, reduced vaginal secretions, and delayed onset of lubrication during sexual stimulation due to estrogen deficiency may contribute to sexual dysfunction observed in some postmenopausal women.^{1,11,28}

These changes, in addition to the structural and epithelial changes described above, increase the likelihood of trauma and pain during sex and can result in dyspareunia. The fear of pain caused by vaginal atrophy can reduce a woman’s genital and subjective sexual response or desire to have sex.³³ Spasm of the levator muscles may further increase pain with penetration leading to dyspareunia.³⁸

URINARY SYMPTOMS. After menopause, estrogen deficiency may result in disorders of the lower urinary tract. For example, a reduction in superficial epithelial cells in the vagina results in less

exfoliation of cells, reduced release of glycogen, and reduced conversion into lactic acid by the vaginal flora.⁹ These changes may increase the vaginal pH to 5 or greater (compared to 3.5 to 4.5) and may result in the cultivation of bacteria and the colonization of vagina by fecal flora. These bacteria can not only cause symptomatic vaginal changes and inflammation but also increase the risk of recurrent UTIs.

Postmenopausal estrogen-deficient atrophic changes within the urinary tract include atrophy in the urethral epithelium and decreased periurethral collagen,^{39,40} which may result in introitus narrowing and prolapse of the urethra (urethral caruncle) in advanced stages. Estrogen loss is also associated with a reduction in collagen content with atrophic changes in pelvic floor tissues. Therefore, postmenopausal estrogen deficiency may play a role in the development or progression of pelvic floor relaxation, stress incontinence, and pelvic organ prolapse.

EVALUATION

MEDICAL HISTORY. Although most cases of vaginal atrophy result from reductions in estrogen production, postmenopausal estrogen deficiency is not the only cause of atrophy-related symptoms.

One goal of taking the medical history in patients with these symptoms is to rule out other or additional causes of vaginal atrophy, such as other conditions associated with estrogen deficiency, the use of certain endocrine therapies, and medically induced menopause.

A second goal is to determine the patient's current sexual activity, status of the relationship with partner(s), history of treatments used, therapeutic goals, and the level of distress associated with the complaints.²⁸

Because patients may be reluctant to volunteer information about their vulvovaginal symptoms, clinicians should specifically ask postmenopausal patients about the presence and severity of these symptoms. For example, clinicians should ask patients if they are having vaginal dryness, pain with penetration, or pain either during or after intercourse.

"Most bothersome symptoms" and approval of efficacious treatments

To be approved by the FDA, new treatments for vulvovaginal atrophy are required to demonstrate efficacy in three areas: improvement in vaginal maturation; change in vaginal pH; and change in severity of the most bothersome vulvovaginal symptom, or MBS.⁴¹

The MBS is derived from a list of vaginal symptoms, including vaginal dryness, vulvovaginal irritation/itching, vulvovaginal soreness, and dyspareunia. At baseline, patients rate each symptom as not present, mild, moderate, or severe and select a single symptom among those classified as moderate or severe as the MBS. Changes in the MBS are tracked and can be used to evaluate improvement in vulvovaginal symptoms.⁴¹

In postmenopausal women with estrogen deficiency and vulvovaginal or urinary symptoms, evaluating the initial MBS and changes in MBS following treatment may help clinicians gain a better understanding of the overall severity of the disorder and impact of therapy.

COMPONENTS OF THE PHYSICAL EXAM. Clinicians should evaluate vaginal atrophy during the pelvic examination of postmenopausal patients, even in women who have not complained of vulvovaginal symptoms. Vaginal atrophy associated with estrogen deficiency can start during the perimenopausal years.

In women with early stages of vaginal atrophy, the vaginal epithelium may be thin, dry, and mildly erythematous.²⁸ As atrophy progresses, the tissues of the vulva become progressively pale, dry, and thin, and the vagina loses elasticity, shortens, and narrows. A thin, watery, yellow vaginal discharge may also be observed. There also may be tenderness to

Clinical pearls for evaluating vaginal atrophy

- In some patients who have severe vaginal atrophy, a unidigital examination may be more comfortable for patients
- When examining these patients, clinicians should consider pausing at the introitus to help patients relax their levator muscles, which can facilitate the exam
- In patients who have a small or narrow vaginal opening, using a forefinger to press down on the opening may facilitate speculum insertion
- Clinicians should slip the speculum right above the forefinger, using the forefinger as a guide
- In some patients with very narrow vaginal openings, it may be easier to evaluate the uterus and ovaries using a digital rectal examination instead of a bimanual exam.

TABLE 2

Differential diagnosis for symptoms of vaginal atrophy^{9,33}

- Candidiasis
- Bacterial vaginosis
- Contact dermatitis (irritant or allergic)
- Trauma
- Foreign body
- Lichen sclerosis
- Lichen planus
- Lichen simplex chronicus
- Vulvar intraepithelial neoplasm
- Vulvar cancer
- Other benign and malignant tumors
- Other medical disorders (e.g., diabetes and lupus)
- Psychological causes

palpation in the vestibule, and the vagina can be easily traumatized and irritated.

To decrease pain and irritation associated with vaginal atrophy during the physical examination, clinicians should use adequate lubricant and consider using a smaller speculum.

See “Clinical pearls for evaluating vaginal atrophy,” page S5.

LABORATORY TESTS. Although vaginal atrophy is typically a clinical diagnosis, an evaluation of vaginal pH may be used to support the diagnosis. Vaginal pH can be assessed by placing a piece of litmus paper on the lateral vaginal wall.⁹ Patients with vaginal atrophy typically have a vaginal pH of 5 or higher.²⁸

Although laboratory assessments of vaginal maturation using vaginal cytology are common in clinical trials, they are generally not needed in clinical practice. One such laboratory test is the vaginal maturation test, which evaluates the relative proportion of parabasal, intermediate, and superficial vaginal epithelial cells in a sample. Premenopausal women typically have more than 15% superficial cells, whereas postmenopausal women with vulvovaginal atrophy usually have less than 5%.⁹

If a wet mount evaluation is performed, immature epithelial cells and white blood cells will be apparent if vaginal atrophy is present.

While vaginal cultures are generally of lim-

ited utility in patients with postmenopausal estrogen deficiency, they may be useful to help clinicians pinpoint the presence of a specific organism involved in vaginal atrophy.

DIFFERENTIAL DIAGNOSIS

Other disorders that can cause symptoms similar to those of vaginal atrophy include infection, trauma, presence of a foreign body, lichen sclerosis, benign and malignant tumors, other medical disorders (e.g., diabetes and lupus), and, potentially, psychological problems (TABLE 2).^{9,28,33} Bacterial vaginosis, one of the most common vaginal infections, can occur from vaginal atrophy.⁹ Irritants such as perfumes, lubricants or moisturizers, and soaps can cause similar symptoms.

In addition, the presence of vulvovaginal dermatoses, such as lichen sclerosis, lichen planus, and lichen simplex chronicus, may cause similar vulvovaginal symptoms.^{9,42} Cancer and precancerous lesions, including vulvar and vaginal intraepithelial neoplasm and vulvar cancer, should also be considered. If any of these disorders are suspected, a biopsy should be performed to obtain diagnosis and suggest treatment options.⁹

CONSIDERATIONS

Despite the frequency and impact of symptoms of vaginal atrophy, they are often underreported and, consequently, undertreated. A recent Web-based survey of postmenopausal women found that only 40% of women are likely to discuss their vaginal symptoms with their physician.⁴³

Even fewer women receive treatment for their symptoms. Estimates suggest that only 20% to 25% of postmenopausal women suffering from symptoms of vaginal atrophy will seek medical attention.^{5,28,34} Consequently, the care of the menopausal woman should include both a physical assessment of vaginal atrophy and dialogue exploring possible existence of symptoms and their effect on vulvovaginal symptoms, sexuality, and quality of life issues.

