

POSITION STATEMENT

The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society

Abstract

Objective: To create an evidence-based position statement published by The North American Menopause Society (NAMS) on the role of local vaginal estrogen therapy (ET) for the treatment of vaginal atrophy in postmenopausal women.

Design: NAMS followed the general principles established for evidence-based guidelines to create this document. A panel of clinicians and researchers acknowledged to be experts in the field of genitourinary disease was enlisted to review, synthesize, and interpret the current evidence on vaginal ET for vaginal atrophy, develop conclusions, and make recommendations. Their advice was used to assist the NAMS Board of Trustees in publishing this position statement.

Results: Randomized controlled trials, albeit limited, have shown that low-dose, local vaginal estrogen delivery is effective and well tolerated for treating vaginal atrophy. All of the low-dose vaginal estrogen products approved in the United States for treatment of vaginal atrophy are equally effective at the doses recommended in labeling.

Conclusions: The choice of therapy should be guided by clinical experience and patient preference. Progestogen is generally not indicated when low-dose estrogen is administered locally for vaginal atrophy. Data are insufficient to recommend annual endometrial surveillance in asymptomatic women using vaginal ET. Vaginal ET should be continued for women as long as distressful symptoms remain. For women treated for non-hormone-dependent cancer, management of vaginal atrophy is similar to that for women without a cancer history. For women with a history of hormone-dependent cancer, management recommendations are dependent upon each woman's preference in consultation with her oncologist.

Key Words: Menopause – Vaginal atrophy – Vaginal estrogen – Postmenopause – Vaginal dryness – Dyspareunia – Cancer treatments – NAMS.

Symptoms resulting from vaginal atrophy are frequent complaints of postmenopausal women. Although vasomotor symptoms typically accompany the loss of ovarian estrogen production, they usually abate over time regardless of whether estrogen treatment is used. In contrast,

vaginal symptoms, which include vaginal dryness, vulvovaginal irritation and itching, and dyspareunia, are usually progressive and unlikely to resolve spontaneously. Left untreated, vaginal atrophy can result in years of vulvovaginal discomfort, with a significant impact on quality of life.

An estimated 10% to 40% of postmenopausal women have symptoms related to vaginal atrophy. Most cases of symptomatic vaginal atrophy require treatment; however, only about 25% of symptomatic women seek medical help. Estrogen therapy (ET), administered either vaginally at a low dose or systemically, is considered the therapeutic standard for moderate to severe vaginal atrophy. Localized vaginal delivery of estrogen is available in North America in government-approved therapies via cream, tablet, and ring for the treatment of vaginal atrophy symptoms, with fewer adverse effects than systemic estrogen.

The Board of Trustees of The North American Menopause Society (NAMS) developed this position statement with assistance from the following Editorial Board: Gloria A. Bachmann, MD (Chair); Shawna L. Johnston, MD; Bruce Kessel, MD; M. Tish Knopf, RN, PhD; and Elizabeth G. Stewart, MD. It was edited, modified, and subsequently approved by the NAMS Board of Trustees on February 23, 2007.

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In response to the need for recommendations for North American clinical practice for menopause-associated health conditions, The North American Menopause Society (NAMS) has created this evidence-based position statement. The objective of this position statement is to evaluate the safety and effectiveness of local vaginal estrogen products for the treatment of vaginal atrophy in postmenopausal women and to provide guidance on their use to physicians, physician assistants, nurse practitioners, nurses, and other healthcare professionals caring for this population, especially those in the fields of obstetrics and gynecology, internal medicine, primary care, geriatrics, and urology.

For this position statement, NAMS systematically reviewed the relevant medical literature. Using the MEDLINE database, a search was made for clinical trials, meta-analyses, and clinical practice guidelines published in English and related to vaginal ET for vaginal atrophy in postmenopausal women. The Medical Subject Headings used for the search were postmenopause, physiological sexual dysfunction (including dyspareunia, vaginismus, and vaginitis), and vaginal disease, with subheadings of epidemiology, etiology, diagnosis, prevention, control, and therapy. The National Guideline Clearinghouse was searched for relevant clinical practice guidelines, and the Cochrane Library was searched for relevant systematic reviews. Priority was given to evidence from randomized controlled clinical trials and to meta-analyses of such trials, followed by evidence from controlled observational studies, using criteria described elsewhere.¹⁻³ Conclusions from other evidence-based guidelines were also reviewed. Because standards of care and treatment options differ throughout the world, the focus was limited to therapies available in North America.

In developing this position statement, NAMS enlisted a five-person Editorial Board composed of experts in endocrinology, gynecology, and female genital diseases. The Editorial Board reviewed, synthesized, and interpreted the published data, developed conclusions, and made recommendations. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established. (Practice parameter standards related to NAMS position statements have been described in an editorial.⁴) The NAMS Board of Trustees was responsible for the final review and approval of this position statement.

CAUSES OF VAGINAL ATROPHY

The vagina is composed of an inner stratified squamous epithelium, a middle muscular layer, and an outer fibrous layer. Before menopause, in the presence of endogenous estrogen levels, the vagina is characterized by a thickened rugated vaginal surface, increased vaginal blood flow, and vaginal lubrication.

Estrogen is a dominant regulator of vaginal physiology. Estrogen-receptor alpha is present in the vaginal tissues of both pre- and postmenopausal women, whereas estrogen receptor beta appears to be present only in premenopausal

vaginal tissues.^{5,6} Exogenous ET has multiple effects on the vagina, including increased blood flow, improved epithelial thickness, reduced pH, and increased secretions.

Diminished estrogen levels

Vaginal atrophy is most commonly associated with the diminished estrogen levels that accompany menopause (spontaneous or induced) and aging. Decreasing estrogen levels are also associated with atrophy of the vulva and lower urinary tract, commonly referred to as *urogenital atrophy*. However, this paper focuses only on vaginal atrophy.

