

Clinical Approach to Recognizing and Managing a Patient With Vaginal Atrophy: A Guide for Physician Assistants

R Lehman

Citation

R Lehman. *Clinical Approach to Recognizing and Managing a Patient With Vaginal Atrophy: A Guide for Physician Assistants*. The Internet Journal of Academic Physician Assistants. 2009 Volume 8 Number 1.

Abstract

Vaginal atrophy is a consequence of postmenopausal estrogen deprivation, causing symptoms such as vaginal dryness, irritation, itching, burning, urinary incontinence, urinary tract infections, and dyspareunia. These symptoms cause extreme discomfort, decrease libido, and significantly impact the quality of life in menopausal women. Considering that symptoms associated with vaginal atrophy do not resolve without treatment, it is important to recognize and treat the condition; however, women do not voluntarily report symptoms and clinicians may not routinely question patients regarding sexual health. It is thus important to raise awareness about vaginal atrophy among clinicians in order to enhance the quality of care in menopausal women. Treatment goals include alleviating symptoms, reversing or minimizing the physiological changes, and improving quality of life for the patient.

CASE PRESENTATION

A 55-year-old woman presents for an annual gynecological visit and complains of vaginal irritation, dryness, dyspareunia, and recurrent urinary tract infections. Despite symptoms being troublesome, the patient hesitates to discuss issues related to sexual health. It has been three years since her natural menopause, and a pelvic exam reveals loss of labial and vulvar fullness, pallor of urethral and vaginal epithelium, and a loss of rugae.

SYMPTOMS AND PREVALENCE

Decreased circulating levels of estrogen associated with menopause lead to vaginal atrophy, which is commonly encountered in 10% to 50% of menopausal women.¹⁻³ Vaginal atrophy causes severe vaginal symptoms, such as dryness, itching, burning, tenderness, pain, and bleeding following sexual intercourse.⁴ Dryness and decreased lubrication can lead to painful intercourse, resulting in women losing interest in sexual activity.⁵ Almost 57% of sexually active menopausal women experience vulvovaginal atrophy and 55% experience sexual dysfunction.⁶ Urinary symptoms in women with vaginal atrophy are very common, with almost 20% of elderly postmenopausal women experiencing bacteriuria, urethral discomfort, increased frequency, hematuria, urgency, and stress incontinence.^{4,7-9}

Despite the high prevalence of symptoms associated with

vaginal atrophy, only 20%-25% of the women seek medical attention.^{10,11} Reluctance to discuss sexual health can be attributed to embarrassment, cultural beliefs, fear about the clinician's response, and lack of sufficient knowledge regarding treatment options. Reluctance on the part of clinicians to discuss sexual health can be due to a lack of expertise in sexual assessment and treatment options, as well as time constraints.

ROLE OF ESTROGEN

Estrogen plays a critical role in maintaining the structure and function of the vulva and increases the vaginal surface area during coitus. Estrogen also enhances glycogen content of the epithelial cells, which is metabolized to lactic acid by lactobacilli and helps maintain vaginal pH at ≤ 4.0 . Together, thickened vaginal epithelium, cervical mucus secretions, acidic pH, and local bacterial flora act as barriers to pathogens.

POSTMENOPAUSAL UROGENITAL CHANGES

With estrogen deficiency, atrophic vaginal epithelium appears pale, smooth, and shiny (Figure 1).¹² Clinical signs of vaginal atrophy are listed in Table 1.^{3,13-15} The postmenopausal vagina has decreased vaginal capillary blood flow and reduced smooth muscle relaxation; therefore, it does not reach the level of engorgement of the estrogen-primed vagina during sexual arousal.

Urinary tract epithelium undergoes atrophic changes with estrogen deprivation, causing urethral and bladder mucosal thinning, urethral shortening, weakening of the sphincter, decreased bladder capacity, increased postvoid residual urine volume, and uninhibited detrusor muscle contractions.^{16,17} These changes can lead to dysuria, increased susceptibility to pathogens, and an increase in urinary frequency.

