


Effective topical treatments for atrophic vaginitis

Topical estrogen products and moisturizers can treat and sometimes even reverse the signs and symptoms of vaginal atrophy. These therapies elevate serum estrogen levels only minimally, so they have a low risk of adverse effects.

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Learning objectives

- Describe female urogenital anatomy and the pathophysiologic changes that occur during the postmenopausal period
- Discuss factors that predispose women to urogenital atrophy
- Review the clinical presentation and laboratory findings associated with atrophic vaginitis
- Identify hormonal and nonhormonal treatment options for urogenital atrophy

Every 7 seconds, another baby boomer turns 50—that is, more than 12,000 people each day.¹ With an average life expectancy of almost 80 years, women now spend one third of their lives after menopause.² These women continue to lead active lives, and maintaining a high quality of life—including the successful management of menopausal symptoms—is important to them. Because of the heightened awareness among patients and providers regarding the potential adverse effects of hormone replacement therapy (HRT), many older women choose to minimize their use of this therapy or find alternative treatments. Clinicians should be familiar with available treatment options and be prepared to evaluate each patient to determine appropriate therapy.

Menopause symptoms

Declining levels of estrogen and rising levels of follicle-stimulating hormone (FSH) herald the onset of menopause. Although a number of symptoms have been associated with the transition to menopause, only vasomotor and urogenital symptoms have been shown to be directly correlated with these changing hormone levels.³ Typical vasomotor symptoms are hot flashes and night sweats, while reported urogenital symptoms include vaginal dryness, itching, dyspareunia, urinary frequency, and urinary tract infections (UTIs) (see Table 1, page 35). Although the onset of symptoms and their severity are unique to each woman, vasomotor symptoms often occur earlier in the menopausal transition and may wane after a number of years. Urogenital symptoms may occur at any time but often become more bothersome later in the menopausal phase and continue into the later years.^{3,4}

Prevalence

Several studies designed to characterize menopausal symptoms have found that approximately 30% to 40% of women experience urogenital symptoms, with the most commonly reported being vaginal dryness and dyspareunia.^{3,5-8} One study found that 47% of women complained of vaginal dryness 3 years after menopause, compared with 25% only 1 year after menopause. In fact, the researchers noted that “vaginal dryness was the only symptom that appeared to increase exponentially with time from the late perimenopause.”³ According to a similar study, 28% of women experienced vaginal symptoms at menopause, increasing to 46% of women 9 years later.⁵ The same group also showed increasing urinary frequency and stress incon-

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IN THIS ARTICLE

Key Points

- The predominant cause of urogenital atrophy is menopause, whether it is natural or secondary to oophorectomy.
- Approximately 30% to 40% of menopausal women experience urogenital symptoms, with vaginal dryness and dyspareunia being the most commonly reported.
- Supplemental estrogen is available in oral, transdermal, and vaginal preparations. Vaginal lubricants and moisturizers are the mainstay of nonhormonal therapy.
- Menopausal symptoms vary widely. Appropriate treatment for urogenital atrophy depends on each woman's symptoms, lifestyle, and risk factors.

Competencies

Medical knowledge	◆◆◆◆◆
Interpersonal & communication skills	◆◆◆◆
Patient care	◆◆◆◆
Professionalism	◆
Practice-based learning and improvement	◆
Systems-based practice	◆

For an explanation of competencies ratings, see the table of contents.

tinence, with 32% reporting these conditions at menopause compared with 59% 9 years later.⁵

Despite the prevalence of urogenital symptoms, only 25% of these women seek medical treatment.^{7,9} Clinicians often do not screen for urogenital symptoms, and many women simply assume they are an irreversible part of aging. Oral HRT has been used universally for menopausal symptom treatment and may still be the best option for women with multiple symptoms and no contraindications to HRT. However, the premature cessation of the estrogen-plus-progestin arm of the Women's Health Initiative trial has led many patients and clinicians to avoid long-term use of oral hormone therapy, regardless of how well they comprehend the risks and benefits of treatment.^{10,11} In addition, 10% to 40% of women already taking oral estrogen still suffer from symptoms of vaginal atrophy.^{7,12} Through proper screening, detection, and management of this condition, clinicians have an opportunity to positively affect quality of life in this growing segment of the population.