The term *vaginal atrophy* describes vaginal walls that are thin, pale, dry, and sometimes inflamed (ie, atrophic vaginitis). When normal premenopausal circulating estrogen levels decrease during perimenopause or after induced menopause, the vagina shortens and narrows. The vaginal walls may exhibit small petechiae (ie, pinpoint, nonraised, round, purple-red spots caused by intradermal or submucous hemorrhage) and become thinner (often only a few cell layers thick), less elastic, and progressively smoother as rugal folds decrease. Vaginal blood flow diminishes. Although the sebaceous glands remain prominent, their secretions diminish and the onset of lubrication during sexual stimulation is delayed.⁷

Basic science information on the vaginal epithelium is scarce. In one model system that used cultures of vaginal-cervical epithelial cells, both aging and diminished estrogen levels were found to be independent factors in decreasing vaginal-cervical paracellular permeability, which, in turn, could have an impact on vaginal dryness.⁸ Cytologic changes in vaginal epithelial cell types are characterized by an increase in parabasal and intermediate cells and a substantial decrease in superficial cells. In premenopausal women, intermediate and superficial cells predominate; few parabasal cells are noted.⁷ Other factors that may also play a role in vaginal health include epidermal growth factor, retinoids, and nitric oxide.

In premenopausal women, the acidic pH of the vaginal fluid is an important component of the nonspecific host defense against pathogens. With estrogen stimulation, the vaginal epithelium produces glycogen, which is broken down to glucose. *Lactobacillus* species metabolize glucose and produce lactic acid, which is responsible for the acid pH of the vagina. When estrogenic stimulation is lacking, lactobacilli decrease, which then shifts the vaginal pH toward alkalinity.⁹ The pH increases to 5.0 or greater from the premenopausal range of 3.5 to 4.5.¹⁰ This higher pH allows colonization of the vagina by fecal flora and other pathogens.

All of these changes increase the likelihood of trauma, infection, and pain, and can result in dyspareunia. Left untreated, vaginal atrophy can ultimately result in a vaginal surface that is friable, with petechiae, ulcerations, tears, and bleeding often occurring from minimal trauma (eg, speculum insertion, intercourse).^{7,11}

Cancer treatments

Symptomatic vaginal atrophy can be associated with cancer treatments such as surgery, pelvic radiation therapy, chemotherapy, and endocrine therapy, as these interventions may result in changes in the vaginal epithelium, impaired vascular supply, and anatomic alterations in the vaginal canal. Many cancer treatments also cause either temporary or permanent ovarian failure, which in the premenopausal woman will result in adverse vaginal changes. The effects of cancer treatments may be associated with painful pelvic examinations, dyspareunia, increased risk of vaginal infections, and a narrower and shortened vagina.¹²

Vaginal symptoms related to an abrupt menopause induced by chemotherapy (eg, discomfort, dryness, dyspareunia) are associated with significantly greater sexual dysfunction and distress,¹³⁻¹⁵ as well as poorer quality-of-life outcomes.¹⁶⁻²⁰

Endocrine therapy for breast cancer is also associated with vaginal symptoms. Selective estrogen-receptor modulators (SERMs) vary in their effect on vaginal tissue. One SERM, tamoxifen, exerts predominantly antiestrogenic effects in the breast; however, it also produces estrogen-agonistic effects in the uterus and vagina. Vaginal discharge is the most common vaginal complaint,^{21,22} and there is a slightly increased incidence of vaginal moniliasis.²³ Another SERM, raloxifene, has been found to have fewer adverse vaginal effects.²⁴⁻²⁷

Compared with tamoxifen, aromatase inhibitors have a significantly greater incidence of vaginal dryness and dyspareunia.^{21,28-30}

PATIENT EVALUATION

Most cases of vaginal atrophy in postmenopausal women result from the lower estrogen levels associated with menopause. The timing of the onset of vaginal atrophy symptoms with respect to time since menopause varies from one woman to another.³¹

Medical history

Peri- and postmenopausal reductions in ovarian estrogen production are not, however, the only potential causes of vaginal atrophy. A goal of the medical history is to rule out other causes, including other hypoestrogenic states (eg, premature ovarian failure, hypothalamic amenorrhea, hyperprolactinemia, and possibly prolonged lactation), some endocrine therapies (eg, SERMs, aromatase inhibitors, and gonadotropin-releasing hormone [GnRH] agonists or antagonists), and medically induced menopause (eg, cancer treatment). Similar symptoms can be experienced by postmenopausal women suffering from infection, trauma, foreign body, allergic reaction, inflammatory conditions of the vulva, benign and malignant tumors, other medical disorders (eg, diabetes, lupus erythematosus), and psychological causes.

Symptoms of vaginal atrophy include dryness (in 75% of postmenopausal women), dyspareunia (38%), and vaginal itching, discharge, and pain (15%).³² Irritative urinary

symptoms—frequency, urgency, and burning with urination—may be reported. Vaginal bleeding may occur if atrophy is severe.

Information to be collected during the patient history includes her partner relationship(s), current sexual activity, history of interventions used, therapeutic goals for vaginal symptoms, and level of perceived distress associated with the reported complaints. Physiological, psychological, and behavioral responses to the symptoms should also be included.

For a woman with a history of cancer, additional information needs to be collected: site of the cancer, hormone dependence of the cancer, type(s) of cancer treatment (past, current), age of the woman at diagnosis and current age, and type of menopause (spontaneous or induced). Vaginal dryness is a common symptom among women treated for cancer, but it may not be related to estrogen loss. For younger women with induced menopause, vaginal dryness is associated with dyspareunia and other distressing changes in sexual functioning.^{15,20}

Vaginal stenosis is a common sequela associated with surgery and radiation therapy for gynecologic malignancies. Interventions (dilators, lubricants) are often useful after therapy to minimize this complication, but routine use in clinical practice is not universal. If such interventions are not initiated, a woman may experience chronic discomfort, painful pelvic examinations, and dyspareunia. Some women may not be able to engage in sexual intercourse. Thus, a history of any interventions used and their outcomes is essential.

Physical examination

Discrepancies may be seen between a woman's symptoms and physical findings on examination. Signs observed during evaluation of the vulva and vagina vary with the degree of atrophy.

