

THE DETECTION AND MANAGEMENT OF VAGINAL ATROPHY

These guidelines have been reviewed by the joint committee of Clinical Practice Gynaecology and Urogynaecology and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

Shawna L. Johnston, MD, FRCSC, Kingston ON
Scott A. Farrell, MD, FRCSC, Halifax NS

SOGC JOINT COMMITTEE – CLINICAL PRACTICE GYNAECOLOGY AND UROGYNAECOLOGY

Céline Bouchard (Co-Chair), MD, FRCSC, Québec QC
Scott A. Farrell (Co-Chair), MD, FRCSC, Halifax NS
Lo-Ann Beckerson, RN, Toronto ON
Margery Comeau, MD, CFPC, Montréal QC
Shawna L. Johnston, MD, FRCSC, Kingston ON
Guylaine Lefebvre, MD, FRCSC, Toronto ON
Alexandra Papaioannou, MD, FRCPC, Hamilton ON

Abstract

Objective: To support the practitioner in the diagnosis of vaginal atrophy and in the management of the related symptoms.

Options: The modalities of evaluation range from basic pelvic examination, examination of the vulva, and laboratory tests.

Outcomes: A comprehensive approach to the detection of vaginal atrophy and a discussion of available therapeutic and non-therapeutic options.

Evidence: Published opinions of experts, supplemented by evidence from clinical trials, where appropriate.

Values: The quality of the evidence is rated using the criteria described by the Canadian Task Force on the Periodic Health Examination.

Benefits, Harms, and Costs: Diagnosis of vaginal atrophy is often a challenge because women are unwilling to report symptoms, which have the potential to significantly decrease their quality of life. Increased clinical suspicion is the first step in the diagnosis of vaginal atrophy, which will prompt the initiation of safe therapies with proven efficacy.

Recommendations:

1. Health-care providers should routinely assess postmenopausal women for the symptoms and signs of vaginal atrophy, a common condition that exerts significant negative effects on quality of life. (III-C)
2. Regular sexual activity should be encouraged to maintain vaginal health. (II-2B)

3. Women experiencing recurrent urinary tract infections should be instructed that consumption of pure cranberry-lingonberry juice, rather than cranberry drink, will decrease their risk of urinary tract infections. (I-A)
4. Vaginal moisturizers applied on a regular basis have an efficacy equivalent to local hormone replacement for the treatment of local urogenital symptoms such as vaginal itching, irritation, and dyspareunia, and should be offered to women wishing to avoid use of hormone replacement therapy. (I-A)
5. Women experiencing vaginal atrophy can be offered any of the following effective vaginal estrogen replacement therapies: conjugated equine estrogen cream (I-A), a sustained-release intravaginal estradiol ring (I-A), or a low-dose estradiol tablet (I-A).
6. Although systemic absorption of estrogen can occur with local preparations, there is insufficient data to recommend annual endometrial surveillance in asymptomatic women using local estrogens. (III-C)
7. For menopausal women experiencing recurrent urinary tract infections and who have no contraindication to local hormone replacement, vaginal estrogen therapy should be offered. (I-A)

Validation: These guidelines have been reviewed by the joint committee of Clinical Practice Gynaecology and Urogynaecology and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

Key Words

Atrophy; administration, intravaginal; vaginal creams; urinary tract infections

J Obstet Gynaecol Can 2004;26(5):503–8.

These guidelines reflect emerging clinical and scientific advances as of the date issued and are subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of the contents may be reproduced in any form without prior written permission of SOGC.

FOR INFORMATION ON THE SELF-DIRECTED LEARNING EXERCISE, SEE PAGE 516.

INTRODUCTION

Vulvovaginal atrophy is a consequence of aging which occurs, particularly after menopause, when estrogen deprivation accelerates the process of deterioration of urogenital tissues.^{1,2-6} The clinical syndromes associated with vulvovaginal atrophy include vaginal dryness and irritation, dyspareunia, and recurrent urinary tract infections.³ This guideline addresses the diagnosis of vaginal atrophy and the management of the related symptoms. The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination (Table).⁷

EPIDEMIOLOGY AND QUALITY OF LIFE

Although vaginal atrophy occurs in the majority of postmenopausal women, not all women will be symptomatic. The onset of symptoms is often insidious, and can occur long after the resolution of other menopausal symptoms, such as hot flashes. Symptoms may also occur in perimenopausal women who do not have visible signs of vulvovaginal atrophy. Smokers may be at higher risk.⁶

