The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 659 • March 2016
Reaffirmed 2018

Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Member contributors included Ruth Farrell, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer

ABSTRACT: Cancer treatment should address female-specific survivorship issues, including the hypoestrogenic-related adverse effects of cancer therapies or of natural menopause in survivors. Systemic and vaginal estrogen are widely used for symptomatic relief of vasomotor symptoms, sexual dysfunction, and lower urinary tract infections in the general population. However, given that some types of cancer are hormone sensitive, there are safety concerns about the use of local hormone therapy in women who currently have breast cancer or have a history of breast cancer. Nonhormonal approaches are the first-line choices for managing urogenital symptoms or atrophy-related urinary symptoms experienced by women during or after treatment for breast cancer. Among women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms, vaginal estrogen should be reserved for those patients who are unresponsive to nonhormonal remedies. The decision to use vaginal estrogen may be made in coordination with a woman's oncologist. Additionally, it should be preceded by an informed decision-making and consent process in which the woman has the information and resources to consider the benefits and potential risks of low-dose vaginal estrogen. Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions:

- Nonhormonal approaches are the first-line choices for managing urogenital symptoms or atrophy-related urinary symptoms experienced by women during or after treatment for breast cancer.
- Among women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms, vaginal estrogen should be reserved for those patients who are unresponsive to nonhormonal remedies.
- The decision to use vaginal estrogen may be made in coordination with a woman's oncologist. Additionally, it should be preceded by an informed decision-making and consent process in which the woman has the information and resources to consider the benefits and potential risks of low-dose vaginal estrogen.
- Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms.

Background

Oncologic care providers are increasingly recognizing that cancer treatment should address female-specific survivorship issues, including the hypoestrogenic-related adverse effects of cancer therapies or of natural menopause in survivors. Obstetrician–gynecologists and other health care providers frequently face the challenge of understanding and addressing these issues among an increasing cohort of women cancer survivors who experience urogenital symptoms, either from cancer therapy or

physiologic menopause. Systemic and vaginal estrogen are widely used for symptomatic relief of vasomotor symptoms, sexual dysfunction, and lower urinary tract infections in the general population. However, given that some types of cancer are hormone sensitive, there are safety concerns about the use of local hormone therapy in women who currently have breast cancer or have a history of breast cancer (1, 2). This document will focus on the use of low-dose vaginal estrogen in women with estrogen-dependent breast cancer.

Nonhormonal methods, including moisturizers, lubricants, and topical anesthetics, are first-line approaches for treating urogenital symptoms or atrophy-related urinary symptoms experienced by women during or after treatment for breast cancer (3, 4). However, for some women, these approaches may have a limited and temporary effect on symptoms and quality of life (5, 6). Vaginal estrogen therapy has been shown to provide women with symptomatic relief of urogenital symptoms associated with perimenopause and menopause (3). Generally, vaginal estrogen delivers lower doses of hormone compared with those formulations developed to provide systemic relief of vasomotor symptoms and, thus, offer a different approach to the management of urogenital symptoms among these patients.

Low-Dose Vaginal Estrogen Preparations and Serum Estrogen Levels

There are three main commercially available preparations of vaginal estrogen in the United States: 1) cream, 2) ring, and 3) tablet (see Table 1 for suggested regimens). (Although there are other forms available, such as compounded vaginal estrogen products, there are concerns regarding the risks of variable composition and potency and the lack of efficacy and safety data [7].) Vaginal estrogen delivers a low dose of hormone to the local vaginal tissue with minimal systemic absorption. Vaginal creams include a 17β-estradiol vaginal cream and a conjugated estrogen cream. The only vaginal tablet product currently available in the United States contains 10 micrograms of estradiol hemihydrate. Although there are two vaginal rings on the market, only the 17β-estradiol (commonly referred to as estradiol) silastic vaginal ring delivers low-dose hormone to the vaginal tissues. The second product, the estradiol acetate ring, provides systemic levels of hormone and is not discussed in this document.

Studies show that use of low-dose vaginal estrogens does not result in sustained serum estrogen levels exceeding the normal menopausal range; the lowest rates of systemic absorption are found in the ring and the tablet (8–15). When used at the appropriate dose, estradiol creams also deliver a low dose of hormone. Because of the heterogeneity of the estrogens in the formulation, data regarding the use of conjugated equine estrogen cream are less definitive compared with the data for estradiol cream. In addition, delivery of a set dose of estrogen is more variable with the creams in contrast to the tablet or ring. Thus, data regarding estradiol levels associated with vaginal creams have greater variability compared with tablet or ring formulations.