In early stages, the epithelium of the vestibule is thin and dry, and the vagina is mildly erythematous. As atrophy progresses, there is loss of the labial fat pad, making the labia majora pendulous and the labia minora less distinct. As the prepuce covering the clitoris decreases, the clitoris itself may appear larger.^{32,33} The tissues of the vulva become progressively pallid, thin, and dry. There may be tenderness to palpation in the vestibule. The vagina loses elasticity, shortens, narrows, becomes less distensible, and can be easily traumatized and irritated. The vaginal epithelium has a dry, glazed appearance ranging from varying degrees of erythema to pallor. Gradual flattening, then loss of rugae occur, and the fornices may become obliterated, making the cervix flush with the vault. Petechiae may be seen in the vestibule or vagina. Sticky yellow secretions may be present.

With vaginal atrophy, vaginal pH is typically greater than 5.0. Wet-mount microscopy shows more than one white blood cell per epithelial cell, immature vaginal epithelial cells with relatively large nuclei (parabasal cells), and reduced or absent lactobacilli. Repopulation with diverse

flora occurs, including enteric organisms commonly associated with urinary tract infections (UTIs).³³ The wet mount of atrophy is identical to that of desquamative inflammatory vaginitis or vaginal lichen planus; therefore, a trial of adequate local estrogen is essential to differentiate these two conditions.

TREATMENT

The primary goals of vaginal atrophy management are to alleviate symptoms and to reverse atrophic anatomic changes. First-line therapies for women with vaginal atrophy include nonhormonal vaginal lubricants and moisturizers, as well as continued sexual activity. For symptomatic vaginal atrophy that does not respond to these options, prescription therapy may be required. The basic premise of treating a condition caused by a lack of adequate hormonal stimulation is to supplement that hormone; the same premise applies to pharmacologic treatment of hypoestrogenic vaginal atrophy. Unlike age-related changes in the urogenital tissues, most vaginal effects of diminished estrogen levels can be reversed.

Exogenous estrogen, delivered either systemically or locally, is the therapeutic standard for prescription therapies. However, even though systemic ET (eg, oral, transdermal) is an effective treatment for a variety of postmenopausal symptoms associated with estrogen deprivation, including vaginal atrophy, it may be contraindicated in or unacceptable to some women because of its potential for systemic adverse effects, especially with long-term use. Vaginally administered local ET can provide sufficient estrogen to reverse atrophic changes in the vaginal tissues and to relieve associated symptoms while limiting systemic absorption. With limited systemic absorption, enterohepatic metabolism does not occur, and thus, lower doses of vaginal estrogen achieve a tissue effect similar to that achieved by oral or transdermal dosing. However, low-dose local estrogen administration has no effect on reducing vasomotor symptoms or on lowering the risk of osteoporotic fracture.

A systematic review of clinical trial results shows that vaginally administered ET significantly improves vaginal cytomorphology and atrophic vaginal symptoms.³⁴ The effects of vaginal ET on other sequelae of urogenital aging, including urinary frequency and urgency, urinary incontinence, and UTIs, are less clear, perhaps because these conditions have more complex multifactorial causes not clearly related to estrogen deficiency or tissue aging.

Types of vaginal estrogen

Various types of estrogen and modes of delivery have been used for the treatment of vaginal atrophy. A list of vaginal estrogen products government approved in the United States and Canada for the treatment of vaginal atrophy (ie, vulval and vaginal atrophy, atrophic vaginitis, kraurosis vulvae) is found in Table 1. Those delivering a localized estrogen dose are an estradiol cream (Estrace Vaginal Cream, available in the United States but not Canada), a conjugated estrogens (CE) vaginal cream

TABLE 1. Vaginal estrogen therapy products government approved for treatment of vaginal atrophy in the United States and Canada

Composition	Product name	Dosing as per labeling
<i>Vaginal cream</i>		
Estradiol	Estrace Vaginal Cream ^a	Initial: 2.0-4.0 g/d for 1-2 wk Maintenance: 1.0 g/d (0.1 mg active ingredient/g)
Conjugated estrogens	Premarin Vaginal Cream	0.5-2.0 g/d (0.625 mg active ingredient/g)
<i>Vaginal ring</i>		
Estradiol	Estring	Device containing 2 mg releases 7.5 µg/d for 90 d
Estradiol acetate	Femring ^{ab}	Systemic-dose device containing 12.4 or 24.8 mg estradiol acetate releases 50 or 100 µg/d estradiol for 90 d
<i>Vaginal tablet</i>		
Estradiol hemihydrate	Vagifem	Initial: 1 tablet/d for 2 wk Maintenance: 1 tablet twice weekly (tablet containing 25.8 µg of estradiol hemihydrate equivalent to 25 µg of estradiol)

^a Available only in the United States, not in Canada.

^b Delivers systemic dose.

(Premarin Vaginal Cream), a sustained-release Silastic ring that delivers estradiol (Estring), and a micronized estradiol hemihydrate vaginal tablet (Vagifem). The optimal treatment regimen and minimum effective dose for each preparation, however, have not yet been established, so the regimens used clinically reflect the treatment protocols used in the studies, commercial product availability, and government-approved labeling.

Another vaginal estrogen product that is available in the United States but not Canada is the estradiol acetate ring (Femring); this product delivers a systemic dose of estrogen and is therefore not considered in this review, even though one of its indications is treatment of vaginal atrophy.

Other vaginal estrogens have been compared in trials but are not available in government-approved products for use in the United States or Canada. These include estriol delivered vaginally via pessary, tablet, cream, and suppository, and estradiol delivered via vaginal ovule. Various custom-compounded recipes are available, however, from a prescriber's order.