Pathophysiology

The female urinary and genital structures arise from a common embryologic origin and are abundant with

receptors highly sensitive to changing estrogen levels. During the reproductive years, the vaginal mucosa is thick with rugae and glycogen-rich cells. The strong presence of lactobacilli helps to maintain a pH of 3.5 to 4.5, which creates an environment both hostile to pathogenic bacteria and protective against UTI. During the menopausal transition, estradiol levels drop from 120 ng/L to about 18 ng/L.¹³ The vaginal canal shrinks in length and diameter, and blood flow to the vagina decreases. As a result, the vaginal mucosa becomes thin and pale, with decreased elasticity and loss of rugae. The tissues become dry and more friable, leading to generalized discomfort and dyspareunia. There are fewer glycogen-rich cells and therefore few or no lactobacilli present. The vaginal pH rises to higher than 5, allowing colonization by more pathogenic bacteria such as streptococci, staphylococci, coliforms, and diphtheroids.¹³ The distance from the urethral opening to the vaginal introitus is reduced secondary to decreased collagen content and tissue atrophy.⁶ This and changes in vaginal flora increase susceptibility to UTI.

Predisposing factors

Urogenital atrophy is a direct result of reduced estrogen levels. The predominant cause is menopause, either natural or secondary to oophorectomy. However, multiple factors have been implicated in the development of atrophic vaginitis (see Table 2). Radiation therapy, chemotherapy, and various immune disorders can contribute to decreased estrogen levels. Additionally, women who require antiestrogenic medicines such as medroxyprogesterone, tamoxifen, danazol, leuprolide, or nafarelin may experience atrophic symptoms.⁷ Women who are in the postpartum period and those who are lactating also experience diminished estrogen levels due to placental loss and the action of elevated prolactin.⁷ Smokers may experience worsened atrophy secondary to increased metabolism of estrogen, but study results have been somewhat conflicting thus far.^{12,14} Finally, women who have never given birth vaginally or who tend to have nonfluctuating levels of estrogen are at increased risk of symptomatic atrophic vaginitis.¹⁵ Continued sexual activity, including masturbation, has been shown to increase genital blood flow, help maintain the elasticity of urogenital tissues, and delay the onset of atrophic symptoms.^{7,12}

Clinical presentation

Atrophy may first be apparent on external genital examination. The examiner will note decreased elasticity of the external genitalia, dryness of the labia, and possibly the presence of vulvular lesions.⁶ The labia majora appear shrunken, and the labia minora may be fused or even disappear altogether.^{7,12} The vaginal introitus is

often narrowed and the depth of the vagina itself reduced.⁷ (A small speculum should be used for the examination, as atrophic tissues are highly susceptible to trauma and the examination can often be painful.) The epithelial walls are generally “pale, smooth, shiny, and dry.”¹³ The thinning epithelium demonstrates loss of rugae and is often friable, leading to submucosal petechial hemorrhage and, occasionally, bleeding.¹² Additionally, a malodorous yellow discharge may be present.⁷ The presence of rectocele or cystocele should be noted. It is important to be aware that bacterial vaginosis, vaginal candidiasis, trichomoniasis, and tissue irritation from incontinence or the use of hygiene products can cause similar symptoms and may mimic or coexist with atrophic vaginitis (see Table 3, page 36). Be sure to evaluate women for these conditions even when you are relatively certain of the diagnosis of atrophic vaginitis.