SUMMARY

Postmenopausal estrogen deficiency can lead to vaginal dryness and discomfort, dyspareunia,

vaginitis, and even recurrent urinary tract infections or symptoms of urinary incontinence, all of which result from atrophic changes in the vagina, vulva, and lower urinary tract. Symptoms of vaginal atrophy in postmenopausal women are commonly prevalent, may be highly distressing, and are often overlooked until problems occur.

Due to the progressive nature of vaginal atrophy, the significant impact of its symptoms on quality of life, and the persistence of its symptoms in the absence of treatment, it is critical that clinicians evaluate the presence and severity of vaginal atrophy in their postmenopausal patients and other patients with prolonged estrogen deficiency. ■

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Therapeutic options for the treatment of vaginal atrophy

Risa Kagan, MD

KEY POINTS

- Vaginal atrophy is a common condition among postmenopausal women. It may lead to symptoms of burning, itching, dryness, irritation, and dyspareunia
- Effective treatments range from nonhormonal over-the-counter creams and gels for mild symptoms, to vaginal hormone therapy for persistent symptoms, to systemic estrogen therapy for treatment of the spectrum of postmenopausal symptoms
- For many women, nonhormonal options for therapy, such as over-the-counter lubricants or moisturizing products, are effective in relieving symptoms of vaginal atrophy
- Local estrogen therapy—supplied as estrogen creams, vaginal estradiol tablets, and estrogen rings—is the treatment of choice for women with vaginal atrophy who do not have any other postmenopausal symptoms, according to the 2010 North American Menopause Society (NAMS) guidelines. Beneficial effects include both improvement of symptoms and restoration of vaginal anatomy
- Compared with locally administered therapy, systemic therapy is indicated for relief of vasomotor symptoms associated with menopause, as well as prevention of postmenopausal osteoporosis. The decision of whether to receive systemic hormone therapy depends on a woman's individual situation and her willingness to be exposed to potential risks of therapy

DISCLOSURE

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Vaginal atrophy is a common condition that affects 7% to 57% of postmenopausal women and may lead to symptoms of burning, itching, dryness, irritation, and dyspareunia.¹⁻⁷ In contrast to vasomotor symptoms associated with menopause, symptoms of vaginal atrophy typically do not resolve without effective treatment and do not diminish over time.^{1,8,9}

Several effective therapeutic options exist for women who are living with vaginal atrophy, and these may be administered across the range of severity for temporary or chronic symptoms.¹⁰ Effective treatments range from nonhormonal over-the-counter creams and gels for mild symptoms, vaginal hormone therapy for persistent symptoms, and systemic estrogen therapy for treatment of the spectrum of postmenopausal symptoms.¹¹⁻¹⁴ This article reviews the therapeutic options available for treatment of vaginal atrophy, as well as the advantages and disadvantages of each option and strategies for optimizing treatment.

NONHORMONAL THERAPIES

For many women, nonhormonal options for therapy, such as over-the-counter lubricants or moisturizing products, are effective in relieving symptoms of vaginal atrophy.⁸ Vaginal moisturizers, such as Replens or K-Y products, have been shown to lower vaginal pH, promote elimination of dead cells, bind vaginal tissue, and increase vaginal moisture and fluid.^{8,14-16} Moisturizers are generally used independently of sexual activity. Clinical data indicate that Replens is effective in improving symptoms of vaginal itching, irritation, and dyspareunia.¹⁴ Water-soluble lubricants are usually used to

alleviate dryness during sexual activity. Although vaginal lubricants have been shown to decrease vaginal irritation during sexual activity, limited evidence about their long-term therapeutic effect is available.⁹

Findings also indicate that other lifestyle changes, including increase in coital activity, smoking cessation, and consumption of cranberry juice (for recurrent urinary tract infections) can also relieve symptoms of vaginal atrophy.⁸

VAGINAL ESTROGEN

Local estrogen therapy is the treatment of choice for women with vaginal atrophy who do not have any other postmenopausal symptoms, according to the 2010 North American Menopause Society (NAMS) guidelines.^{11,17} The beneficial effects of estrogen therapy include both the improvement of symptoms associated with vaginal atrophy and the restoration of the vaginal anatomy.¹ Local estrogen therapy was associated with significant symptom improvement in vaginal atrophy in a meta-analysis of 10 trials and was found to be equally efficacious compared with systemic therapy.¹⁸

Research has shown that low-dose vaginal estrogen is effective and well tolerated for treating vaginal atrophy and has been shown to reduce vaginal symptoms, including dyspareunia and vaginal dryness, and to restore vaginal pH and normal vaginal cytology.^{8,19} Local estrogen therapy also offers the benefit of lowered potential for systemic exposure and reduced adverse effects.^{1,8}

Estrogen for local vaginal application may come in various forms, including estrogen creams, vaginal estradiol tablets, and estrogen rings.^{8,20}

ESTROGEN CREAMS. Conjugated estrogen vaginal cream in dosages of 0.5–2.0 g has been evaluated in clinical trials and found to be effective in relieving vaginal symptoms.^{8,21,22} Treatment with vaginal estradiol cream has also been shown to be effective.²³ Advantages of the cream form include dosing flexibility and lower cost.⁵ Women self-administer vaginal estrogen cream using an applicator; creams are

usually applied daily for a few weeks, then two times a week thereafter.⁵

A Cochrane review of local estrogen therapy products found equal efficacy for all products but that use of estrogen creams was associated with increased risk for systemic absorption. Two trials of conjugated estrogen cream showed significant adverse effects of uterine bleeding, breast pain, and perineal pain.¹³ It was also potentially associated with the ability of women to inadvertently use higher doses than recommended.¹³

ESTROGEN TABLETS. Another option for local estrogen therapy is the vaginal estradiol tablet. Vaginal estrogen tablets are self-administered using an applicator; tablets are used daily for the first 2 weeks then twice a week thereafter.⁵ In clinical studies involving estrogen doses as low as 10 µg, estradiol administered by vaginal tablet was shown to be effective in improving vaginal atrophy, relieving vaginal symptoms, decreasing vaginal pH, and increasing maturation of the vaginal and urethral epithelium.³ High vaginal pH (>6.0) has been correlated with high levels of parabasal cells (20% or more), an indicator of an estrogen-deficient epithelium commonly seen in postmenopausal vaginal atrophy.²⁴

Research has shown that low-dose vaginal estrogen is effective and well tolerated for treating vaginal atrophy and has been shown to reduce vaginal symptoms, including dyspareunia and vaginal dryness, and to restore vaginal pH and normal vaginal cytology