Large cohort studies have reported the prevalence of vaginal dryness in women from 27% to 55%⁸⁻¹⁰ and dyspareunia from 32% to 41%.^{9,10} The estimated incidence of urinary tract infections in postmenopausal women ranges from 4% to 15%.¹¹

Investigators using questionnaires often report higher rates of vaginal atrophy than clinical experience would suggest, perhaps indicating that many women will admit to this problem only in this anonymous format. In one survey, although half of the respondents noted moderate to severe vaginal discomfort, only one-third of this subgroup had sought medical care for their symptoms.⁸ Contrary to the assumptions of health-care providers that women receiving systemic hormone

replacement therapy will not experience symptoms of vaginal atrophy, it is estimated that approximately 40% of women taking oral hormone replacement have persistent vaginal dryness.¹²

While the clinical conditions resulting from urogenital aging are not life-threatening, the symptoms can exert a significant negative effect on quality of life. Stenberg *et al.* noted that 32% of women complaining of vaginal dryness had lost interest in sexual relations.⁹ Further, some postmenopausal women experience recurrent episodes of urinary tract infection with severe, disabling symptoms.

PATHOPHYSIOLOGY

Estrogen receptors have been identified in the vulva,¹ vagina,¹ bladder,¹ urethra,¹ pelvic floor musculature,² and endopelvic fascia.² These structures thus share a similar hormonal responsiveness, including susceptibility to the estrogen deprivation that can occur in menopause, in postpartum (especially during lactation), or in the context of hypothalamic amenorrhea.

Urogenital atrophy involves a decrease in the size of the uterus, ovaries, vaginal canal, and vulva.¹³ Atrophy of the endometrium is part of the process that results in menopause. The vaginal wall connective tissue components, including collagen, elastin, and smooth muscle, all degenerate. The vaginal epithelium becomes less cellular and thinner, and glycogen production declines.¹³

Blood flow to the vagina is reduced and is associated with decreased transudation during sexual arousal and increased susceptibility to trauma and pain. Lactobacilli numbers decrease and the vaginal pH increases, leading to an environment more receptive to colonization by pathogenic bacteria.¹³ Vaginal length and diameter shrink, the vaginal fornices disappear, and the rugal folds of the vagina are lost. These changes, which produce a variety of symptoms, are a consequence of declining estrogen levels in the menopause.¹³

Evaluation of Evidence Criteria and Classification of Recommendations

Level of Evidence*	Classification of Recommendation†
I Evidence obtained from at least 1 properly randomized clinical trial.	A There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1 Evidence from well-designed controlled trials without randomization.	B There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2 Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than 1 centre or research group.	C There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.
II-3 Evidence obtained from comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*The quality of evidence reported in these guidelines has been ranked according to the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.⁷

†Recommendations included in these guidelines have been ranked according to the method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Examination.⁷

CLINICAL INVESTIGATION

The cornerstone of clinical investigation is the pelvic examination, during which examination of the vulva may demonstrate loss of the connective tissue substance that results in shrinkage of the labia majora. The labia minora may disappear completely and there is often a decrease in the introital opening. Vaginal examination will reveal shrinkage of the vaginal canal as well as thinning of the vaginal epithelium. The classic appearance of vaginal atrophy includes loss of rugae and a pale, dry appearance. The epithelial tissues are often friable and submucosal petechial hemorrhages may be visualized.

Laboratory markers of vaginal atrophy include a vaginal pH greater than 5.0 and a change in the maturation index of the vaginal wall towards a predominance of basal cells.¹⁴ Culture of the vagina may reveal pathogenic bacteria not normally found in the vagina. Although these measures provide some objective assessment of vaginal health, they are not particularly useful clinically.

RECOMMENDATION

- 1. Health-care providers should routinely assess postmenopausal women for the symptoms and signs of vaginal atrophy, a common condition that exerts significant negative effects on quality of life. (III-C)**

MANAGEMENT OPTIONS

A. TREATMENT OF VAGINAL ATROPHY

The management of urogenital atrophy and the consequent changes in pelvic organ function will depend upon the specific symptomatology. When a woman is symptomatic, options for management include lifestyle modification, nonhormonal treatment (vaginal lubricants or moisturizers), and hormonal treatments, both systemic and local.