Figure 1

Figure 1. Photograph of external genitalia in vaginal atrophy¹²



Reprinted with permission.

Figure 2

Table 1. Signs of vaginal atrophy^{3,13-15}

Pale, smooth, or shiny epithelium with loss of rugae
Sparsity of pubic hair
Dryness of labia, fusion of labia minora
Introital stenosis
Changes in the quantity and quality of vaginal secretions
Vulva loss of collagen content, adipose tissue, and water-retaining ability
Shortening and narrowing of the vaginal canal, decreased blood supply
Thinning of vaginal wall with loss of elasticity
Friable surface that bleeds with minimal trauma
Clitoral atrophy with loss of protective covering, making it prone to irritation
Shift in vaginal pH from acidic to alkaline and consequent alteration in the normal vaginal flora—lactobacilli replaced by fecal flora and other pathogenic bacteria

DIFFERENTIAL DIAGNOSIS

Symptoms associated with vaginal atrophy can have other etiologies, such as infections, chronic inflammatory processes, or psychologic causes, especially in younger women (Table 2).¹⁸

Figure 3

Table 2. Other causes of symptoms associated with vaginal atrophy¹⁸⁻²⁰

Vaginal infections (candidiasis and trichomoniasis)
Reactions to soaps, bubble baths, condoms, spermicides
Deodorant tampons and pads
Irritations from birth control devices left too long inside the vagina
Trauma
Skin conditions (eczema or lichen sclerosis)
Diabetes mellitus, lupus erythematosus, inflammatory bowel disease
Benign and malignant tumors
Psychological causes
Medications that can lead to candidiasis or dryness of epithelium
Surgically or medically induced menopause
Hypoestrogenic states (eg, peri- and postmenopause, premature ovarian failure, prolonged lactation)
Endocrine therapies (eg, aromatase inhibitors)
Injury to pelvic nerves leading to persistent vulvar pain
Cigarette smoking ^{19,20}
Bacterial vaginosis

DIAGNOSIS

A complete evaluation for the diagnosis of vaginal atrophy includes medical and sexual history, physical examination, and laboratory evaluation. Although most of the vaginal complaints in menopausal women are due to atrophy, a complete evaluation would help eliminate other possible causes. Upon examination, several signs of vaginal atrophy will be evident (Figure 1¹² and Table 1^{13,13-15})

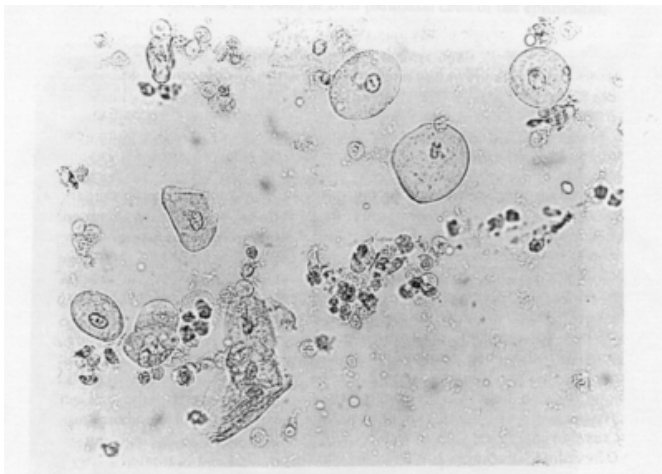
Vaginal pH and vaginal maturation index (VMI) are considered surrogate markers of vaginal health.^{12,21} VMI is a ratio of parabasal, intermediate, and superficial squamous cells found on a cytological smear.¹⁵ Clinicians can test vaginal pH of the lateral vaginal wall using standard pH paper. Measurement of pH can be of substantial value; it can easily be assessed in an office setting, is inexpensive and reproducible, correlates well with VMI, and is frequently used in lieu of the VMI.