Advantages of the estrogen tablet, compared to the cream, include enhanced control of a specific dose, reduced potential for systemic absorption, decreased potential for leakage, and increased adherence compared with vaginal creams.^{3,21,25} Study results suggest that the vaginal estradiol tablet and estrogen cream can initially increase systemic estrogen

to a small degree when inserted in a very atrophic vaginal epithelium, until the epithelium is thickened (or keratinized). There may be absorption differences according to where local estrogen is placed in the vagina. There is a controlled crossover trial of 10 postmenopausal women that evaluated the site of placement of 17 β -estradiol tablets and endometrial safety. When the tablet was placed in the outer one third of the vagina, absorption of estrogen to the uterus was significantly reduced.²⁶

ESTROGEN RINGS. A third alternative for the administration of local estrogen therapy is the estrogen ring. Among estrogen rings, a sustained-release estradiol ring, which releases 7.5 μ g estradiol every 24 hours for 90 days, has been shown to be more effective than placebo and as effective as vaginal cream and vaginal tablets in relieving the symptoms of vaginal atrophy and restoring vaginal pH and cytology.^{22,27,28}

Women might refrain from discussing vaginal symptoms with a health-care professional because of persisting cultural taboos about sex, embarrassment over sexual problems, or even self-blame about negative sexual experiences or sexual dissatisfaction

Among the advantages of the vaginal ring treatment option is that it eliminates compliance issues and the risk of endometrial hyperstimulation due to overtreatment.²² In a comparison of the ring and the cream, the ring had better patient adherence and was identified as more acceptable to patients because of comfort, ease of use, and delivery system.¹³ In addition, the estrogen ring offers minimized frequency of application compared with either the cream or tablet form; rings deliver a constant supply of hormone for as long as 3 months, while local estrogen cream or tablets may require at least biweekly application.¹

However, it has been noted that insertion of the ring can be difficult for women with limited vaginal capacity or manual dex-

terity. In women with pelvic organ prolapse, the product may become dislodged. During intercourse, sexual partners may be aware of the ring, but the ring can be removed if desired for sexual activity.⁹ The vaginal estrogen ring can be inserted by a doctor or the patient, but is usually self-administered and changed every 3 months. Rates of favorable results with low-dose vaginal estrogen are high, with 80% to 90% of women reporting improvement.⁸ The 7.5- μ g estradiol ring provides local therapy, but .05 mg/d and .1 mg/d rings are also available for both local and systemic estrogen therapy.⁵

SYSTEMIC ESTROGEN THERAPY

Systemic estrogen therapy is indicated for relief of multiple menopausal symptoms in addition to vaginal atrophy and can improve patient quality of life.²⁹ It may be administered orally, vaginally, or transdermally or by injection or nasal spray.¹³ The hormone progesterone is used to reduce the risk of endometrial cancer associated with systemic estrogen therapy.¹¹

Compared with locally administered therapy, systemic therapy is indicated for relief of vasomotor symptoms associated with menopause as well as prevention of postmenopausal osteoporosis.¹ To reduce the risk associated with systemic hormone therapy, lower doses and less frequent administration may be used.^{11,30-32} Although lower doses of estrogen therapies do not require concomitant daily use of progesterone, most clinicians use progesterone either every 3 months, 6 months, or yearly (only with ultra-low dosages) to “challenge” the endometrium if there is any proliferation.^{33,34} The other option for monitoring the endometrium is a pelvic sonogram.³¹ When local estrogen therapy is considered solely for vaginal atrophy, no additional progesterone is generally recommended.^{8,11,26}

Estimates suggest that among women who take systemic hormone therapy, 40% still experience persistent vaginal dryness.⁹ In light of this, and considering the reluctance of many women to discuss vaginal symptoms,

TABLE 1

Hormonal treatments for vaginal atrophy¹

Product	Form and delivery	Dosage and administration	Advantages	Disadvantages
Premarin Vaginal Cream	Vaginal conjugated estrogen cream (local)	0.625 mg conjugated estrogens used cyclically (3 weeks on, 1 off) at the lowest dose necessary to control symptoms (0.5–2.0 g cream daily for vaginal atrophy; 0.5 g for dyspareunia) ³⁵	Flexibility of dosage and frequency of administration	Potential for poor dose control during administration, which can lead to adverse events Compliance with dosing regimen
Estrace	Estradiol vaginal cream (local)	0.01% estradiol in nonliquefying cream applied 2–4 g/d 1–2 weeks, then 1–2 g/d 1–2 weeks, then 1 g/d 1–3 times/week as maintenance ³⁶	Flexibility of dosage and frequency of administration	Potential for poor dose control during administration, which can lead to adverse events Compliance with dosing regimen
Vagifem	Estradiol tablet (local)	10 µg estradiol* 1 tablet daily for 2 weeks followed by 1 tablet twice weekly ³⁷	Ease of use with applicator Specific titrated dose in each table	Compliance with dosing regimen
Estring	Vaginal ring (local)	7.5 µg of 17β-estradiol in 24 hours in a consistent, stable manner for 90 days ³⁸	Minimized frequency of application (extended release over 3-month period)	Occasionally may fall out, but may be reinserted after washing Patients may have difficulty with insertion and removal
Femring	Vaginal ring (local and systemic) [†]	0.05 mg/d or 0.1 mg/d estradiol for 3 months ³⁹	Minimized frequency of application (extended release over 3-month period)	Occasionally may fall out, but may be reinserted after washing Patients may have difficulty with insertion and removal

*The 25-µg tablet was discontinued July 30, 2010.⁴⁰

[†]Femring is both local and systemic therapy and is included to demonstrate the difference from Estring, which is only local therapy.

clinicians should inquire about persistent vaginal symptoms, as local estrogen therapy may be needed to achieve symptom control.¹¹ Forms of local therapy are summarized in TABLE 1.^{1,35–40}

OPTIMIZING TREATMENT FOR VAGINAL ATROPHY

Postmenopausal women should be evaluated for signs and symptoms of vaginal atrophy, which can have a significant negative impact on patient quality of life.^{9,41} As noted, women might refrain from discussing vaginal symptoms with a health-care professional

because of persisting cultural taboos about sex, embarrassment over sexual problems, or even self-blame about negative sexual experiences or sexual dissatisfaction.⁸ Therefore, it is important for clinicians not only to initiate conversations about vaginal symptoms with members of at-risk groups, but once a diagnosis of vaginal atrophy is made, also to identify the optimal treatment for that individual patient and to continue to reevaluate the treatment response, medication adherence and compliance, and patient satisfaction with treatment. Individualization and reevaluation is of key importance for successful therapy.