Laboratory findings

Although atrophic vaginitis can be diagnosed clinically, several laboratory values can be helpful. Serum hormone testing will demonstrate the anticipated rise of FSH and fall of estradiol levels consistent with menopause. A pH strip inserted to the proximal third of the vaginal vault can be used to evaluate for the more alkaline environment associated with vaginal atrophy.¹³ A vaginal smear from the upper third of the lateral wall of the vagina will show a significantly reduced number of superficial cells and an increase in intermediate and parabasal cells. This relationship may be reported as the maturation index, a reflection of the percentage of each cell type present, with a lower value being indicative of a shift toward a predominance of parabasal cells.¹³

Treatment options

Menopausal symptoms vary widely. When choosing appropriate treatment for urogenital atrophy, take into account the woman’s symptoms, lifestyle, and risk factors. Therapeutic options include both hormonal and nonhormonal treatments, many of which can be used in combination. Supplemental estrogen is available in oral, transdermal, and vaginal preparations. Vaginal lubricants and moisturizers are the mainstay of nonhormonal therapy. Finally, modest lifestyle changes can aid in reducing the severity of atrophic symptoms. Thus far, there has been no evidence that phytoestrogens or herbal supplements provide any benefit in atrophic vaginitis.¹² There is limited evidence that the consumption of cranberry or lingonberry juice can reduce the frequency of UTI.¹²

Effectiveness of exogenous estrogen

Providing exogenous estrogen to the estrogen-deprived urogenital tissues is the most effective means of treating

the symptoms of atrophy. Multiple studies have demonstrated significant improvement in symptoms of vaginal dryness and irritation, dyspareunia, and recurrent UTI with use of vaginal estrogen preparations.^{9,14,15} Clinical signs of improvement are also apparent. With the addition of estrogen, there is a return of thickened squamous epithelium and glycogen-rich cells, and a resultant rise in the maturation index. Lactobacilli recolonize the vagina, and vaginal pH falls to premenopausal levels.⁹

Vaginal estrogen

Either oral or transdermal HRT is useful for patients who are experiencing multiple menopausal symptoms and for whom these treatments are not contraindicated. However, approximately 10% to 40% of women still experience urogenital symptoms while using systemic estrogen.^{7,12} For these patients, and for those who require treatment of urogenital symptoms alone, vaginal delivery of estro-

TABLE 1
Symptoms of atrophic vaginitis

Dyspareunia
Dysuria
Frequent urinary tract infections
Incontinence
Irritation
Itching
Urinary frequency
Vaginal dryness
Vulvar/vaginal burning and itching
Yellow malodorous discharge

TABLE 2
Predisposing factors for atrophic vaginitis

Anti-estrogenic medications: danazol, leuprolide, medroxyprogesterone, nafarelin, tamoxifen
Cigarette smoking
Declining ovarian function due to chemotherapy, menopause, oophorectomy, radiation therapy
Decreased or absent sexual activity
Lactation
Nulliparity

Data from Bachmann GA and Nevadunsky NS,⁷ and SOGC clinical practice guidelines.¹²

gen has proven extremely effective. Additionally, because of the ready absorption of estrogen by the urogenital tissues and the avoidance of hepatic first-pass metabolism, significantly lower doses are needed.

Available formulations include conjugated equine estrogens cream, estradiol cream, estradiol vaginal tablets, and an estradiol-releasing vaginal ring (see Table 4). All formulations are similarly effective in relieving the signs and symptoms of urogenital atrophy. They differ in delivery method, dosing, amount of estrogen absorbed systemically, and patient preference. It is important to note that contra-indications to estrogen therapy include estrogen-sensitive tumors, thromboembolic disorders, undiagnosed vaginal bleeding, and pregnancy.^{7,16} Use caution when prescribing vaginal estrogen for patients with cardiovascular or liver disease.¹⁶

Estrogen creams

Vaginal estrogen cream is available as conjugated equine estrogens cream and estradiol cream. The conjugated equine estrogens cream provides 0.625 mg of conjugated estrogens per gram of cream. The manufacturer's recommended dosage is 0.5 to 2 g inserted vaginally once a day. However, after 2 weeks patients are often able to reduce the dosage to three times a week or less and still achieve symptom control.¹⁰ The estradiol cream provides 0.1 mg of estradiol per gram of cream. The recommended dosage is 2 to 4 g per day for 1 to 2 weeks, then half of the starting dosage for 1 to 2 weeks, and finally tapering to 1 g one to three times per week for maintenance dosing.