In atrophic epithelium, immature round or oval vaginal

epithelial cells with relatively large nuclei (parabasal cells) can easily be visualized using wet mount microscopy.^{15,22} Smears of atrophic vaginal epithelium from the upper one-third of the vagina demonstrate an increase in the proportion of parabasal cells vs superficial mature cells.^{4,15} In response to local estrogen therapy (ET), mature squamous cells increase, with a concomitant decrease in parabasal cells (Figure 2).^{23,24}

Figure 4

Figure 2: Photomicrograph of wet mount, vaginal epithelium.²⁴



Reprinted with permission.

MANAGEMENT

LIFESTYLE MODIFICATIONS

Recommended lifestyle practices to alleviate symptoms associated with vaginal atrophy include regular sexual activity and masturbation. Regular sexual activity and masturbation increase blood flow to the pelvic organs,²⁵ and semen is thought to contain sexual steroids, prostaglandins, and essential fatty acids that may help maintain vaginal integrity. Avoiding the use of synthetic, tight-fitting undergarments, panty liners, or perfumed products that may cause genital irritation is highly recommended for any patient experiencing genital discomfort.

NONHORMONAL THERAPY

There are several over-the-counter vaginal moisturizers and lubricants that are considered first-line nonhormonal treatments to treat vaginal symptoms.³ These are suitable for patients who are concerned about hormone use or in those patients for whom hormone therapy is contraindicated.

Lubricants are combinations of protectants and thickening

agents in a water base and are temporary measures to relieve vaginal dryness. They must be applied frequently for continuous relief. Lubricants can be helpful early in the course of vaginal atrophy; however, with time, these agents offer little relief and do not restore the integrity of the vagina.

Polycarbophil-based moisturizers are gels that produce a moist film over the vaginal tissue. They need to be placed in the vagina up to 3 times weekly.²⁶ The film remains attached to mucin and the epithelial cell surface and assists in the retention of water to lubricate the vaginal wall, thus reducing the incidence of vaginal itching, irritation, and dyspareunia. Bioadhesive polymer gels and polycarbophil moisturizers have been reported to restore vaginal pH and improve cytological morphology^{15,26} and could provide long-term relief of dryness. They also need to be applied less frequently.²⁷

More than 30% of menopausal women use alternate therapies such as acupuncture, herbal supplements, or OTC plant-based progestones to treat symptoms.¹⁵ Patients should be encouraged to talk to their PA about such alternate therapies, as they may offer little or no relief. Vaginal application of Vitamin E oil before coitus may provide symptomatic relief.^{3,28,29} In one study, postmenopausal women treated with 0.500 µg vitamin D as calcitriol demonstrated improved growth, differentiation, and maturation of vaginal epithelium when compared with women who were not treated, indicating that vaginal tissue may be a new target organ for therapeutically applied vitamin D analogues.³⁰

HORMONAL THERAPY

Because vaginal atrophy is primarily caused by estrogen deprivation associated with menopause, ET is the main choice for therapy, with demonstrated efficacy in reversing the atrophic changes associated with menopause and markedly improving symptoms.⁸

Systemic hormone therapy in the form of oral or transdermal hormone replacement is indicated for women seeking relief from menopausal symptoms such as hot flashes, sleep disturbances, and vaginal atrophy.³ In women with an intact uterus, concomitant progestin therapy is required. According to the Women's Health Initiative, adverse events associated with systemic hormone therapy include endometrial bleeding, breast tenderness, and increased risk of venous thromboembolism, stroke, and breast cancer.^{31,32} Although

systemic hormone therapy is effective for vaginal atrophy, local therapy is best in women whose primary complaints are vulvovaginal.