It is recommended that hormone therapy be considered only when an indication for therapy has been clearly identified; contraindications ruled out; and the potential individual benefits and risks adequately discussed with the patient to support informed decision making.¹¹ According to NAMS, a comprehensive history and physical examination are essential prior to initiation of hormone therapy, including assessment of risk factors for stroke, CHD, VTE, osteoporosis, and breast cancer. These results should be discussed with patients prior to initiating therapy. Mammography should be performed according to national guidelines and age but preferably within the 12 months before initiation of therapy.¹¹

Ultimately, the decision of whether to receive systemic hormone therapy depends on a woman's individual situation and her willingness to accept known risks. Similarly, the acceptance of risk may depend on the reason for consideration of treatment. For example, a woman may be more willing to accept the risk associated with hormone therapy if she is currently experiencing systemic symptoms than she would be if the hormone therapy treatment were intended to lower risk of future possible osteoporotic fractures. Likewise, short-term use of hormone therapy might be more acceptable for a younger woman than long-term use would be for an older woman.¹¹ Extending duration of hormone therapy should also be considered in the context of a woman's individual risk-benefit profile.¹¹

SUMMARY

Locally administered therapeutic options for vaginal atrophy, including estrogen rings, tablets, and creams, are effective in providing relief of vaginal atrophy symptoms while minimizing risks associated with systemic absorption. Still, for some women, the benefits of systemic therapy—especially when it is for short-term treatment of presenting symptoms—outweigh the risks. Identification of therapy indications, ruling out of contraindications, and discussion of potential individual benefits and risks with a clinician are

paramount in determining which treatment option is suitable for each woman. ■

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Impact of vaginal atrophy on quality of life and sexuality

Michael Krychman, MD

KEY POINTS

- Vaginal atrophy is a significant health issue for postmenopausal women
- Vaginal atrophy has implications on the female sexual response cycle and can negatively impact overall sexual functioning
- Women often suffer in silence with this condition
- Safe effective treatments are available and should be used

Vaginal atrophy is a common medical condition that is linked to menopause.^{1,2} This condition is associated with sexual dysfunction disorders—women with vaginal atrophy are nearly four times more likely to experience sexual function disorders compared with those women with normal vaginal tissue.³ Pain and other symptoms contribute to or perpetuate low sexual desire or interest; decrease or discontinuation of sexual activity contributes to a cycle of intimacy avoidance, further diminishing desire.¹

In addition to the impact on sexuality and intercourse, vaginal atrophy has been shown to affect urinary function and may even impact activities of daily living, including sitting and exercise. These broad-range effects have been reported to cause significant emotional distress and reduced quality of life in postmenopausal women.^{3,4} Embarrassment, cultural or religious taboos, and perceptions that these symptoms are an unavoidable part of normal aging may hinder women from initiating discussions about symptoms with their health-care professionals.¹

DISCLOSURE

The author is a consultant to Pfizer, Boehringer Ingelheim, Johnson and Johnson, and Sempria Laboratories and is a speaker for Warner Chilcott and Boehringer Ingelheim.

Various forms of documented effective treatment do exist, ranging from nonhormonal, over-the-counter moisturizers and lubricants for mild symptoms to local, minimally absorbed estrogen therapy for persistent symptoms.⁵⁻⁹ Systemic estrogen therapy, used appropriately and with awareness of associated benefits and risks, may also be an option for treatment of the spectrum of postmenopausal symptoms.⁹ Vaginal atrophy and intercourse-associated pain, or dyspareunia, are not life threatening or physically debilitating; however, they are life altering and can have a significant impact on sexual satisfaction and overall quality of life.^{3,4}

Here, I will review the effect of vaginal atrophy, as well as address means by which clinicians can enhance patient sexual function and quality of life by initiating conversations with patients, discussing symptoms potentially associated with vaginal atrophy, and initiating effective treatment.

CROSS-LINKED SYMPTOMS OF VAGINAL ATROPHY

In addition to the systemic and familiar symptoms of menopause, such as hot flashes, mood swings, or night sweats, menopause is often associated with vulvar and vaginal changes; awareness of the association of these vaginal symptoms with menopause is lower among women compared with awareness of the systemic symptoms.¹⁰ In this condition, there is loss of collagen, adipose tissue, and capacity for water retention in the vulva, resulting in thinning of the epithelial surface; loss of the protective covering of the clitoral glans, causing in an increased vulnerability to irritation;

thinning of the vaginal mucosa; loss of vaginal rugal folds; altered vaginal maturation index; reduced normal lactobacilli flora; changes in pH; and decreased vaginal blood flow and secretions normally associated with sexual arousal.^{1,2,11}

As a result of these changes at the cellular level, three categories of vaginal signs and symptoms may occur:

- vulvar and vaginal changes
- urinary complications
- and pain or discomfort associated with intercourse, or dyspareunia.¹²⁻¹⁴

Reported prevalence of symptoms related to vaginal atrophy in postmenopausal women include vaginal dryness (27% to 55%), vaginal irritation or itching (19%), loss of interest in sex in women with vaginal dryness (32%), dyspareunia (32% to 41%), and difficulty with vaginal lubrication (39%).^{1,15,16} These symptoms are a common—and commonly overlooked—accompaniment of female aging.

Urogenital atrophy is also often associated with urinary symptoms such as increased frequency and urgency of urination, painful urination, and increased incidence of urinary tract infections. These also have direct implications for quality of life and sexuality. In response to urinary symptoms, many women remain at home or close to home, change the liquids they consume or the amount they consume, and rely on increased use of sanitary protection. Pain and embarrassment related to urinary symptoms may worsen sexual function,¹ and vaginal atrophy has also been associated with recurrent cystitis and pyelonephritis.¹⁷

These symptoms become more common as women age—estimates of the prevalence of vaginal dryness increase with age. The frequency of stress urinary incontinence increases with age, and it has been observed that sexual interest, desire, arousal, lubrication, and orgasm are negatively influenced by this condition, which is also correlated with vaginismus and dyspareunia.¹⁸ Stress urinary incontinence is not directly attributable to vaginal atrophy; however the prevalence of this condition increases with age and it may worsen

vaginal atrophy symptoms.² Decreased levels of sexual desire also tend to manifest with increasing age—to 49 years of age, 10% of women have low level of desire, but prevalence is 22% for those 50 to 65 years old, and 47% for those 66 to 74 years.¹⁸

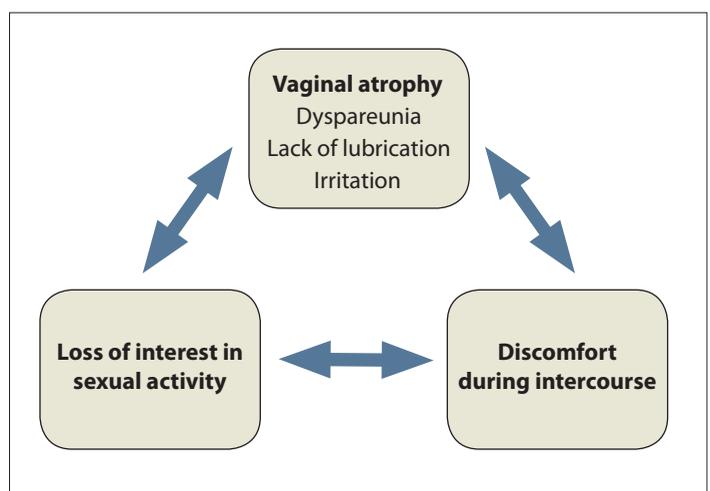
In addition to becoming more common with aging, symptoms of vaginal atrophy may become worse unless appropriate treatment is given, creating a vicious cycle of sexual dysfunction. For example, women with sexual dysfunction—including those with low levels of sexual interest, arousal disorder, lubrication disorder, or dyspareunia associated with vaginal atrophy—may in turn adopt a strategy of sexual avoidance.^{1,4,19} Avoidance may impact sexual frequency and can negatively impact the relationship. In addition, vaginal blood flow and secretions associated with arousal that help to maintain a healthy cytological environment in the vagina may be reduced; therefore, this avoidance may contribute to worsening of the symptoms of vaginal atrophy.¹ This relationship is illustrated in **FIGURE 1**.