A Cochrane review of results from 16 clinical trials conducted on 2,129 postmenopausal women using one of three types of estrogen products—CE vaginal cream, the estradiol hemihydrate vaginal tablet, and the estradiol vaginal ring—concluded that all were equally effective for relief of subjective vaginal atrophy symptoms such as vaginal dryness, irritation, and dyspareunia.³⁴

Vaginal cream

Vaginal cream has been in use longer than the other types of vaginal ET. Vaginally administered CE cream (Premarin

Vaginal Cream) contains 0.625 mg of conjugated estrogens per gram. Efficacy in randomized controlled trials has been shown with doses ranging from 0.5 to 2.0 g (delivering 0.3 mg to 1.25 mg CE) in schedules ranging from once daily to two or three times weekly.³⁵⁻³⁹ Women report relief of symptoms with doses as low as 0.5 g (0.3 mg CE) administered once nightly for 2 weeks and thereafter three times weekly for 12 weeks.⁴⁰ (See "Evidence.") No randomized controlled trial data are available for a vaginal cream containing estradiol (Estrace Vaginal Cream).

Localized therapy with an estrogen vaginal cream typically consists of a loading dose of 2 to 4 g/d for 2 weeks. After the initial therapeutic response is attained, the frequency can be reduced. A maintenance schedule of one to three doses per week is usually sufficient, but it should be titrated to the lowest dose and frequency of vaginal estrogen that provides the desired effect. With cream delivery, ensuring that doses equivalent to low and ultralow amounts of estrogen is dependent on the amount of cream inserted by the user, since the cream is not in a prepackaged dosing unit. Dosing is recommended at least 12 hours before coital activity.

Estradiol ring

The sustained-release estradiol ring (Estring) contains 2 mg of micronized estradiol, and it releases 7.5 µg of estradiol every 24 hours. One ring is placed in the vagina every 90 days. Effective relief of atrophic symptoms has been consistently documented in randomized controlled trials with this preparation.^{36,37,41-45} (See "Evidence.")

The vaginal ring has been shown in randomized trials to be significantly more effective than placebo⁴² and as effective as CE cream^{36,37} or vaginal tablets containing either estradiol⁴⁵ or estriol.⁴³ The vaginal ring produced similar endometrial proliferation as 0.625 mg CE cream in one of these studies³⁶ but less in another study when compared to 1.25 mg CE cream.³⁷

During the 90 days that the ring stays in the vagina delivering a sustained dose of estradiol, it may change position or dislodge with bowel movements, Valsalva maneuvers, douching, or vaginal sexual intercourse. Ideally, users remove and replace their own vaginal rings, though discomfort and limited dexterity can make such self-care difficult. There is no need to remove the ring during coital activity, although opinions are mixed about tampon use with the ring. There are no data to suggest that an allergic reaction occurs from the Silastic plastic.

Vaginal tablet

The vaginal tablet (Vagifem) contains 25.8 µg micronized estradiol hemihydrate, which is equivalent to 25 µg of estradiol. Efficacy in randomized controlled trials has been shown with a regimen of one 25-µg vaginal tablet inserted (into the posterior vaginal vault) once daily for 2 weeks, followed by one 25-µg vaginal tablet inserted twice weekly.^{38,39,45-48} (See "Evidence.")

Randomized controlled trials indicate that the marketed vaginal tablet is more effective than placebo^{46,49,50} and as efficacious as the estradiol ring,⁴⁵ and CE cream.^{38,39}

Evidence

Various subjective outcome measures have been used to quantify the effect of estrogen treatment on the vagina, including improvements in atrophic symptoms, gross vaginal appearance, lower urinary tract symptoms, and patient preference. Objective outcome measures have included decreases in vaginal pH, increases in the number of vaginal lactobacilli, shifts in the vaginal and/or urethral cytology to favor superficial cells, and/or changes in sterile urine culture. Serum estradiol, follicle-stimulating hormone levels, endometrial thickness on ultrasound, endometrial histology, and the occurrence of bleeding after progestogen administration have been used to determine the safety, not the efficacy, of vaginal ET.

The evidence base regarding vaginal ET is not robust. Thus, results should be interpreted with caution. A 2002 literature review by Crandall⁵¹ identified 22 randomized controlled trials evaluating vaginal ET for postmenopausal women with symptoms or signs of vaginal atrophy. A 2003 Cochrane review³⁴ identified 29 trials, but only 16 (a total of 2,129 women) met their inclusion criteria. Of those, only three were placebo controlled (see Table 2).

Comparative analyses of these trials are limited by variations in methods and outcome measures, small sample sizes, and substantial heterogeneity in results. For example, some trials of the same estrogen preparation used different doses or dosing schedules. Some trials included preparations that are not approved for use in the United States or Canada. Several trials that reported comparative efficacy of preparations were not blinded. In addition, long-term effects (at least 1 y) of treatment have not been well documented. Nevertheless, there is general consensus among governmental regulatory bodies that the data confirm the efficacy of vaginal ET for the treatment of vaginal atrophy, especially if the underlying reason for the condition is estrogen deficiency.

Vaginal symptoms

Relief of vaginal atrophy symptoms with vaginal ET has been studied in uncontrolled open-label studies and in comparative (equivalency) studies of different estrogen preparations. Only four randomized, double-blind, placebo-controlled trials exist, and each studied a different product and each used different outcome measures.

In a trial using the estradiol ring,⁴² therapy significantly improved dyspareunia compared with placebo after 24 weeks; however, other atrophic symptoms were not studied. In a trial using the marketed estradiol tablet,⁴⁶ significant improvement in moderate to severe vaginal atrophy was noted. After 12 weeks of therapy, symptoms persisted in just 10.7% of treated women, compared with 29.9% of placebo recipients ($P < 0.0001$). Subjective symptoms of vaginal dyspareunia were reported in 8% and 24.4% in the treatment and placebo groups, respectively ($P < 0.002$). The complaint

TABLE 2. Clinical trials of vaginal estrogen therapy for vaginal atrophy in postmenopausal women^a