Table 1. Low-Dose Vaginal Estrogen Preparations and Suggested Regimens ⇦

Formulation	Composition	FDA-Approved Dosages*
Vaginal cream	17β-estradiol	The usual dosage range is 2–4 g (marked on the applicator) daily for 1 week or 2 weeks, then gradually reduced to one half of the initial dosage for a similar period. A maintenance dosage of 1 g one to three times a week may be used after restoration of the vaginal mucosa has been achieved.†
Vaginal cream	Conjugated equine estrogen	Cyclic administration of 0.5 g intravaginally (daily for 21 days then off for 7 days) for treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Twice weekly administration of 0.5 g intravaginally (for example, Monday and Thursday) for treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.‡
Vaginal ring	17β-estradiol	2-mg ring releasing 7.5 micrograms/d for 90 days
Vaginal tablet	Estradiol hemihydrate	10 micrograms/d for 2 weeks and then 10 micrograms/d two times a week

Abbreviation: FDA, U.S. Food and Drug Administration.

*FDA-approved dosages of conjugated estrogen and estradiol creams are greater than those currently used in clinical practice that are proven to be effective.

†In clinical practice, these protocols also are used: 1 g every night for 2 weeks, then two times per week or 0.5 g twice weekly.

‡In clinical practice, this protocol also is used: 0.5 g twice weekly.

The Use of Vaginal Estrogen by Women With a Current or Prior History of Breast Cancer

Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms (16). A nested case–control analysis of a cohort study of women with breast cancer who either did or did not use vaginal estrogen showed no increase of recurrence in vaginal estrogen users (17). In another study, the risk of recurrence in women who used vaginal cream was not increased, irrespective of the total dose prescribed (18).

Concerns remain about recurrence risk with use of vaginal estrogen in women with breast cancer who use aromatase inhibitors. Specifically, the threshold for systemic estrogen levels associated with breast cancer recurrence risk has yet to be determined (19). Some authors note that even a small increase in systemic estradiol levels may have a detrimental effect on recurrence risk and that more data are needed before recommendations can be made regarding the use of vaginal estrogen among this population (16, 20). Typically, aromatase inhibitors decrease circulating estradiol levels from 20 pg/mL to less than 1–3 pg/mL (20, 21). Studies have demonstrated an initial increase of serum estradiol with the use of low-dose vaginal estrogen (estradiol ring or the 25-microgram estradiol tablet) among women taking an aromatase inhibitor, though these levels were not sustained over time and increased cancer recurrence was not noted (11).

The use of vaginal estrogens may be appropriate for women with urogenital symptoms who use tamoxifen (22). Low and temporary increases of plasma estrogen do not appear to increase recurrence risk in women using tamoxifen because of a competitive interaction with the estrogen receptor (16). Because of these effects, women on aromatase inhibitors who experience urogenital symptoms refractory to nonhormonal approaches may benefit from the short-term use of estrogen with tamoxifen to improve symptoms, followed by a return to normal aromatase inhibitor therapy for the duration of the treatment course (20).

Conclusion

Nonhormonal approaches are the first-line choices for managing urogenital symptoms or atrophy-related urinary symptoms experienced by women during or after treatment for breast cancer. Among women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms, vaginal estrogen should be reserved for those patients who are unresponsive to nonhormonal remedies. Treatment should be individualized based on each woman's risk–benefit ratio and clinical presentation. The decision to use vaginal estrogen may be made in coordination with a woman's oncologist. Additionally, it should be preceded by an informed decision-making and consent process in which the woman has the information and resources to consider the benefits and potential risks of low-dose vaginal estrogen. When the decision is made to use vaginal estrogen, it should be prescribed at the lowest dose to affect vaginal symptoms and for a limited period until symptoms are improved.