EFFECT OF VAGINAL ATROPHY ON SEXUAL INTEREST AND RESPONSE

Menopause-associated decline in the estrogen level has been associated with decreases in contractions underlying the orgasmic

FIGURE 1

Impact of vaginal atrophy on sexual function



response.⁴ However, the direct effect of decreased estrogen levels on sexual interest and coital frequency has not been fully elucidated. Decreased levels of estrogen resulting from menopause have been associated with a decline in women's sexual interest, orgasm capacity, and frequency of coitus.^{20,21} A study by Dennerstein and colleagues found that the frequency of sexual activities and libido were decreased most in postmenopause, with dyspareunia playing an important role.²² Research has also shown that lower estradiol levels resulting from menopause are associated with higher incidence of vaginal dryness, pain, and dyspareunia compared with patients with higher estradiol levels (≥ 50 pg/mL).²³

Estrogen therapy has been shown to increase vaginal lubrication and decrease atrophic conditions associated with menopause.²³ In addition, some research findings indicate that estrogen treatment may enhance sexual desire and enjoyment, have direct effects on vaginal lubrication, and improve orgasmic response.^{21,23} These findings are somewhat contradicted by other studies of female sexuality and sexual activity during phases of the menstrual cycle, including those studies that examined women while receiving oral contraceptives, all of which demonstrated an inhibitory effect on female sexual desire and response associated with elevated estrogen levels.^{21,23,24}

In addition to the direct effects of estrogen on sexual desire and response, vaginal atrophy often results indirectly in reduced sexual activity. Vulvovaginal changes and other symptoms of vaginal atrophy can lead to a degradation of the vaginal surface, making it vulnerable to trauma, ulcerations, tears, and bleeding, even on minor contact.²⁵ Pain and discomfort, especially during intercourse, coupled with the associated physiological changes may lead to sexual dysfunction, vaginal contraction, and rigidity.

BARRIERS TO EFFECTIVE DIAGNOSIS AND TREATMENT OF VAGINAL ATROPHY

Often, vaginal complaints are the primary reason for consultations with the gynecologist or

women's health-care professional. It is estimated that vaginal complaints account for as many as 10 million office visits each year. The number of complaints may be higher if all related issues such as pain and discomfort are included.²⁶

However, for many women, the sexual problems that originate with vaginal atrophy may be difficult or embarrassing to discuss. A recent population study found that only 22% of women had discussed sexual issues with a physician/health-care professional since the age of 50.²⁷ Persisting cultural taboos about sex, embarrassment over sexual problems, or even self-blame about negative sexual experiences or sexual dissatisfaction—even when related to pain—can lead women to refrain from discussing their symptoms with a health-care professional.¹

Some women fail to seek a solution because they may attribute their symptoms to the normal effects of aging. Not realizing that the symptoms are related to an estrogen deficiency and are effectively and easily treatable conditions, some women—especially those who are elderly—may opt to discontinue sexual intercourse altogether.¹³

The cessation of coitus can have direct impact on relationship intimacy and can result in decrements in relationships and reduced quality of life. Dyspareunia, sexual dysfunction, and discontinuation of sex may negatively affect a woman's sexual self-schema and how she perceives herself as a sexual being and may alter her perception of her own attractiveness as she ages.¹ A woman's sexual dysfunction may also impact her partner's sexual performance.⁵

Although some women accept their symptoms and do not seek treatment, others initially may try over-the-counter or home remedies, thereby postponing seeking the advice of a health-care professional. It is estimated that only 25% of women with the symptoms of vaginal atrophy seek medical treatment.¹³ However, the actual prevalence of the condition is unknown, because only a portion of symptomatic women seek treatment.^{10,13} This

delay often leads to women seeing a health-care professional only after excoriation of the vulva or other severe symptomatology emerges, complicating treatment.⁵

Barriers may exist on the part of the health-care professional as well. Health-care professionals often feel uncomfortable discussing sexual topics with an older female patient.¹⁰ They may wait for the patient to initiate the conversation or focus the limited time available for a gynecologic visit on the patient's stated concerns.

Clinicians may be reluctant to investigate and probe about concerns not mentioned by the patient, thereby "opening the floodgates" and potentially causing time-management issues. The REVEAL survey found that only 36% of health-care professionals "often" discussed with patients the potential issue of pain associated with intercourse.¹⁰ In older patients, management of multiple medical conditions may take precedent, or the gynecologist may be reluctant to incorporate additional medications into an already complex treatment regimen.¹⁰ Also, clinicians may be poorly educated or personally embarrassed about the sexual response and sexual dysfunction issues in the older female patient. Many health-care providers are poorly educated about sexual functioning and dysfunction and often feel ill-prepared to address treatment issues or concerns.

Despite these potential barriers, it is imperative for clinicians to understand that 1) vaginal atrophy is a common and distressing condition, and 2) simple and effective treatments exist that can provide significant relief for patients and lead to drastic improvements in their overall quality of life.

PATIENT BARRIERS TO OPTIMIZING SEXUAL HEALTH: A TEACHABLE MOMENT FOR CLINICIANS

Given these potential barriers to identification and effective treatment, how can ObGyns and others who work as women's health professionals best help their postmenopausal patients who are suffering in silence?

It is important to acknowledge the high

prevalence of postmenopausal sexual function difficulties, including vaginal atrophy, and to routinely incorporate investigative questions

Discussing postmenopausal sexual health concerns

- **INITIATE THE CONVERSATION.** Vaginal atrophy is associated with sexual dysfunction and emotional distress. These symptoms may present themselves before signs are noted during pelvic examination.¹⁴ Keeping in mind the progressive nature of vaginal atrophy, it is important for clinicians to broach the subject of issues of postmenopausal sexual health and vaginal concerns with a private discussion taking place in a comfortable and professional atmosphere.^{1,29} Patients should be prepared for the potential impact of menopause on vaginal function and be made aware that effective treatment options are available.
- **MAKE IT ROUTINE.** Considering under-reporting of symptoms and reluctance to discuss them, clinicians routinely should incorporate questions related to sexual or vaginal health during annual gynecologic examination of patients in postmenopausal risk groups. Incorporating questions about sexual activity in the review of systems, or even in social history, is important.¹ (For example: "Many women in menopause have concerns related to sexual health. Do you have any?") These questions create a sexually positive environment and may open the door for discussion of concerns as patients age, legitimize patient concerns in the area of postmenopausal sexual health, and help patients become comfortable discussing menopause-related gynecologic issues as they occur.
- **INCLUDE SEXUAL HEALTH IN PATIENT ASSESSMENT.** To comprehensively characterize symptoms, an initial workup should include a comprehensive medical history, sexual history, and psychosocial history, with an evaluation of the patient's sexual health (level of interest, arousal, orgasm).^{1,20} You may consider assessing your intake forms and include sexual-health questions, including those that address vaginal atrophy.
- **CONDUCT A PHYSICAL EXAMINATION.** Assessment of vaginal atrophy should be part of the routine pelvic examination of postmenopausal women, regardless of whether the patient complains of symptoms.^{1,20} When atrophic changes are noticed on examination, you can mention your physical findings and begin to probe further about sexual concerns. To help minimize patient discomfort, this discussion can be done after the exam, when the patient is fully clothed.¹
- **VALIDATE PATIENT CONCERNS AND PROVIDE ANSWERS.** Sex is a sensitive issue, and women who are having sexual problems may feel alone, embarrassed, or sexually inept. It is important to validate their concerns, empathize, and avoid being dismissive. Older women in particular may consider sexual difficulties to be a natural part of aging and avoid seeking treatment.⁵ Clinicians can respond to their patients' concerns by validating them and reassuring patients that vaginal atrophy is a very common problem.³⁰ Clinicians can discuss the availability of effective treatment options for symptoms of vaginal atrophy and inform patients of relative benefits and risks of each treatment option.²⁹

on the topic of sexual complaints into your patients' discussions and examinations.²⁸ Education of patients is also critical; it is important to provide patients with both validation of their concerns and effective treatment options. For specific suggestions on overcoming barriers to optimizing postmenopausal sexual health, see "Discussing postmenopausal sexual health concerns" on page S17.