Reference	Design	Estrogen type	Efficacy	Side effects	Acceptability
Cream vs placebo					
Nachtigall, ³⁵ 1994	12 wk, R, PG, C; N = 30	1.25 mg CE vaginal cream daily vs nonhormonal vaginal gel 3×/wk	CE cream > gel in cell morphology; CE cream = gel in vaginal atrophy, pH	None in either group	Not measured
Bygdeman and Swahn, ⁵⁴ 1996	12 wk, R, C, PG; N = 39	5 mg DN vaginal cream 3×/wk vs nonhormonal vaginal gel daily for 2 wk, then 3×/wk	DN cream > gel in vaginal dryness index; DN cream = gel in vaginal itching, irritation, dyspareunia, pH	None in either group	Not measured
Ring vs placebo					
Casper and Petri, ⁴² 1999	24 wk, R, DB, PC, PG; N = 84	2 mg E ₂ vaginal ring (7.5 µg/d) vs placebo	E ₂ ring > placebo in MV, pH, dyspareunia	E ₂ ring = placebo in endometrial thickness	Not measured
Ring vs tablet					
Henriksson et al, ⁴³ 1994	12 wk, R, C, PG; N = 146	2 mg E ₂ vaginal ring (6.5-9.5 µg/d) vs 0.5 mg E ₃ vaginal pessary 2×/wk	E ₂ ring = E ₃ pessary in vaginal dryness, itching, dyspareunia; E ₂ ring > E ₃ pessary in MV; E ₂ ring = E ₃ pessary in phys assessment, pH	E ₃ pessary > E ₂ ring in itching; no serious side effects reported	E ₂ ring > E ₃ pessary in comfort
Casper and Petri, ⁴² 1999	12 wk, R, C, PG; N = 219	2 mg E ₂ vaginal ring (7.5 µg/d) vs 0.5 mg E ₃ vaginal pessary	E ₃ pessary = E ₂ ring in pH, phys assessment, patient response	E ₂ ring = E ₃ pessary in side effects	E ₂ ring > E ₃ pessary
Lose and Englev, ⁴⁴ 2000	24 wk, R, C, PG; N = 251	2 mg E ₂ vaginal ring (7.5 µg/d) for 24 wk vs 0.5 mg E ₃ vaginal pessary daily for 3 wk then every second day for remainder of 24-wk period	E ₃ pessary > E ₂ ring in vaginal dryness; E ₂ ring = E ₃ pessary in dyspareunia	E ₂ ring = E ₃ pessary in side effects	E ₂ ring > E ₃ pessary
Weisberg et al, ⁴⁵ 2005 (orig, unpubl. data 2000)	48 wk, R, C, PG; N = 185	2 mg E ₂ vaginal ring (7.5 µg/d) vs 25 µg E ₂ vaginal tablet daily for 2 wk then 2×/wk	E ₂ tab > E ₂ ring in subjective assessment	E ₂ tab > E ₂ ring in bleeding/spotting; equal in endometrial thickness	Not measured
Ring vs cream					
Barentsen et al, ⁴¹ 1997	24 wk, R, C, CO; N = 165	2 mg E ₂ vaginal ring (7.5 µg/d) vs 0.5 mg E ₃ vaginal cream daily for 2 wk then 3×/wk	E ₂ ring = E ₃ cream in patient ratings, vaginal atrophy, dryness, pH, MV; E ₂ ring > E ₃ cream in pruritus	E ₂ ring = E ₃ cream in endometrial thickening, bleeding	E ₂ ring > E ₃ cream
Nachtigall, ³⁷ 1995	15 wk, R, C, PG; N = 192	2 mg E ₂ vaginal ring (7.5 µg/d) vs 2 g CE vaginal cream (1.25 mg) 3×/wk	E ₂ ring = CE cream in phys assessment, vaginal atrophy, pH	CE cream > E ₂ ring in endometrial thickness, bleeding	E ₂ ring > CE cream
Ayton et al, ³⁶ 1996	12 wk, R, C, PG; N = 194	2 mg E ₂ vaginal ring (7.5 µg/d) vs 0.625 mg CE vaginal cream 21 of 28 d	E ₂ ring = CE cream in vaginal dryness, dyspareunia, physical assessment, MV, pH	E ₂ ring = CE cream in endometrial thickness, bleeding	E ₂ ring > CE cream
Tablet vs placebo					
Foidart et al, ⁴⁹ 1991	24 wk, R, DB, PC, PG; N = 109	3.5 mg E ₃ vaginal suppository vs placebo; 2×/wk for 3 wk then 1/wk	E ₃ suppository > placebo in patient ratings, vasomotor symptoms, pH	E ₃ suppository = placebo in endometrial thickening	Not measured

(Continued on next page)

TABLE 2 (continued)

Reference	Design	Estrogen type	Efficacy	Side effects	Acceptability
Eriksen and Rasmussen, ⁴⁶ 1992	12 wk, R, DB, PC, PG; N = 164	25 µg E ₂ vaginal tablet vs placebo; 1/d for 2 wk then 2×/wk	E ₂ tablet > placebo in vaginal atrophy, dryness, itching, dyspareunia	Not measured	Not measured
Garcia, ⁵⁰ 1993	16 wk, R, DB, PC, PG; N = 30	3.5 mg E ₂ vaginal ovules vs placebo; 2×/wk for 3 wk then 1×/wk	E ₂ ovule > placebo in symptom improvement	Not measured	Not measured
Tablet vs tablet					
Dugal et al, ⁴⁷ 2000	24 wk, R, C, PG; N = 96	25 µg E ₂ vaginal tablet vs 0.5 mg E ₃ vaginal tablet; once daily for 2 wk then 2×/wk	E ₂ tablet = E ₃ tablet in vaginal irritation, atrophy, itching, dyspareunia; E ₃ > E ₂ in vaginal dryness	E ₂ tablet = E ₃ tablet in endometrial thickness	E ₂ tablet > E ₃ tablet
Tablet vs cream					
Rioux et al, ³⁹ 2000	24 wk, R, C, PG; N = 159	25 µg E ₂ tablet daily for 2 wk then 2×/wk vs 2 g CE cream (1.25 mg) daily for 3 of 4 wk	E ₂ tablet = CE cream in vaginal dryness, irritation	CE cream > E ₂ tablet in endometrial proliferation, bleeding, E ₂ levels; E ₂ tablet < CE cream in side effects	E ₂ tablet > CE cream
Manonai et al, ³⁸ 2001	12 wk, R, C, PG; N = 53	25 µg E ₂ vaginal tablet daily 2 wk then 2×/wk vs 0.625 mg CE vaginal cream daily for 2 wk then 2×/wk	CE cream > E ₂ tablet in dryness, dyspareunia; E ₂ tablet = CE cream in vaginal health index, MV, pH	CE cream = E ₂ tablet in endometrial thickness	E ₂ tablet > CE cream

C, comparative trial; CE, conjugated estrogens; DB, double-blind; DN, dienestrol; E₂, estradiol; E₃, estriol; MV, vaginal maturation value; PC, placebo-controlled; PG, parallel group; R, randomized.