Local therapy provides sufficient estrogen to activate estrogen receptors in the local tissues to enhance vaginal secretions, thicken vaginal epithelium, improve vascularization, and increase glycogen production and restore vaginal pH.^{21,33-36} The lower doses of vaginal estrogen therapy offer several advantages, including faster relief of local symptoms compared with systemic therapy.^{37,38} Almost 90% of patients experience symptomatic relief within weeks of starting treatment, with significant improvement in vaginal cytology observed within 2 weeks and sustained until week 52.^{3,23,39} Thickening and maturation of the vaginal epithelium make it less prone to bleeding, and increased vaginal-cervical paracellular permeability results in increased cellular secretions and lubrication.⁴⁰

Lower doses of topical vaginal estrogens, like all transdermal estrogens, bypass first-pass metabolism by the liver.⁴¹ Although there is some systemic absorption of estrogen initially across the thin atrophic epithelium, it decreases as the tissue begins to mature and thicken.⁴ These factors limit systemic exposure, resulting in fewer adverse events.²⁸ The dose of estrogen is low enough in all topical formulations to not cause excessive endometrial proliferation.^{3,38,42} According to NAMS 2007 position statement on the role of vaginal estrogen, progestogens are generally not indicated in women using normal dosages of vaginal estrogen for atrophy.³

Currently, several local estrogen therapies exist—estradiol cream, conjugated estrogen cream, sustained-release estradiol ring, and micronized estradiol hemihydrate vaginal tablet.¹⁸

Vaginal creams. Vaginal creams contain low-dose estrogen. Vaginal estriol cream at doses of 5 mg twice weekly significantly reduced the rate of UTIs when compared with placebo,⁴³ possibly by increasing the integrity of vaginal and urethral mucosa and by supporting the growth of *Lactobacillus*.^{43,44} In patients with introital stenosis, creams may be used to prepare the vagina for future application of the vaginal ring or tablet. Messiness during application can result in poor patient adherence.^{37,41} In addition, creams are not provided in prepackaged doses, so calculating precise dosing is not possible and can lead to

higher systemic estrogen levels when compared with vaginal tablets or rings.^{41,42}

Vaginal rings. Estradiol or estradiol acetate rings contain a central drug-containing core surrounded by a drug-free membrane that releases a steady concentration of estrogen for 90 days.³ Vaginal rings are associated with good patient adherence and need to be inserted about once every 3 months. Rings have demonstrated superior efficacy to placebo and comparable efficacy to creams and tablets in relieving the symptoms, restoring vaginal pH, and improving vaginal cytology in almost 90% of women.^{45,46} Serum estradiol levels did not rise following insertion of the ring, and a noted absence in endometrial proliferation even after 1 year of use has been documented.⁴⁷ Women with limited vaginal capacity may have difficulty inserting and removing the ring, and with bowel movements, sexual intercourse, douching, Valsalva maneuvers, and, in menopausal women with pelvic organ prolapse, dislodgement of the ring may occur.¹⁰

Vaginal tablets. Low doses of estrogen can be administered in the vagina through hydrophilic slow-release tablets to effectively relieve symptoms, decrease vaginal pH, and promote maturation of the vaginal and urethral epithelium.^{23,48,49} One tablet is inserted in the vagina once daily for the first two weeks, then twice a week thereafter for the purpose of maintenance therapy. Once the tablet comes in contact with vaginal mucosa, a gel layer is formed, allowing for rapid diffusion of estradiol. Circulating levels of estradiol, however, remain within the menopausal range of 3-10 pg/mL.⁵⁰ When compared with vaginal estrogen creams, tablets provide a more consistent dose of estrogen, reduce the potential for leakage, and are associated with greater adherence.^{37,51,52}

ADVERSE EVENTS AND CONTRAINDICATIONS

Thorough patient assessment, including medical history and physical examination, is necessary prior to starting treatment to rule out risk for or history of estrogen-sensitive tumors, end-stage liver failure, and estrogen-related thromboembolization.³ Vaginal ET is inappropriate for women with undiagnosed vaginal/uterine bleeding. The most common adverse events reported with vaginal ET are breast pain and vaginal bleeding, although nausea and perineal pain may also occur.^{46,53} The risk of adverse events is reduced when compared with systemic therapy.⁵⁴

EMERGING THERAPIES

Emerging therapies for vaginal atrophy include microdose transdermal ET,⁵⁵ intravaginal dehydroepiandrosterone (DHEA),⁵⁶ synthetic conjugated estrogen creams,⁵⁷ ultra-low-dose vaginal estradiol tablets,²³ systemic therapy with selective estrogen receptor modulators (SERMS) (lasofoxifene and ospemifene), local therapy with vaginal SERMS, and formed-in-place estrogens and androgens.⁵⁸