LIFESTYLE MODIFICATION

Since a decline in estrogen levels is the primary etiology behind vulvovaginal atrophy, lifestyle factors that accelerate this decline should be avoided. Smoking results in increased metabolism of estrogen and is associated with higher rates of osteoporosis as well as vaginal atrophy.⁶ While evidence concerning the association between smoking and vaginal atrophy is conflicting, smoking cessation should be encouraged for a constellation of reasons.⁷ Continued regular vaginal coital activity provides protection from urogenital atrophy, presumably by increasing the blood flow to the pelvic organs.¹⁵ Masturbation has also been shown to increase genital blood flow in menopausal women and may help maintain urogenital health.¹⁶ Research has failed to demonstrate any beneficial effect of dietary estrogen¹⁷ or supplements such as dong quai¹⁸ on vaginal atrophy. While a Cochrane Review of the effect of the consumption of cranberry

juice on the risk of urinary tract infection found the evidence to be inconclusive,¹⁹ a recent clinical trial found that a cranberry-lingonberry juice concentrate reduced the risk of urinary tract infection.²⁰ Use of perfumed products and other materials that may cause contact dermatitis of the vulva should be discouraged.

RECOMMENDATIONS

- 2. Regular sexual activity should be encouraged to maintain vaginal health. (II-2B)**
- 3. Women experiencing recurrent urinary tract infections should be instructed that consumption of pure cranberry-lingonberry juice, rather than cranberry drink, will decrease their risk of urinary tract infections. (I-A)**

NONHORMONAL TREATMENTS

Vaginal Moisturizer

Replens, the only vaginal moisturizer available in Canada, has been demonstrated through clinical trials to have a beneficial effect equivalent to that of local hormone replacement, including positive changes on the maturation index of the vaginal epithelium and increases in vaginal moisture and vaginal fluid.²¹ In prospective randomized studies, when compared to local hormone replacement, Replens resulted in equivalent improvement of vaginal itching, irritation, and dyspareunia.²²

Vaginal Lubricants

There are several lubricants available to women in Canada. While vaginal lubricants can be used to decrease immediate irritation during coital activity, there is no evidence that these products have any long-term therapeutic effect.

RECOMMENDATION

- 4. Vaginal moisturizers applied on a regular basis have an efficacy equivalent to local hormone replacement for the treatment of local urogenital symptoms such as vaginal itching, irritation, and dyspareunia, and should be offered to women wishing to avoid use of hormone replacement therapy. (I-A)**

HORMONAL TREATMENTS

Systemic Hormone Replacement

Systemic hormone replacement is indicated for women who are seeking to treat a variety of symptoms associated with the estrogen deprivation of menopause. A woman who is experiencing general symptoms of menopause such as hot flashes and sleep disturbance in association with vaginal atrophy may choose systemic hormone replacement. However, systemic hormone replacement may be unacceptable for a variety of reasons, and in some women it is not an effective means of relieving vulvovaginal atrophy.^{12,23}

Local Hormone Replacement

The goal of local hormone replacement is to provide sufficient estrogen to reverse atrophic changes in the local tissues and relieve associated symptoms, while at the same time avoiding systemic effects. At present, there are 3 modalities for providing local estrogen replacement: estrogen cream, the estradiol-containing vaginal ring, and estradiol-containing vaginal tablets. All of these modalities have been proven to reverse vulvovaginal atrophy and associated symptoms.²³⁻²⁵

Conjugated equine estrogen vaginal cream. Estrogens are commonly prescribed in the form of a conjugated equine estrogen (CEE) cream (Premarin cream), each gram of which contains 0.625 mg of conjugated estrogens. Daily administration of as little as 0.3 mg CEE (0.5 g cream) each evening for 2 weeks and 3 times weekly thereafter for 6 months has been shown to correct vaginal atrophy both symptomatically and cytologically.²⁶ To achieve similar effects on the vaginal epithelium, oral CEE is needed in much higher doses,²⁷ suggesting a superior efficacy of the local route.