TREATMENT PARADIGM

As I've discussed, vaginal atrophy is a common cause of sexual function problems in postmenopausal women; providing appropriate therapy, including locally applied hormonal therapy, can reduce the effect of this condition. Effective treatment for vaginal atrophy begins with the initiation of a frank and open dialogue about symptoms and sexual function; it continues with a full assessment of potential factors that may impact sexual health. For best results, it is important for health-care professionals to take a comprehensive approach to evaluation and treatment of vaginal atrophy in postmenopausal women. This approach incorporates local estrogen treatment, non-hormonal products to address dryness and irritation (which may be helpful during coitus), and other measures to address overall patient health, such as incorporating exercise and improving diet.¹⁶

Nonhormonal treatments, including over-the-counter moisturizing products, such as Replens and K-Y products, play a role in addressing vaginal symptoms. These products may help rehydrate the tissues on an ongoing basis. Lubricants may be used during coitus for further comfort. Constructive psychological and physical lifestyle change—such as eating a balanced healthy diet, increasing physical exercise, decreasing alcohol and tobacco use—may also positively impact sexual health by enhancing well-being, self-worth, and body image and increasing overall stamina. Increasing sexual activity can also play an important role in improving vaginal function.^{4,16}

Locally applied, minimally absorbed hormone therapy has been shown to be effective

in slowing the vaginal remodeling associated with decreased estrogen levels. It is restorative in nature; however, data concerning effects on sexual desire and sexual frequency are more mixed.^{21,24} Hormone therapy is not recommended for treatment of diminished libido in isolation.⁹ Treatment of moderate-to-severe vaginal atrophy with local hormone therapy can be effective in relieving dyspareunia, a common cause of intercourse avoidance.⁹ These therapies, in cream, tablet, or ring form, have also been shown to provide significant relief from distressing symptoms related to vaginal atrophy.^{1,13,31} Conjugated equine estrogen cream is FDA approved for the treatment of moderate-to-severe dyspareunia. Locally applied, minimally absorbed estrogen may improve coital satisfaction by enhancing lubrication and increasing blood flow and sensation in vaginal tissues.⁹ Previous articles in this supplement have provided additional information on diagnosis and treatment of vaginal atrophy.

SUMMARY

Vaginal atrophy is a commonly overlooked problem, with significant negative impact on both sexual function and patient quality of life. Symptoms are progressive without treatment and contribute to a harmful cycle of intercourse-associated discomfort and sexual avoidance, which, in turn, contributes to worsening vaginal atrophy. These symptoms go beyond sexual function, potentially impacting activities of daily living, including sitting and exercise. Avoidance or pain during sex may impact a patient's relationship with her partner and result in diminished self-esteem and relational intimacy. Urinary symptoms may be associated with discomfort and patient isolation.

Despite this broad impact, the patient suffers in silence, normalizing symptoms as "just part of getting older," or being too embarrassed to raise the issue with her health-care professional. A broad range of effective treatment options is available for vaginal atrophy, with significant potential to mitigate the impact of this condition on sexual function and quality of life.

By incorporating sexual health concerns into the patient evaluation and discussion, diagnosing vaginal atrophy, and providing effective treatment, including nonhormonal and hormonal treatments, health-care professionals can improve the sexual function and quality of life of their postmenopausal patients. ■

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Systemic effects and endometrial safety of local estrogen therapy

Steven R. Goldstein, MD

KEY POINTS

- Vaginal administration of estrogen is effective and well tolerated for treatment of symptoms of vulvovaginal atrophy
- Estradiol tablets, estrogen creams, and estrogen rings are the three local estrogen formulations available in the United States
- Relief of symptoms is achieved with low dosages of estrogen and limited systemic exposure
- Vaginal administration is not associated with clinically important increases in serum estrogen levels or changes in endometrial proliferation

Vaginal atrophy is a prevalent condition resulting from estrogen deficiency that can occur at any time in a woman's life but is more common after menopause.¹ The precise prevalence of vaginal atrophy is difficult to ascertain. A recent review of vaginal atrophy found reports ranging from 4% of women in early perimenopause to 47% of postmenopausal women. Fortunately, in most women, local or systemic estrogen preparations relieve vaginal atrophy symptoms.²

Interest in the potential for lower systemic hormonal exposure with use of local vaginal estrogen therapy has grown since the results of the Women's Health Initiative (WHI) were made public almost 10 years ago.³ Vaginal administration of low-dose estrogen provides sufficient estrogen to relieve symptoms and reverse the atrophic changes associated with menopause, with the added benefit of limited

systemic absorption.⁴ Therefore, local vaginal treatment is typically recommended for women seeking estrogen therapy solely for the treatment of vaginal atrophy.⁵

Estradiol tablets, estrogen creams, and estrogen rings are the three local estrogen formulations available in the United States. This review presents the clinical evidence about the safety of these formulations.

SYSTEMIC ABSORPTION OF VAGINAL ESTROGEN THERAPY

Absorption of estradiol and other steroid hormones is rapid, particularly through the thin vaginal epithelium characteristic of postmenopausal women.⁶ All three available formulations—the 17 β -estradiol-releasing ring, 17 β -estradiol tablets, and conjugated equine estrogen (CEE) and estradiol creams—are water-soluble and easily absorbed through the vaginal epithelium.⁷ Absorption with the ring or tablets may be slower than with creams.⁸ The concentration gradient across the epithelium determines the absorption rate; therefore, dosage may affect the extent of systemic exposure. Moreover, the distribution of absorbed estrogen within the pelvic region may differ depending on the anatomic position of administration. Some evidence suggests that delivery of estrogens to the lower one third of the vagina may limit distribution to the uterus, thereby lowering the risk of hyperplasia, and may be preferable for the treatment of vaginal atrophy.^{8,9}

An important difference between local vaginal and oral administration of estrogen is that vaginal administration circumvents metabolic and physiologic barriers to estrogen

DISCLOSURE

The author has received honoraria from Amgen, Boehringer Ingelheim, Eli Lilly, Nordisk, Merck, and Pfizer. He is a consultant to Cook ObGyn and Philips Ultrasound; a speaker for Eli Lilly and Warner Chilcott; and Director, Sonosite.

absorption.⁶ Consequently, substantially lower dosages of estrogen are required when applying estrogen directly to the vagina, compared with oral administration.¹⁰ Although circulating levels of estrogen do increase with local administration, serum estrogen levels typically remain relatively low.