FOLLOW-UP

Current recommendations are to continue use of local estrogen therapy for as long as necessary for symptom control.³ A retrospective study conducted in >13,000 women showed that duration of local estrogen therapy in the real-life setting is >12 months.³⁷ Due to the lack of long-term follow-up data, it cannot be commented on as to whether women who are being treated with local estrogen therapy beyond 6 months would need progesterone to counter the possible adverse effects of estrogen.⁵⁹ Initiating progesterone treatment is subject to the discretion of the clinician, and it is highly recommended that patients who bleed while using local estrogen therapy or following a course of intermittent progesterone should have some form of endometrial surveillance, either ultrasound or endometrial sampling, at the discretion of the clinician.

SUMMARY

Vaginal atrophy is a condition commonly encountered in primary care and one that can be easily and successfully treated by PAs. Women may be reluctant to discuss sexual or vaginal health; therefore, it is important for clinicians to query patients about symptoms and to maintain a high index of suspicion. Symptoms range from minor vaginal dryness to severe dyspareunia and may include vaginal discharge, bleeding, pruritus, or urinary complaints. Atrophy is secondary to estrogen loss and therefore will respond best to hormonal therapy, however, other options exist for women who are unable or who do not desire to take estrogens. This condition severely impacts a woman's quality of life, and it is incumbent upon clinicians who treat women in this age group to familiarize themselves with vaginal atrophy and its treatment.

ACKNOWLEDGEMENTS AND DISCLOSURES

The author wishes to thank Anu Santhanagopal, PhD, of DesignWrite, LLC, for providing writing and editorial assistance. Funding to support the preparation of this manuscript was provided by Novo Nordisk, Inc. The author

has been on advisory boards for Amgen and Novo Nordisk.

References

1. Santoro N, Komi J: Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med*; 2009; 6: 2133-2142.
2. Pastore LM, Carter RA, Hulka BS, Wells E: Self-reported urogenital symptoms in postmenopausal women: Women's Health Initiative. *Maturitas*; 2004; 49: 292-303.
3. North American Menopause Society: The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of the North American Menopause Society. *Menopause*; 2007; 14: 355-369.
4. Bachmann GA, Nevadunsky NS: Diagnosis and treatment of atrophic vaginitis. *Am Fam Physician*; 2000; 61: 3090-3096.
5. Gracia CR, Freeman EW, Sammel MD, Lin H, Mogul M: Hormones and sexuality during transition to menopause. *Obstet Gynecol*; 2007; 109: 831-840.
6. Levine KB, Williams RE, Hartmann KE: Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause*; 2008; 15: 661-666.
7. Molander U, Milsom I, Ekelund P, Mellstrom D: An epidemiological study of urinary incontinence and related urogenital symptoms in elderly women. *Maturitas*; 1990; 12: 51-60.
8. American College of Obstetricians and Gynecologists: Genitourinary tract changes. *Obstet Gynecol*; 2004; 104: 56S-61S.
9. Cohen BL, Barboglio P, Gousse A: The impact of lower urinary tract symptoms and urinary incontinence on female sexual dysfunction using a validated instrument. *J Sex Med*; 2008; 5: 1418-1423.
10. Johnston SL, Farrell SA, Bouchard C, Farrell SA, Beckerson LA, Comeau M, Johnston SL, Lefebvre G, Papaioannou A: The detection and management of vaginal atrophy. *J Obstet Gynaecol Can*; 2004; 26: 503-515.
11. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ: A study of sexuality and health among older adults in the United States. *N Engl J Med*; 2007; 357: 762-774.
12. Freedman MA: Vaginal pH, estrogen and genital atrophy. *Menopause Manag*; 2008; 17: 9-11.
13. Goldstein I: Current management strategies of the postmenopausal patient with sexual health problems. *J Sex Med*; 2007; 4 Suppl 3: 235-253.
14. Nelson HD: Menopause. *Lancet*; 2008; 371: 760-770.
15. Mehta A, Bachmann G: Vulvovaginal complaints. *Clin Obstet Gynecol*; 2008; 51: 549-555.
16. Resnick NM: An 89-year-old woman with urinary incontinence. *JAMA*; 1996; 276: 1832-1840.
17. Lovatsis D, Drutz HP: The role of estrogen in female urinary incontinence and urogenital aging: a review. *Ostomy Wound Manage*; 1998; 44: 48-53.
18. North American Menopause Society: Common clinical issues during perimenopause and beyond. In: *Menopause Practice: A Clinician's Guide* 3rd ed. Cleveland, OH: North American Menopause Society; 2007: 29-101.
19. Baron JA, La Vecchia C, Levi F: The antiestrogenic effect of cigarette smoking in women. *Am J Obstet Gynecol*; 1990; 162: 502-514.
20. Karamanidis D, Tamiolakis D, Koutsougeras G, Tripsanas CH, Retzos K, Karidis S, Liberis B: Cigarette smoking and the degree of maturation of the vaginal