Marked systemic absorption of estrogen (demonstrated by a fall in follicle-stimulating hormone and luteinizing hormone levels) can occur in women who use estrogen vaginal cream, especially at the beginning of treatment when the vaginal epithelium is thin.²⁸ In a prospective trial of 20 women (with atrophic endometrium at treatment onset) treated with 0.3 mg CEE cream per vagina 3 times weekly for 6 months, only 1 woman developed proliferative tissue on endometrial biopsy. Botsis *et al.* documented an absence of endometrial proliferation by ultrasound in women using similar doses of CEE cream for 6 months.²⁹ No cases of endometrial carcinoma causally associated with the use of CEE cream have been reported. Recommendations for annual endometrial surveillance by ultrasound or endometrial biopsy, and the use of low-dose progestin cotherapy, in asymptomatic (i.e., non-bleeding) women using appropriate doses of vaginal CEE cream, are not supported by evidence. Women who experience postmenopausal bleeding while using local estrogen warrant full evaluation. The available literature would also suggest that CEE cream can also be safely applied to atrophic introital skin.

Although currently not available in Canada, vaginal creams containing estradiol and estriol have also been successfully used to treat vaginal atrophy.^{30,31} As with the conjugated estrogen cream, systemic absorption is minimal, though it can occur.^{30,31}

Sustained-release intravaginal estradiol ring. A flexible silicone ring with an estradiol-loaded core (Estring) can be inserted in the upper vagina to release 5 µg to 10 µg a day of estradiol slowly and constantly over a 3-month period. Smith *et al.* demonstrated significant improvement in the symptoms of atrophic vaginitis, with restoration of normal vaginal pH and cytology, in more than 90% of women using the Estring.³² Serum estradiol levels did not rise,³³ and several authors noted

a lack of endometrial proliferation,³³ even after 1 year of use.³⁴

Advantages of the ring include not only uniform sustained and local release of low doses of estradiol (as compared to doses delivered intermittently with local CEE cream), but also ease of insertion and improved compliance. Nachtigall *et al.* found the estradiol ring to be equally effective but more acceptable when compared to CEE vaginal cream for treatment of urogenital estrogen deficiency.³³ However, women with limited vaginal capacity or limited manual dexterity may not be able to insert and remove the ring easily, and in women with pelvic organ prolapse, repetitive dislodgement of the ring may occur. Its 3-month duration of action makes feasible the insertion and removal of the ring by a health-care professional. Though uncommon, partners may be aware of the ring during coitus.

Intravaginal estradiol tablet. Low doses of 17β-estradiol can be administered in the vagina using a hydrophilic slow-release tablet containing 25 µg 17β-estradiol (Vagifem). Maintenance therapy involves the administration of 1 tablet into the upper vagina every 3 days using a preloaded single-use applicator. Upon contact with the vaginal mucosa, a gel layer forms, allowing for rapid diffusion of estradiol.

Eriksen and Rasmussen reported significant benefit over placebo with the vaginal tablet administered twice weekly.³⁵ After 12 weeks of treatment, 89% of women demonstrated reversal of atrophic changes in the vagina and reported relief from vaginal dryness. Similarly, a recent multicentre, open, randomized Canadian trial by Rioux *et al.* reported equal therapeutic efficacy with 17β-estradiol tablets and CEE cream for the treatment of vaginal atrophy.²⁴ The authors identified a lack of significant systemic hormone absorption or endometrial effect with the intravaginal estradiol tablet. Other studies have reported similar findings.^{36,37}

As with the estradiol ring, the major advantages of the estradiol tablet are its ease of use and high long-term patient compliance. Rioux *et al.* noted that a higher number of women in their study found the tablet to be more acceptable than the cream.²⁴ At study completion, 90% of tablet users but only 68% of cream users continued with the treatment.

Selective estrogen receptor modulators. Whereas tamoxifen causes an increase in the vaginal maturation index,³⁸ raloxifene does not modify the vaginal index of the vaginal epithelium, nor has it been associated with increased frequency or severity of vaginal complaints during clinical trials.³⁹ Two studies examining the concomitant use of raloxifene with CEE vaginal cream or polycarbophil gel found no independent effect of raloxifene on the vaginal mucosa.^{12,39}

RECOMMENDATIONS

5. Women experiencing vaginal atrophy can be offered any of the following effective vaginal estrogen replacement therapies: conjugated equine estrogen cream (I-A), a sustained-release intravaginal estradiol ring (I-A), or a low-

dose estradiol tablet (I-A).