^aAdapted from Suckling et al,³⁴ 2003/2005.

of dryness was also significantly reduced in treated women compared with those receiving placebo (14.7% vs 28.2%, $P < 0.002$) after 12 weeks of study.

In a 16-week, placebo-controlled trial of a vaginal ovule (tablet) delivering 3.5 mg estriol, women receiving estriol had improved symptoms of dyspareunia and vaginitis compared with placebo recipients, but the results did not reach statistical significance.⁵⁰ In a 24-week trial of a vaginal suppository (tablet) containing 3.5 mg estriol,⁴⁹ therapy significantly improved symptoms of urogenital complaints and relieved vasomotor symptoms as well, including hot flashes, when compared with placebo. Estriol formulations are not available as government-approved products in the United States or Canada.

One randomized 12-week trial comparing CE cream with a nonhormonal, polycarbophil vaginal moisturizing gel (Replens)³⁵ documented that both the gel and CE cream statistically improved vaginal moisture, fluid volume, and elasticity over baseline. However, a Cochrane analysis of the results³⁴ found the estrogen cream to be more effective than the gel for all three outcomes.

In the other clinical trials not using a placebo control, investigators compared efficacy of vaginal rings versus tablets, rings versus creams, and tablets versus creams, all in different doses (see Table 2). For improvement in

signs and symptoms of vaginal atrophy, therapeutic equivalence was shown between the estradiol ring and CE cream,^{36,37} the estradiol ring and estriol products (pessary, cream, tablet),⁴¹⁻⁴⁴ CE cream and estradiol tablets,^{38,39} and the estradiol ring and estradiol tablets.⁴⁵ Small statistical differences in some symptoms were found in the Cochrane review,³⁴ although these may not translate into marked clinical differences in symptom relief among preparations.

Vaginal appearance

Some investigators have used improvements in gross vaginal appearance to assess the therapeutic efficacy of vaginal ET, and objective scoring tools have been developed for this purpose.^{52,53} As with the symptoms of vaginal atrophy, the signs (eg, pallor, dryness, friability, petechiae) are significantly improved with all vaginal estrogen preparations, and no one product appears to offer a distinct therapeutic advantage.^{34,51} The nonhormonal moisturizing gel improved vaginal appearance to a degree equivalent to CE cream,³⁵ possibly as a result of its hydrophilic moisturizing effect on vaginal tissue.

Vaginal pH

Vaginal ET restores vaginal pH to premenopausal levels by reestablishing the normal number of lactobacilli in the

vaginal flora. Among the randomized controlled trials of vaginal ET in postmenopausal women with vaginal atrophy, several evaluated pH as a primary outcome.^{35,37,38,41,43,54} Compared with baseline, all vaginal estrogen preparations significantly decreased pH from pretreatment values of approximately 6.0 to less than 5.0. Moisturizing vaginal gels also decrease pH, but comparative analyses have shown that the estrogen creams and rings are more effective for reducing pH than either estrogen tablets or the nonhormonal moisturizing gel. No statistical differences in efficacy in improving pH were found between the estrogen creams and rings.^{37,41}

Similar results for pH were found in other trials assessing postmenopausal women with urinary symptoms. In a randomized, placebo-controlled trial of 93 postmenopausal women with recurrent UTI,⁵⁵ vaginally applied estriol cream (0.5 mg once nightly for 2 weeks, then twice weekly for 8 months) significantly decreased vaginal pH (mean pH change from 5.5 to 3.8) compared with placebo ($P < 0.001$). Investigators also reported the reappearance of vaginal lactobacilli after 1 month in 61% of treated women versus none in the placebo group ($P < 0.001$). Results from a preliminary, randomized, placebo-controlled trial of 67 postmenopausal women with recurrent urinary symptoms (37 of whom were already being treated with systemic ET)⁵⁶ showed that vaginal pH was significantly lowered (from >5.0 to premenopausal norm of <4.5) with CE cream (1 g on alternate days) but not with placebo cream.

Data from studies using patients as their own controls also point to a beneficial effect of vaginal ET on pH value. In an open-label, single-arm study of an estradiol-releasing vaginal ring (release rate 7.5 $\mu\text{g}/\text{d}$) in 222 postmenopausal women with vaginal atrophy,⁵⁷ 12 weeks of therapy significantly decreased vaginal pH to 4.6 from a pretreatment value of 6.0 ($P < 0.0001$). In the Ayton et al³⁶ study comparing the estradiol ring and CE cream, vaginal pH was lowered from a mean pretreatment value of 6.3 in both groups to values of 4.6 (ring) and 4.7 (CE cream) after 12 weeks of therapy.

Vaginal cytology

ET induces vaginal mucosal maturation, shifting the atrophic mucosa from a predominantly parabasal cell population to a superficial cell population, based on cytologic evaluation. The restoration of normal vaginal cytology is frequently used as an objective outcome measure to assess the hormonal treatment effect.

In randomized trials, the estradiol ring,⁴² CE cream,³⁵ and estradiol tablets⁴⁶ exerted a clear cytologic effect on the vaginal mucosa compared with placebo or a moisturizing gel. The effect seemed to be rapid, generally observed within 4 weeks of treatment onset, and was maintained or further improved over treatment courses ranging from 12 to 48 weeks. The cytologic maturation effect seems to be equal in trials comparing creams, rings, or tablets.^{36,38,41-43,45} A lower dose of estradiol administered in a clinical trial via

vaginal tablet (10 μg twice weekly, after 3 weeks of a priming dose of 10 μg daily) has also been shown to improve vaginal cytology.⁵⁸

Nonvaginal conditions

The therapeutic benefit of vaginal ET has been observed in conditions other than vaginal atrophy, including treatment of sexual dysfunction due to vaginal atrophy and prevention of frequent UTIs, possibly by relieving irritation during intercourse.^{38,47,55,59-62} However, these conditions are not included in the focus of this position statement.