- squamous epithelium in postmenopausal women. *Clin Exp Obstet Gynecol*; 2001; 28: 274-276.
21. Bachmann GA, Leiblum SR: The impact of hormones on menopausal sexuality: a literature review. *Menopause*; 2004; 11: 120-130.
22. Castelo-Branco C, Cencelo MJ, Villero J, Nohales F, Julia MD: Management of post-menopausal vaginal atrophy and atrophic vaginitis. *Maturitas*; 2005; 52 Suppl 1: S46-S52.
23. Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W: Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. *Obstet Gynecol*; 2008; 112: 1053-1060.
24. Friedrich EG: *Vaginitis 2nd*. Philadelphia, PA: WB Saunders Co.; 1983: 9-33.
25. Society of Obstetricians and Gynaecologists of Canada: The detection and management of vaginal atrophy. Number 145, May 2004. *Int J Gynaecol Obstet*; 2005; 88: 222-228.
26. van der Laak JA, de Bie LM, de Leeuw H., de Wilde PC, Hanselaar AG: The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerised cytometry. *J Clin Pathol*; 2002; 55: 446-451.
27. Palacios S: Managing urogenital atrophy. *Maturitas*; 2009; 63: 315-318.
28. Robb-Nicholson C: My doctor prescribed a low-dose vaginal estrogen cream, applied twice a week, for atrophic vaginitis. I've heard this dose is so low that it carries no health risk. Do you agree? *Harv Womens Health Watch*; 2007; 15: 7.
29. North American Menopause Society: Vulvovaginal symptoms. In: *Menopause Guidebook 6th ed*. Cleveland, OH: North American Menopause Society; 2006: 19-21.
30. Yildirim B, Kaleli B, Duzcan E, Topuz O: The effects of postmenopausal vitamin D treatment on vaginal atrophy. *Maturitas*; 2004; 49: 334-337.
31. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*; 2002; 288: 321-333.
32. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smolter S: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*; 2004; 291: 1701-1712.
33. Freedman M: Sexuality in post-menopausal women. *Menopausal Med*; 2000; 8: 1-5.
34. McCoy NL: Female sexuality during aging. In: *Functional Neurobiology of Aging*. Hof R and Mobbs CV eds. New York, NY: Academic Press; 2001: 769-779.
35. Sarrel PM: Effects of hormone replacement therapy on sexual psychophysiology and behavior in postmenopause. *J Womens Health Gend Based Med*; 2000; 9 Suppl 1: S25-S32.
36. Galhardo CL, Soares JM, Jr., Simoes RS, Haidar MA, Rodrigues de LG, Baracat EC: Estrogen effects on the vaginal pH, flora and cytology in late postmenopause after a long period without hormone therapy. *Clin Exp Obstet Gynecol*; 2006; 33: 85-89.
37. Shulman LP, Portman DJ, Lee WC, Balu S, Joshi AV, Cobden D, Wang Q, Pashos CL: A retrospective managed care claims data analysis of medication adherence to vaginal estrogen therapy: implications for clinical practice. *J Womens Health (Larchmt)*; 2008; 17: 569-578.
38. North American Menopause Society: Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of the North American Menopause Society. *Menopause*; 2007; 14: 168-182.
39. Nilsson K, Heimer G: Low-dose oestradiol in the treatment of urogenital oestrogen deficiency-a pharmacokinetic and pharmacodynamic study. *Maturitas*; 1992; 15: 121-127.
40. Barentsen R, van de Weijer PHM, Schram JHN: Continuous low dose estradiol released from a vaginal ring versus estriol vaginal cream for urogenital atrophy. *Eur J Obstet Gynecol Reprod Biol*; 1997; 71: 73-80.