6. Although systemic absorption of estrogen can occur with local preparations, there is insufficient data to recommend annual endometrial surveillance in asymptomatic women using local estrogens. (III-C)

B. TREATMENT OF URINARY TRACT INFECTION

Estrogen replacement has been proven to prevent urinary tract infection in women with urogenital aging.³ In a randomized double-blind study by Raz and Stamm, the incidence of recurrent urinary tract infection in postmenopausal women treated with intravaginal estrogen was significantly reduced to 0.5 episodes per patient-year compared to 5.9 episodes per patient-year in women treated with placebo.³ As expected, the authors also observed a significant decrease in vaginal pH in their study participants treated with estrogen, as well as the reappearance of vaginal lactobacilli in 61% of treated women compared to no reappearance of vaginal lactobacilli in the placebo group.³ Ericksen has shown a similar beneficial prophylactic effect for postmenopausal urinary tract infection using a sustained-release intravaginal estradiol ring as compared to a placebo ring.⁴⁰

RECOMMENDATION

7. For menopausal women experiencing recurrent urinary tract infections and who have no contraindication to local hormone replacement, vaginal estrogen therapy should be offered. (I-A)

CONCLUSION

Vaginal atrophy causes symptoms that can significantly affect quality of life. Because women may not volunteer symptoms of vulvovaginal atrophy, it is incumbent upon the health-care practitioner to enquire about this problem. Effective treatment options are available and should be offered to women complaining of symptoms associated with vaginal atrophy.

REFERENCES

1. Iosif CS, Batra S, Ek A, Astedt B. Estrogen receptors in the female urinary tract. *Am J Obstet Gynecol* 1981;141:817-20.
2. Smith P, Heimer GM, Norgren A, Ulmsten U. Steroid hormone receptors in pelvic muscles and ligaments in women. *Gynecol Obstet Invest* 1990;30:27-30.
3. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993;329:753-7.
4. Griebing TL, Nygaard IE. The role of estrogen replacement therapy in the management of urinary incontinence and urinary tract infection in postmenopausal women. *Endocrinol Metab Clin North Am* 1997;26(2):347-60.
5. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee.

- Obstet Gynecol 1994;83:112-8.
6. Kalogeraki A, Tamiolakis D, Relakis K, Karvelas K, Froudarakis G, Hassan E, et al. Cigarette smoking and vaginal atrophy in postmenopausal women. *In Vivo* 1996;10:597-600.
7. Woolf SH, Battista RN, Anderson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group; 1994. p. xxxvii.
8. Van Geelen JM, van de Weijer PH, Arnolds HT. Urogenital symptoms and resulting discomfort in non-institutionalized Dutch women aged 50-75 years. *Int Urogynecol J Pelvic Floor Dysfunct* 2000;11:9-14.
9. Stenberg A, Heimer G, Ulmsten U, Cnattingus S. Prevalence of genitourinary and other climacteric symptoms in 61-year-old women. *Maturitas* 1996;24:31-6.
10. Utian WH, Schiff I. North American Menopause Society-Gallup Survey on women's knowledge, information sources, and attitudes to menopause and HRT. *Menopause* 1994;1:39-48.
11. Foxman B. Urinary tract infection in postmenopausal women. *Curr Infect Dis Rep* 1999;1(4):367-70.
12. Pinkerton JV, Shifren JL, La Valleur J, Rosen A, Roesinger M, Siddhanti S. Influence of raloxifene on the efficacy of an estradiol-releasing ring for treating vaginal atrophy in postmenopausal women. *Menopause* 2003;10:45-52.
13. Bachman GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. *Am Fam Physician* 2000;61:3090-6.
14. Nilsson K, Risberg B, Heimer G. The vaginal epithelium in the postmenopause - cytology, histology and PH as methods of assessment. *Maturitas* 1995;21:51-6.
15. Leiblum S, Bachmann G, Kemmann E, Colburn D, Schwartzman L. Vaginal atrophy in the postmenopausal woman: the importance of sexual activity and hormones. *JAMA* 1983;249:2195-8.
16. Laan E, van Lunsen RHW. Hormones and sexuality in postmenopausal women: a psychophysiological study. *J Psychosom Obstet Gynecol* 1997;18:126-33.
17. Upmalis DH, Lobo R, Badley L, Warren M, Cone FL, Lamma CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized placebo-controlled trial. *Menopause* 2000;7:236-42.
18. Hirate JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. *Fertil Steril* 1997;68:981-6.
19. Jepson RG, Mihaljevich L, Craig J. Cranberries for preventing urinary tract infections (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford Update Software; 2003.
20. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women. *BMJ* 2001;322(7302):1571.
21. Bygdeman M, Swah ML. Replens versus dienoestrol cream in symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas* 1996;23:259-63.
22. Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women. *Fertil Steril* 1994;61:178-80.
23. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the hormone and urogenital therapy committee. *Obstet Gynecol* 1998;92:722-7.
24. Rioux JE, Devlin MC, Gelfand MM, Steinberg WM, Hepburn DS. 17- β -Estradiol vaginal tablets versus conjugated equine estrogen cream to relieve menopausal atrophic vaginitis. *Menopause* 2000;7:156-61.
25. Casper F, Petri E. Local treatment of urogenital atrophy with an estradiol-releasing vaginal ring: a comparative and a placebo-controlled multicenter study. Vaginal ring study group. *Int Urogynecol J Pelvic Floor Dysfunct* 1999;10:171-6.
26. Handa VL, Bachus KE, Johnston WW, Robboy SJ, Hammond CB. Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium. *Obstet Gynecol* 1994;84:215-8.
27. Mandel FP, Geola FL, Meldrum DR, Lu JH, Eggena P, Sambhi MR, et al.