Vaginal ET for medication-associated vaginal conditions

Vaginal ET may be considered to treat vaginal atrophy symptoms associated with medications such as GnRH agonists and antagonists, aromatase inhibitors, and SERMs.

GnRH agonists have been used to create a hypoestrogenic state to manage diseases that are estrogen responsive, notably endometriosis and uterine leiomyomata. GnRH agonists can cause vasomotor symptoms and vaginal dryness as well as a reduction in bone mineral density. For women who have vaginal dryness due to GnRH agonists, management is the same as for other women—vaginal ET. Recent studies have examined the use of hormone therapy (HT) in conjunction with GnRH agonists to ameliorate the hypoestrogenic symptoms.⁶³

Breast cancer survivors using adjuvant therapy with the aromatase inhibitors anastrozole and, to a lesser degree, tamoxifen have been reported to have increased complaints of vaginal dryness and dyspareunia.^{21,28} Although it has been known for some time that there is an initial increase in systemic estrogen levels during the first weeks of vaginal ET use with levels decreasing after 1 month,⁶⁴ a recent report of this occurring in postmenopausal women with breast cancer using both aromatase inhibitors and vaginal ET has raised further concerns regarding the use of vaginal ET in this patient population.⁶⁵

The SERM raloxifene is neutral with regard to the vagina. Randomized controlled studies have examined raloxifene in combination with a vaginal moisturizer versus vaginal CE cream (N = 187) or in combination with an estradiol ring (N = 91) in postmenopausal women with vaginal atrophy. Raloxifene was not associated with a significant vaginal negative effect in either trial,^{27,66,67} demonstrating that raloxifene can be successfully used with vaginal estrogens and moisturizers in healthy postmenopausal women with symptomatic vaginal atrophy.

Although there is cytological evidence of tamoxifen being estrogenic in the vagina, this finding does not match clinical complaints of women using this SERM. Tamoxifen has been associated with an increase in vaginal discharge and vaginal dryness in some studies.^{68,69} The use of low-dose vaginal ET combined with tamoxifen has not been studied.

Adverse effects

All low-dose, local vaginal ET products that are government approved in the United States and Canada differ

slightly in their adverse-event profiles. In general, creams are thought to be associated with more adverse effects than the ring or tablets, perhaps because there is greater potential for patients to apply higher-than-recommended dosing with cream. However, the Cochrane review³⁴ reported no significant differences among the delivery methods in terms of hyperplasia, endometrial thickness, or the proportion of women with adverse events. See Table 2 for a comparison of the clinical trials of vaginal ET for vaginal atrophy.

Vaginal bleeding and breast pain

The most commonly reported adverse effects associated with vaginal ET are vaginal bleeding and breast pain, although nausea and perineal pain also occur. In randomized clinical trials, vaginal bleeding was associated with both the estradiol ring and CE cream³⁶ as well as the estradiol tablet.⁴⁵ Breast tenderness depends on the absorption of the vaginal estrogen and the subsequent serum estrogen level achieved; therefore, management strategies might have to be revised.

Paresthesias and benign endometrial disorders

Isolated cases of paresthesias and benign endometrial disorders have been reported with estrogen delivered via both estradiol and estriol vaginal tablets; however, there was no difference between the two types.⁴⁷

Candidiasis

Two studies found itching and vaginal discomfort suggestive of candidiasis.^{36,37} The incidence of vulvovaginal candidiasis in postmenopausal women is largely unstudied, but preliminary data suggest that women who experience spontaneous menopause and use vaginal ET may be at higher risk.⁷⁰

Systemic absorption

A small endocrine research series suggested that vaginal administration of estradiol increases serum and endometrial levels of estradiol more than the oral route.^{64,71,72} In at least one study, vaginal administration of micronized estradiol resulted in absorption of estrogen into the endometrium; the authors compared this finding to a "uterine first-pass effect."⁷³ Even the lowest dose of estradiol used in this study (7.5 µg daily or 25 µg twice weekly) showed evidence of systemic absorption, and the study found that it was absorbed gram for gram.⁷²

Serum estradiol levels were used to indicate systemic absorption in the Cochrane review.³⁴ Results showed significantly higher levels of estradiol (but within the postmenopausal range) in the CE cream group compared with the estradiol tablet group and in the estradiol tablet group compared with the estradiol ring group (see Table 2). There are no data for systemic absorption comparing the cream with the ring.

Endometrial hyperplasia and adenocarcinoma

Concerns exist about the stimulatory effects of vaginal ET on the endometrium. Although endometrial hyperplasia is dependent upon estrogen dose and duration, few studies have

assessed the risk of endometrial hyperplasia and adenocarcinoma in women using unopposed vaginal estrogen (ie, no progestogen added). The Cochrane review³⁴ reported no significant differences among vaginal rings, tablets, or creams for hyperplasia, endometrial thickness, and the proportion of women with adverse events. Use of the estradiol vaginal tablet was associated with endometrial proliferation similar to that of estriol vaginal tablets in one study⁴⁷ and less than CE cream in another.³⁸ Because the cream dosing is measured by the woman, there is the potential of using more estrogen than prescribed, underscoring the need for patient counseling regarding proper use of the applicator for dosing.

Two cases of moderate endometrial proliferation or hyperplasia in an endometrial polyp were found with the estradiol ring in the Nachtigall³⁷ trial of ring versus CE cream, and two cases of hyperplasia (one simple and one complex without atypia) were found with the CE cream in the Rioux et al³⁹ trial of cream versus vaginal tablet. See Table 2 for details of these clinical trials.

PATIENT MANAGEMENT

Key clinical concerns when managing patients with vaginal atrophy include patient selection, choice of vaginal ET, the need for concomitant progestogen therapy, length of treatment with vaginal ET, and ongoing monitoring.