References

1. Rippy L, Marsden J. Is HRT justified for symptom management in women at higher risk of developing breast cancer? Climacteric 2006;9:404–15. [PubMed] [Full Text] ⇦
2. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 2004;11:11–33. [PubMed] ⇦
3. Management of menopausal symptoms. Practice Bulletin No. 141. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:202–16. [PubMed] [*Obstetrics & Gynecology*] ⇦
4. Goetsch MF, Lim JY, Caughey AB. Locating pain in breast cancer survivors experiencing dyspareunia: a randomized controlled trial. Obstet Gynecol 2014;123:1231–6. [PubMed] [*Obstetrics & Gynecology*] ⇦
5. Loprinzi CL, Abu-Ghazaleh S, Sloan JA, vanHaelst-Pisani C, Hammer AM, Rowland KM Jr, et al. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. J Clin Oncol 1997;15:969–73. [PubMed] ⇦
6. Suckling JA, Kennedy R, Lethaby A, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD001500. DOI: 10.1002/14651858.CD001500.pub2. [PubMed] [Full Text] ⇦
7. Compounded bioidentical menopausal hormone therapy. Committee Opinion No. 532. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:411–5. [PubMed] [*Obstetrics & Gynecology*] ⇦
8. Lasley BL, Santoro N, Randolf JF, Gold EB, Crawford S, Weiss G, et al. The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. J Clin Endocrinol Metab 2002;87:3760–7. [PubMed] [Full Text] ⇦
9. Schmidt G, Andersson SB, Nordle O, Johansson CJ, Gunnarsson PO. Release of 17-beta-oestradiol from a vaginal ring in postmenopausal women: pharmacokinetic evaluation. Gynecol Obstet Invest 1994;38:253–60. [PubMed] ⇦
10. Mitchell ES, Woods NF, Mariella A. Three stages of the menopausal transition from the Seattle Midlife Women's Health Study: toward a more precise definition. Menopause 2000;7:334–49. [PubMed] ⇦
11. Wills S, Ravipati A, Venuturumilli P, Kresge C, Folkerd E, Dowsett M, et al. Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or a selective estrogen receptor modulator. J Oncol Pract 2012;8:144–8. [PubMed] [Full Text] ⇦

12. Rigg LA, Hermann H, Yen SS. Absorption of estrogens from vaginal creams. N Engl J Med 1978;298:195–7. [PubMed] ⇦

13. Pschera H, Hjerpe A, Carlstrom K. Influence of the maturity of the vaginal epithelium upon the absorption of vaginally administered estradiol-17 beta and progesterone in postmenopausal women. Gynecol Obstet Invest 1989;27: 204–7. [PubMed] ⇦

14. Santen RJ, Pinkerton JV, Conaway M, Ropka M, Wisniewski L, Demers L, et al. Treatment of urogenital atrophy with low-dose estradiol: preliminary results. Menopause 2002;9: 179–87. [PubMed] ⇦

15. Simunic V, Banovic I, Ciglar S, Jeren L, Pavicic Baldani D, Sprem M. Local estrogen treatment in patients with urogenital symptoms. Int J Gynaecol Obstet 2003;82:187–97. [PubMed] [Full Text] ⇦

16. Ponzone R, Biglia N, Jacomuzzi ME, Maggiorotto F, Mariani L, Sismondi P. Vaginal oestrogen therapy after breast cancer: is it safe? Eur J Cancer 2005;41:2673–81. [PubMed] ⇦

17. Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Res Treat 2012;135:603–9. [PubMed] ⇦

18. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J Natl Cancer Inst 2001;93:754–62. [PubMed] [Full Text] ⇦

19. Trinkaus M, Chin S, Wolfman W, Simmons C, Clemons M. Should urogenital atrophy in breast cancer survivors be treated with topical estrogens? Oncologist 2008;13:222–31. [PubMed] [Full Text] ⇦

20. Kendall A, Dowsett M, Folkerd E, Smith I. Caution: vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol 2006;17:584–7. [PubMed] [Full Text] ⇦

21. Biglia N, Peano E, Sgandurra P, Moggio G, Panuccio E, Migliardi M, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrinol 2010;26: 404–12. [PubMed] [Full Text] ⇦

22. Management of gynecologic issues in women with breast cancer. Practice Bulletin No. 126. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012; 119:666–82. [PubMed] [*Obstetrics & Gynecology*] ⇦

Copyright March 2016 by the American College of Obstetricians and Gynecologists. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, posted on the Internet, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Requests for authorization to make photocopies should be directed to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400.

ISSN 1074-861X

The American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

The use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. Committee Opinion No. 659. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016; 127:e93–6.