- Biological effects of various doses of vaginally administered conjugated equine estrogens in postmenopausal women. *J Clin Endocrinol Metab* 1983;57:133–9.
28. Johnston A. Estrogens: pharmacokinetics and pharmacodynamics with special reference to vaginal administration and the new estradiol formulation—Estring. *Acta Obstet Gynecol Scand* 1996;75 (Suppl 163): 16–25.
 29. Botsis D, Kassanos D, Kalogirou D, Antoniou G, Vitoratos N, Karakitsos P. Vaginal ultrasound of the endometrium in postmenopausal women with symptoms of urogenital atrophy on low-dose estrogen or tibolone treatment: a comparison. *Maturitas* 1997;26:57–62.
 30. Mattsson LA, Cullberg G. Vaginal absorption of two estradiol preparations. A comparative study in postmenopausal women. *Acta Obstet Gynecol Scand* 1983;62:393–6.
 31. Losif CS. Effects of protracted administration of estriol on the lower genitourinary tract in postmenopausal women. *Arch Gynaecol Obstet* 1992;251:115–20.
 32. Smith P, Heimer G, Lindskog M, Ulmsten U. Oestradiol-releasing vaginal ring for the treatment of postmenopausal urogenital atrophy. *Maturitas* 1993;16:145–54.
 33. Henriksson L, Stjernquist M, Boquist L, Cedergren I, Sellinus I. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. *Am J Obstet Gynecol* 1996;174:85–92.
 34. Nachtigall LE. Clinical trial of estradiol vaginal ring in the United States. *Maturitas* 1995;22 (Suppl):S43–S47.
 35. Eriksen PS, Rasmussen H. Low-dose 17 β -estradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo controlled study. *Eur J Obstet Gynecol Reprod Biol* 1992;44:137–44.
 36. Mettler L, Olsen PG. Long-term treatment of atrophic vaginitis with low-dose oestradiol vaginal tablets. *Maturitas* 1991;14:23–31.
 37. Mattsson LA, Cullberg G, Eriksson O, Knutsson F. Vaginal administration of low-dose oestradiol – effects on the endometrium and vaginal cytology. *Maturitas* 1989;11:217–22.
 38. Lahti E, Vuopala S, Kauppila A, Blanco G, Roukonen A, Laatikainen T. Maturation of vaginal and endometrial epithelium in postmenopausal breast cancer patients receiving long-term tamoxifen. *Gynecol Oncol* 1994;55:410–4.
 39. Parsons A, Merritt D, Rosen A, Heath H 3rd, Siddhanti S, Plouffe L. Study groups on the effects of raloxifene HCl with low-dose premarin vaginal cream. *Obstet Gynecol* 2003;101:346–52.
 40. Eriksen BC. A randomized, open, parallel-group study on the preventative effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol* 1999;180:1072–9.