41. Crandall C: Vaginal estrogen preparations: a review of safety and efficacy for vaginal atrophy. *J Womens Health*; 2002; 11: 857-877.
42. Suckling JA, Kennedy R, Lethaby A, Roberts H: Local oestrogen for vaginal atrophy in postmenopausal women (review). *Cochrane Database Syst Rev*; 2006; 4: 1-91.
43. Raz R, Stamm WE: A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*; 1993; 329: 753-756.
44. Palacios S, Castelo-Branco C, Cencelo MJ, Vazquez F: Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. *Maturitas*; 2005; 50: 98-104.
45. Manonai J, Theppisai U, Suthutvoravut S, Udomsubpayakul U, Chittacharoen A: The effect of estradiol vaginal tablet and conjugated estrogen cream on urogenital symptoms in postmenopausal women: a comparative study. *J Obstet Gynaecol Res*; 2001; 27: 255-260.
46. Weisberg E, Ayton R, Darling G, Farrell E, Murkies A, O'Neill S, Kirkegard Y, Fraser I: Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. *Climacteric*; 2005; 8: 83-93.
47. Nachtigall LE: Clinical trial of the estradiol vaginal ring in the U.S. *Maturitas*; 1995; 22 Suppl : S43-S47.
48. Mainini G, Scaffa C, Rotondi M, Messalli EM, Quirino L, Ragucci A: Local estrogen replacement therapy in postmenopausal atrophic vaginitis: efficacy and safety of low dose 17b-estradiol vaginal tablets. *Clin Exp Obstet Gynecol*; 2005; 32: 111-113.
49. Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M: Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Obstet Gynecol*; 2008; 111: 67-76.
50. Santen RJ, Pinkerton JV, Conaway M, Ropka M, Wisniewski L, Demers L, Klein KO: Treatment of urogenital atrophy with low-dose estradiol: preliminary results. *Menopause*; 2002; 9: 179-187.
51. Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS: 17b-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause*; 2000; 7: 156-161.
52. Dugal R, Hesla K, Sordal T, Aase KH, Lilleeidet O, Wickstrom E: Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy. *Acta Obstet Gynecol Scand*; 2000; 79: 293-297.
53. Ayton RA, Darling GM, Murkies AL, Farrell EA,

Weisberg E, Selinus I, Fraser IS: A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. *Br J Obstet Gynaecol*; 1996; 103: 351-358.

54. Cicinelli E: Intravaginal oestrogen and progestin administration: advantages and disadvantages. *Best Pract Res Clin Obstet Gynaecol*; 2008; 22: 391-405.

55. Bachmann GA, Schaefer M, Uddin A, Utian WH: Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women. *Menopause*; 2009; 16: 877-882.

56. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L,

Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dube R, Cote I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J: Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Menopause*; 2009; 16: 907-922.

57. Freedman M, Kaunitz AM, Reape KZ, Hait H, Shu H: Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy. *Menopause*; 2009.

58. Simon JA: Vulvovaginal atrophy: new and upcoming approaches. *Menopause*; 2009; 16: 5-7.

59. Suckling J, Lethaby A, Kennedy R: Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev*; 2003; CD001500.

Author Information

Rebecca A. Lehman, MPAS, PA-C

Nova Southeastern University