Patient selection

Postmenopausal women with moderate to severe vaginal atrophy symptoms who have not responded to nonprescription therapy may be candidates for local vaginal ET. Vaginally administered ET is appropriate for women who have previously used systemic ET or estrogen-progestogen therapy (EPT) as well as for women who have never used ET/EPT and who become symptomatic. Vaginal ET is inappropriate for women with undiagnosed vaginal/uterine bleeding and may not be appropriate for women with estrogen-dependent neoplasia because of potential effects on cancer recurrence. The role of vaginal ET in women at risk of thrombosis has not been studied.

For women who have been treated for non-hormone-dependent cancers, management of vaginal atrophy should be similar to that for women without a cancer history, with the exception of women treated with pelvic irradiation. For these women, low-dose, local vaginal therapy may be indicated after treatment to stimulate epithelial regeneration, promote healing, and improve vaginal elasticity and lubrication.

For women with a history of hormone-dependent cancers, moisturizers and lubricants are recommended as first-line treatment.⁷⁴⁻⁷⁶ Randomized clinical trials of systemic HT in breast cancer survivors have not shown benefit and raise concerns about possible harm and increased risk of cancer recurrence.^{77,78} On the other hand, data are lacking for the safety of low-dose vaginal therapy. Recognizing that systemic absorption of estrogen from low-dose vaginal ET products is minimal,⁴⁵ it is not known

whether even a small amount of absorption will have any negative outcomes in women with hormone-dependent cancers. However, some women with hormone-dependent cancers who report moderate to severe vaginal atrophy and who have symptoms unresponsive to nonhormonal therapies may want to discuss the risks and benefits of low-dose local ET for symptom relief.^{15,79} Some cancer survivors, however, avoid therapies associated with any potential risk due to fears of recurrence, despite their level of reported symptom distress.^{79,80}

The cancer experience includes many factors that influence psychological adjustment during and after treatment. Therefore, it is important that a management approach to a complaint of vaginal atrophy takes into account the larger physical and psychological symptom experience in the context of the individual woman's life. A comprehensive assessment and management approach including education, counseling, and support has been shown to improve outcomes in cancer survivors with distressful complaints of vaginal dryness and dyspareunia.⁷⁴

Choice of vaginal ET

Almost all systemic and vaginal ET/EPT products are government approved for treating moderate to severe symptoms of vulvar and vaginal atrophy, such as vaginal dryness, dyspareunia, and atrophic vaginitis. When HT is considered solely for these indications, local (not systemic) vaginal ET is generally recommended. Because the evidence indicates similar efficacy among these low-dose, local vaginal ET products, the choice of which vaginal ET to use may be based on patient preference.⁸¹

Need for progestogen

NAMS, in its March 2007 position statement on the use of estrogen and progestogen in peri- and postmenopausal women,⁸¹ indicates that progestogen is generally not indicated when low-dose estrogen is administered locally for vaginal atrophy. In the Cochrane review,³⁴ the authors conclude that the available data cannot answer the question of whether women need progestogen to counter the adverse effects from possible vaginal absorption of estrogen that is delivered by ring, cream, or tablet beyond 6 months.

Therapy length and monitoring

Improvement in vaginal atrophy symptoms typically occurs within a few weeks of starting vaginal ET; however, some women may need to use vaginal estrogen for 4 to 6 weeks before adequate improvement is observed.

Although efficacy seems to be similar for the available products, creams may offer more immediate soothing comfort, although some users consider them messy. If there is significant stenosis of the vaginal vault, an estrogen cream used with a dilator may be necessary before an estrogen ring or tablet can be inserted into the vaginal vault. There are no data to suggest any advantage for initial use of both systemic and local vaginal estrogen in cases of severe atrophy.

Overall, subjective improvement occurs in 80% to 90% of women treated with local vaginal estrogen.⁸² Vaginal atrophy unresponsive to estrogen may be due to undiagnosed dermatitis/dermatosis or vulvodynia, so treatment failure warrants future evaluation and careful examination.

For women with vaginal atrophy, low-dose, local vaginal ET should be continued as long as they have discomfort from symptoms. There are no safety data extending beyond 12 months, but no time limits for therapy use have been established.

If a woman is at high risk for endometrial cancer, is using a greater dose of vaginal ET, or is having symptoms (spotting, breakthrough bleeding), closer surveillance may be required. In these cases, some clinicians may perform a cost-effective annual progestogen challenge test or a transvaginal ultrasound assessment for particularly high-risk patients (eg, obese women). However, data are insufficient to recommend annual endometrial surveillance in asymptomatic women using vaginal ET.^{34,83,84}

CONCLUSIONS AND RECOMMENDATIONS

- The primary goals of vaginal atrophy management are to relieve symptoms and reverse atrophic anatomic changes.
- First-line therapies for women with vaginal atrophy include nonhormonal vaginal lubricants and moisturizers.
- For symptomatic vaginal atrophy that does not respond to nonhormonal vaginal lubricants and moisturizers, prescription therapy may be required.
- Randomized controlled trials in postmenopausal women, albeit limited, have shown that low-dose, local, prescription vaginal estrogen delivery is effective and well tolerated for treating vaginal atrophy while limiting systemic absorption.
- All low-dose vaginal estrogen products approved in the United States for treating vaginal atrophy—estradiol vaginal cream, CE vaginal cream, the estradiol vaginal ring, and the estradiol hemihydrate vaginal tablet—are equally effective at the doses recommended in labeling. The choice is dependent on clinical experience and patient preference.
- Progestogen is generally not indicated when low-dose estrogen is administered locally for vaginal atrophy.
- If a woman is at high risk for endometrial cancer, is using a greater dose of vaginal ET, or is having symptoms (spotting, breakthrough bleeding), closer surveillance may be required. There are insufficient data to recommend annual endometrial surveillance in asymptomatic women using vaginal ET.
- Vaginal ET should be continued as long as distressful symptoms remain.
- For women treated for non-hormone-dependent cancer, management of vaginal atrophy is similar to that for women without a cancer history. For women with a history of hormone-dependent cancer, management

recommendations are dependent upon each woman's preference in consultation with her oncologist.

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