ESTROGEN CREAM. Several small studies have examined elevations in plasma estrogen concentrations with administration of low-dose vaginal creams containing either CEEs or estradiol across a range of doses.^{11,12} After 24 weeks of treatment at the highest dose of CEE cream used (1.25 mg/d), 21 of 59 (47%) women had a serum estradiol level outside the postmenopausal range (>49 pg/mL), although the magnitude of the elevation was not reported.¹² In another study,¹¹ of 20 women treated for 6 months, CEE cream (0.3 g/d) produced only a minimal increase in estradiol and estrone levels.

Circulating levels of estradiol were measured in seven postmenopausal women treated with estradiol 10 µg vaginal cream for relief of symptoms of vaginal atrophy.¹³ After 3 weeks of daily administration, followed by an additional 9 weeks of twice-weekly treatment, circulating estradiol levels remained within the postmenopausal range.

No change in circulating mean estradiol (E2) levels have been reported with estriol cream, a vaginal estrogen therapy not available in the United States^{14,15}; according to a Cochrane Review, this is the only cream not associated with systemic absorption.¹⁶

Results from a Cochrane analysis of local estrogen therapy concluded that systemic absorption is greater with the CEE cream compared with the vaginal tablet.¹⁶ Because the administration of vaginal creams requires that patients measure and apply a dose themselves, the potential exists for them to use more estrogen than prescribed, increasing the likelihood of possible significant systemic absorption.⁴ Administration of estrogen with vaginal ring or tablets is not subject to the same potential for human error.

ESTROGEN RING. The estrogen ring formulation indicated for treatment of vaginal atrophy in

the United States releases a consistent stable dose of approximately 7.5 µg of 17β-estradiol/24 h for 90 days.¹⁷ In an open-label study¹⁸ involving 129 women treated with a vaginal ring, no increase in serum estrogen levels were found after 3, 12, or 15 weeks of therapy. Similar results were found in 30 women aged ≥60 years using the ring for 6 months; no significant changes in serum estradiol or estrone levels were found.¹⁹ However, the same study showed that the use of the vaginal ring was associated with an increase in bone density, suggesting that some degree of systemic absorption occurred.

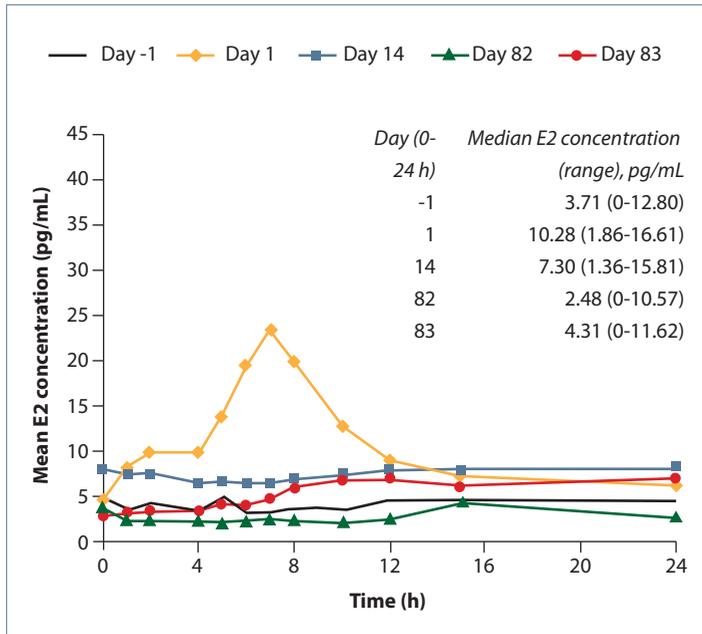
ESTROGEN TABLETS. Vaginal estradiol tablets (10-µg and 25-µg dosages) provide localized effects without appreciable absorption.^{20,21} In a study²⁰ of 12 weeks of therapy with either 10 µg or 25 µg of estradiol, systemic absorption of estrogen was low and consistent over time. There was no evidence of accumulating levels of circulating estradiol. In a recently published comprehensive assessment²¹ of estradiol absorption following a dosage regimen of 10-µg and 25-µg estradiol vaginal tablets, postmenopausal women (60 to 70 years of age) with vaginal atrophy showed similar results. Findings revealed that systemic estrogen exposure is minimized with the ultra-low-dosage 10-µg estradiol vaginal tablet, compared with the 25-µg dose. As shown in **FIGURE 1** (page S22),²¹ following treatment with the 10-µg tablet, the E2 concentrations remained within the normal reference range for postmenopausal women; aside from a transient elevation on treatment day 1, values were low and similar to baseline (day -1). The profile of systemic exposure to E2 was similar with the 25-µg tablet, but absolute values were higher than with the lower dose (data not shown).

Because the 10-µg dose is adequate for optimum symptom relief with lower circulating E2 concentrations, the 25-µg tablet is no longer available (as of July 30, 2010).²²

ENDOMETRIAL EFFECTS

The primary concern regarding use of any estrogen therapy in women who have an intact

FIGURE 1
Time course of mean estradiol (E2) plasma concentrations during 24 h after vaginal administration of E2 10-µg tablets



Source: Eugster-Hausmann et al, *Climacteric*, 2010;13(3):219-227. ©2010 Informa Healthcare.²¹ Reproduced with permission.

uterus is the risk of endometrial hyperplasia and carcinoma associated with unopposed estrogen. Although available evidence suggests that low doses of locally administered vaginal estrogen are generally safe for the endometrium, data are limited. The Cochrane Review reported that of all the included studies, one case (2%) of hyperplasia was found among women using the vaginal ring and two cases (4%) in women using CEE cream.¹⁶ In a study²³ comparing CEE with tablets, endometrial proliferation occurred in seven cases (14%) among women using CEE cream and one woman (2%) using tablets. One woman in each group had endometrial proliferation in this study comparing cream and tablets over a period of 12 weeks. In the study¹² comparing the tablet versus CEE cream over 24 weeks, five (13%) women in the cream group and four (6%) in the tablet group had endometrial proliferation on biopsy.

The endometrial safety of the 10-µg estradiol vaginal tablet was most recently evaluated for the treatment of vaginal atrophy in 336 non-

hysterectomized postmenopausal women.²⁴ As shown in **FIGURE 2**,²⁴ baseline endometrial thickness was 2.04 mm as determined by transvaginal ultrasonography (double layer) compared with 1.94 mm after 52 weeks of treatment. At study's end, there was no evidence of increased endometrial proliferation or hyperplasia.

A 12-month study comparing the safety of the vaginal ring and the estradiol 25-µg vaginal tablet in 185 postmenopausal women identified significant endometrial thickening (>5 mm) in three cases in the ring group and in two cases in the tablet group.²⁵ In another clinical study evaluating the 10-µg estradiol dose, there was one case of endometrial adenocarcinoma stage II, which was considered unlikely to have developed in response to the relatively short course of study treatment.²⁶

Although endometrial hyperplasia has been seen with low-dose vaginal estrogen, it is rare, and the concomitant use of a progestin is not indicated.^{4,27} A recent 6-month pilot study²⁸ of intravaginal administration of estriol 1 mg and progesterone 30 mg in 19 postmenopausal women found no cases of endometrial hyperplasia and, similar to results with unopposed estrogen, minimal systemic accumulation of estriol over the course of the study.

Overall, studies of endometrial effects of vaginally administered estrogen suggest that the incidence of hyperplasia or increased endometrial thickness is low and does not differ if treatment is administered as vaginal creams, rings, or tablets.¹⁶ Well-controlled studies with larger sample sizes need to be carried out to determine the benefit of using vaginal estriol and progesterone in postmenopausal women with vaginal atrophy.