It is important to emphasize to patients that the creams must be used at the lowest effective dose. Estrogen is readily absorbed through the vaginal mucosa, and systemic levels can be achieved, especially at higher doses, increasing the risk of endometrial proliferation and hyperplasia.¹⁶ Furthermore, higher dosing increases the risk of systemic adverse effects commonly associated with estrogen administration, such as headache, breast tenderness, and vaginal bleeding and may also elevate the risk of an estrogen-dependent neoplasm.⁷

Estradiol tablets

A vaginal tablet containing 25 mcg of estradiol is available. Patients use the supplied applicator to insert 1 tablet vaginally daily for 2 weeks, after which the dosing is reduced to 1 tablet twice a week. This dosing schedule limits the systemic absorption of estradiol while still

TABLE 3

Differential diagnosis of atrophic vaginitis

- Tight-fitting clothing
- Tissue irritation due to
 - Hygiene products
 - Incontinence
 - Lubricants
 - Spermicides
- Vaginal infections
 - Bacterial vaginosis
 - Candidiasis
 - Trichomoniasis

Data from Ballagh SA.¹⁵

allowing effective treatment of atrophic symptoms. In most women, systemic estradiol levels remain within the postmenopausal range.¹⁷

A comparative study showed that the tablets are as effective as conjugated equine estrogens cream for symptoms of atrophic vaginitis. The vaginal cream was dosed at 2 g daily for 21 days with 7 days off, repeated cyclically. The two products showed similar levels of symptom improvement as early as week 2 and continuing through week 24.¹⁸ Patients experienced fewer adverse effects with and expressed increased overall preference for the tablets. Uterine bleeding, breast pain, and perineal pain were reported by 9% of women in the tablet group, compared with 34% of women using the cream.¹⁸ Additionally, only 5% of the women using the tablet displayed

hormone levels above the postmenopausal range, compared to 47% in the cream group.¹⁸ One woman in the vaginal tablet group showed endometrial proliferation on biopsy, while 13 patients in the conjugated equine estrogens cream group demonstrated endometrial proliferation and two had hyperplasia.¹⁸

Estradiol-releasing ring

A flexible silicone ring, containing a total of 2 mg of 17beta-estradiol, can be inserted into the upper third of the vaginal vault, where it remains in place for 3 months. There is no need to remove the ring for activities such as bathing or intercourse, although some women may choose to do so. If so, the ring is simply rinsed with cold water and later reinserted. The ring provides a continuous release of estradiol averaging 7.5 mcg per day, only 8% of which is systemically absorbed.¹⁹

A multicenter study demonstrated that the ring produced a significant improvement in vaginal dryness, vulvar pruritus, dyspareunia, dysuria, and urinary urgency in more than 90% of the treatment group within 3 months and that the improvement was maintained over a year.²⁰ In a later study, Eriksen also demonstrated a significant reduction in UTIs in postmenopausal women over a period of 36 weeks.¹⁴ With use of the ring, systemic estradiol levels do not rise above postmenopausal levels (20-30 pmol/L), making endometrial proliferation less likely, as several studies have established that a level greater than 60 pmol/L must be maintained to precipitate endometrial proliferation.^{19,20}

Overall patient acceptance of the ring has been very high, and most women report having no difficulty with ring insertion or removal. The most commonly reported

adverse effects are headache and leukorrhea.¹⁹ It may be reasonable for women who would benefit from vaginal estrogen treatment but who are physically unable to use vaginal products to have a health care provider insert the ring once every 3 months.

Selective estrogen receptor modulators

While the antiestrogenic effects of tamoxifen have been shown to exacerbate signs and symptoms of urogenital atrophy, raloxifene appears to have little effect on urogenital tissues. In clinical trials, there was no change in the vaginal maturation index and no worsening of vaginal symptoms.¹² Additionally, concurrent use of raloxifene with conjugated equine estrogens cream had no independent effect on the vaginal tissues.¹²

Safety

Low-dose vaginal estrogens are an excellent alternative for women who experience symptoms of urogenital atrophy and who wish to avoid or do not require systemic estrogen. The limited systemic absorption minimizes the risks of adverse effects and endometrial hyperplasia. A recent review recognized that short-term treatment with vaginal estrogen for women with an intact uterus does not necessarily require opposing progestin.¹⁶ However, long-term safety information is limited, as most trials using vaginal estrogen preparations have a duration of less than 6 months. As more women enter the menopausal years, the need for long-term use of these preparations may grow.

Patients and clinicians should be aware that vaginal tissue readily absorbs estrogen into the bloodstream, making systemic adverse effects with long-term use a possibility. This is especially true with the higher dosing levels of the estrogen creams. Cyclic dosing can help reduce systemic estrogen exposure. Additionally, clinicians should consider adding an opposing progestin or implementing a progestin challenge test after 3 months of topical estrogen therapy, then annually thereafter.¹⁵ Women who respond to this challenge with withdrawal bleeding can then be referred for endometrial ultrasound or biopsy as appropriate.

Nonhormonal topical treatments

Women who are unable or reluctant to use topical hormonal therapy may find commercially available vaginal lubricants or moisturizers helpful. The vaginal lubricants can often provide temporary relief of dryness and dyspareunia. A widely available vaginal moisturizer (Replens) has been shown to significantly decrease the signs and symptoms of vaginal atrophy in clinical trials.

Replens is a bioadhesive vaginal moisturizer which, when used 3 times a week, can improve atrophic symptoms within 2 to 4 weeks.^{21,22} One study comparing use

of 2 g of conjugated estrogens cream daily with Replens 3 times a week found “statistically significant return of vaginal moisture and vaginal fluid volume” within 12 weeks in the Replens group, compared to the 4 weeks it took to achieve the same effects in the estrogens cream group.²¹ Additionally, both groups experienced an increase in vaginal elasticity and a reduction of vaginal pH to premenopausal levels. These results were later duplicated in a Swedish study comparing Replens to a vaginal estrogen cream.²² The return of a more acid environment may also reduce the risk of vaginal infections and UTIs, although this premise has not yet been fully evaluated.

In a third trial, which compared Replens with a palm oil lubricant as placebo, there was no statistically significant difference between groups.²³ Both reported a 60% decrease in vaginal dryness and improvements in dyspareunia (60% in the Replens group compared to 40% in

TABLE 4
Treatment options for atrophic vaginitis

Conjugated equine estrogens cream (Premarin)
<ul style="list-style-type: none"> • 0.625 mg conjugated estrogens per g of cream • Dosage 0.5-2 g inserted vaginally daily • May be able to reduce dosage and/or frequency after 2 wk
Estradiol 0.01% cream (Estrace)
<ul style="list-style-type: none"> • 0.1 mg of estradiol per g of cream • 2-4 g inserted vaginally daily for 1-2 wk, then half of starting dosage for 1-2 wk, then 1 g one to three times per wk
Estradiol vaginal tablets (Vagifem)
<ul style="list-style-type: none"> • 25-mcg tablet with applicator • 1 tablet inserted vaginally daily for 2 wk, then 2 times per wk
Vaginal ring (Estring)
<ul style="list-style-type: none"> • Silicone ring inserted into the upper third of the vaginal vault every 3 mo • Ring releases 7.5 mcg of estradiol daily • Removal for bathing or intercourse not necessary
Vaginal moisturizer (Replens)
<ul style="list-style-type: none"> • Available as prefilled applicators or a single tube of product with a reusable applicator • One applicator inserted vaginally 3 times per wk

the placebo group).²³ These products provide a welcome alternative for women seeking nonhormonal treatment for symptoms of vaginal atrophy.

Conclusion

Although urogenital atrophy is a natural consequence of declining estrogen levels, the unwelcome consequences of vaginal dryness and irritation, dyspareunia, and frequent UTIs can significantly reduce quality of life. As the population of postmenopausal women grows, more of them will require treatment for atrophic vaginitis. Rather than wait for patients to complain of symptoms, clinicians can provide screening during routine visits. Various topical estrogen products, in addition to OTC vaginal moisturizers, provide many efficacious treatment options. Many women view this approach as a welcome alternative to systemic hormone therapy. □

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