CARDIOVASCULAR EFFECTS

Systemic estrogen use is known to increase the risk of thrombosis; the degree of risk depends on the dose and duration of therapy. Data evaluating the relationship of local estrogen therapy with venous thromboembolism or other thrombotic events are limited. It is reasonable to assume that because systemic exposure is low with local estrogen therapy,

the increase in the risk of thrombosis is low as well. Nonetheless, local estrogen therapy is contraindicated in women with active deep vein thrombosis, pulmonary embolism, arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions.^{17,29,30}

IMPACT ON BREAST CANCER

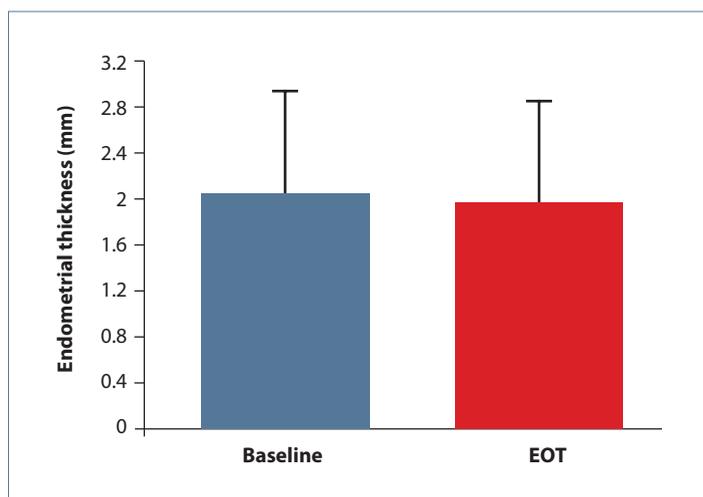
The estrogen plus progestin arm of the WHI³¹ was stopped prematurely because of the increased risk of invasive breast cancer observed in the active treatment arm. This finding with systemic estrogen plus progestin therapy in nonhysterectomized women raised concerns about the impact of even small elevations of circulating estrogen on breast cancer risk. Moreover, results from a meta-analysis of studies of systemic hormone therapy in women with a history of breast cancer concluded that the risk of recurrence is increased (relative risk, 3.41; 95% confidence interval, 1.59–7.33).³²

Regrettably, evidence on the impact of local vaginal estrogen therapy on breast cancer is limited.⁴ In a prospective observational study³³ of 18,314 women, vaginal estrogen therapy was not associated with an increased risk of breast cancer with no prior history.

Although systemic absorption of estrogen with local estrogen therapy is likely to be minimal, it is unknown whether this limited absorption will affect outcomes in women with hormone-dependent cancers.⁴ Use of adjuvant therapy with aromatase inhibitors (AI) for estrogen-dependent breast cancer is associated with a high incidence of vaginal atrophy symptoms.³⁴ AIs act by blocking 95% of estrogen synthesis, typically resulting in circulating estradiol levels of <1 pg/mL.³⁵ 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 study³⁶ involving seven women receiving AI therapy. 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 <10 pg/mL (median <5 pg/mL) by day 28, any rise above base-

FIGURE 2

Endometrial thickness at baseline (n=336) and after 52 weeks (n=293) of treatment (EOT) with estradiol 10- μ g tablets



Source: Ulrich et al. *Climacteric*. 2010;13(3):228-237. ©2010 Informa Healthcare.²⁴ Reproduced with permission.

line serum estradiol levels may have an impact on AI efficacy.

A preliminary study³⁵ on the use of local estrogen therapy in breast cancer survivors has been conducted. In this study, both low-dose vaginal estradiol tablet and estriol cream relieved vaginal atrophy, whereas a nonhormonal moisturizer provided only transient relief. Safety was evaluated by measuring serum estradiol levels and changes in endometrial thickness, both of which were found to be minimal and clinically insignificant, although an evaluation of a longer duration of treatment is warranted. Because of the impact of moderate or severe vaginal atrophy on quality of life, women who do not respond to nonhormonal therapies may consider discussing the risks and benefits of local estrogen therapy.

TOLERABILITY

Vaginal estrogen use is generally well tolerated. In a comparative clinical trial,³⁷ withdrawals due to adverse events were low (9 of 13 [7%] using the ring and 5 of 63 [8%] using CEE cream). This study found that 8 of 131 (6%) estradiol ring users and 5 of 63 (8%) CEE cream users experienced vaginal

bleeding. In another 48-week trial,²⁵ 4 of 59 (7%) women randomized to use estradiol 25- μ g tablets had vaginal bleeding. In this trial, none of the 126 women assigned to the estradiol ring group reported vaginal bleeding.

The incidence of breast tenderness, which is considered a marker of systemic exposure,¹⁶ is low for all three types of local estrogen therapy. However, evidence suggests that the incidence of breast tenderness may be higher with use of CEE cream. In the trial comparing use of the estradiol ring with CEE cream, breast tenderness contributed to discontinuation of study treatment in both groups.³⁷ In placebo-controlled trials of CEE cream, breast pain was reported in 8 of 143 (6%) women using a 12-week regimen of cream daily for 21 days followed by 7 days of no treatment. In the control group, breast pain occurred in 1 of 72 (1.4%) subjects.³⁰ Among those using a twice-weekly regimen, the incidence of breast pain was 3% in the active treatment group compared with none of 68 (0%) in the control group. The incidence of breast pain was <1% in pivotal trials of both the vaginal ring¹⁷ and estradiol 10- μ g tablets.²⁹

PATIENT PREFERENCE

Because the three available vaginal estrogen therapies do not show major differences in efficacy or safety, the choice of treatment may be determined by patient preference. In clinical trials, >80% of patients rate treatment with the estradiol ring or tablets as excellent to good. In the study comparing the ring to CEE cream, 84% of ring users rated treatment as excellent or good compared with 43% of cream users.^{25,37}

A retrospective analysis³⁸ of patient adherence to vaginal estrogen therapy in 13,074 women found that those prescribed vaginal creams discontinued treatment significantly sooner than those prescribed tablets (50% discontinuation at 30 days with cream and at 142 days with tablets; $P < .001$) and filled fewer prescriptions. Better adherence with the tablets occurred despite higher out-of-pocket costs for vaginal tablets.

SUMMARY AND CLINICAL IMPLICATIONS

- Vaginal estrogen therapy is safe and well tolerated in postmenopausal women with vaginal atrophy, although these conclusions are based on experience in small trials, largely of short duration.
- As with all forms of estrogen therapy, the Food and Drug Administration and NAMS have recommended the use of the lowest possible effective dose of vaginal estrogen for treating vaginal atrophy.^{5,39}
- Local estrogen treatments are associated with minimal systemic absorption.
- Endometrial hyperplasia with local vaginal therapy is rare. Use of progestin therapy is generally not needed in patients using low-dose local vaginal estrogen therapy.⁴
- In the absence of more rigorous studies suggesting otherwise, vaginal estrogens are not indicated for women receiving adjuvant AI therapy for breast cancer, and the potential for recurrence should be discussed with patients with a history of any hormone-sensitive cancer.
- Because efficacy and safety of the local estrogen formulations appear to be similar, the preparation preferred by the patient and the provider should be used. Therapy should be continued as long as the troublesome symptoms remain. ■

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