Dana-Farber Breast Oncology Center

Consensus Statement Regarding Use of Vaginal Estrogen in Patients with a History of Breast Cancer

Consensus: Obtained at a Breast Oncology Center meeting on 02/08/2023.

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Q2. Can vaginal estrogen be used in women with a history of hormone receptor (HR)-negative breast cancer?	Patients with a history of HR-negative breast cancer who have GSM symptoms that are refractory to vaginal moisturizers containing hyaluronic acid and lubricants can attempt a course of vaginal estrogen. When vaginal estrogen is used, the standard recommendations regarding application, dose and frequency should be followed as sub-optimal treatment will most likely result in lack of benefit.
Q3. Can vaginal estrogen be used in women with a history of HR-positive breast cancer who are taking tamoxifen or aromatase inhibitors?	The BOC group agreed that a course of vaginal estrogen can be used for patients with a history of breast cancer on tamoxifen who have GSM symptoms refractory to non-hormonal based local treatment. For patients with a history of breast cancer who are taking an aromatase inhibitor and have GSM symptoms refractory to non-hormonal based local treatment, the BOC consensus group recommended to decide on the use of vaginal estrogen on a case-by-case bases. A shared decision between the provider and the patient should take into consideration the possible increased recurrence risk, the lack of evidence of increase in mortality, and the severity of the GSM symptoms.
Q4. Should other medications be used for the treatment of GSM symptoms in women with a history of breast cancer?	Although there are efficacy data on the treatment of GSM symptoms with vaginal dehydroepiandrosterone (DHEA), topical testosterone, and oral ospemifene, the BOC group agreed that currently there are insufficient safety data to recommend DHEA, topical testosterone, or ospemifene in women with a history of breast cancer.

Introduction

Genitourinary syndrome of menopause (GSM), previously known as vulvovaginal atrophy or urogenital atrophy, is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder.[1] Symptoms of GSM include vaginal dryness, genital pain, lack of lubrication, dyspareunia, urinary urgency and frequency, dysuria, and recurrent urinary tract infections. Most post-menopausal women experience symptoms of GSM at some point in their lifetime, and symptoms tend to be progressive. The prevalence of GSM increases with age.

Estradiol is the most potent form of estrogen and the main form of estrogen in women during reproductive years. In pre-menopausal women, estradiol levels vary from 10 to 800 pg/mL, depending on the phase of the menstrual cycle. After menopause, estradiol levels are typically ≤30 pg/mL, and most of the estradiol comes from the conversion of androstenedione (produced in the adrenal glands) to estrone in the peripheral tissue (mainly fat). Estrogen receptors are found in the vagina, vulva, labia, urethra, and bladder. Vaginal dryness is a consequence of reduced vaginal lubrication caused by a decrease in vaginal blood flow due to reduced levels of estrogen. A decline in estrogen also leads to loss of subcutaneous fat in the labia majora, clitoral atrophy, and reduced vaginal elasticity. Furthermore, estrogen level decline leads to thinning of the vaginal epithelium, causing decreased local glucose production. As glucose is broken down into lactic acid by *Lactobacillus* in the vaginal flora, less glucose production leads to a rise in local pH, facilitating the growth of other bacteria.[2]

Women with a history of breast cancer have a high prevalence of GSM symptoms secondary to a hypoestrogenic state through several different mechanisms. First, chemotherapy can lead to premature ovarian insufficiency in patients with either hormone receptor (HR; estrogen receptor and/or progesterone receptor)-positive or HR-negative breast cancer. Second, tamoxifen and aromatase inhibitors are commonly used in patients with HR-positive disease, and both drugs can cause symptoms of GSM. A study evaluating urogenital symptoms in patients with a history of breast cancer taking endocrine therapy showed that 58% of women taking an aromatase inhibitor and 32% of women taking tamoxifen rated at least 1 vaginal atrophy symptom as moderate/severe, significantly more than in the control group (2%, $p<0.01$).[3] Third, many pre-menopausal women undergo ovarian function suppression with GnRH agonists or bilateral oophorectomy.

Symptoms of GSM can significantly impact the quality of life of women with a history of breast cancer. It is well known that side effects from endocrine therapy are an important cause of treatment discontinuation, with higher rates of non-adherence in young women.[4] As patients with a history of breast cancer may not spontaneously report symptoms of GSM, it is important that clinicians inquire about these symptoms during medical visits.

Vaginal estrogen is an effective treatment for GSM symptoms, and it is preferred over systemic hormones when only GSM symptoms are present. There are several commercially available formulations of vaginal estrogen in the United States, including vaginal creams, tablets, inserts, and rings. All FDA approved products had their efficacy

evaluated in randomized clinical trials prior to approval. Low-dose vaginal estrogen is usually defined as ≤50 µg of estradiol or ≤0.3 mg of conjugated estrogens (present in ≤0.5 g cream). Ultra-low-dose vaginal estrogens are those with ≤10 µg of estradiol, like vaginal tablets (**Table 1**).

Table 1. Vaginal estrogen formulations[5, FDA labels]

Formulation	Estradiol content	Dosing	Comments
Estradiol vaginal tablet (Vagifem©, Yuvafem©)	One tablet contains 10 µg of estradiol	Initial: 1 tablet inserted intravaginally once daily for 2 weeks Maintenance: 1 tablet inserted vaginally twice a week	
Estradiol vaginal insert (Imvexxy©)	One softgel insert contains 4 µg or 10 µg of estradiol	Initial: 1 softgel (4 or 10 µg) inserted intravaginally once daily for 2 weeks, then gradually reduced to maintenance dose Maintenance: 1 softgel (4 µg or 10 µg) inserted twice weekly	Select the initial dose (4 µg or 10 µg) based on clinical symptom severity Adjust maintenance dose based on patient response
Estradiol vaginal ring (Estring©)	One ring delivers 7.5 µg of estradiol per day	1 ring inserted intravaginally. Ring should be removed and replaced every 90 days.	
Estradiol vaginal cream (Estrace©)	1 g of cream contains 100 µg of estradiol	Initial: 0.5 to 1 g of cream intravaginally daily for 2 weeks Maintenance: 0.5 to 1 g two to three times a week	May also be applied directly to vulvar and vestibular tissues Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.
Conjugated Equine estrogen cream (Premarin©)	1 g of cream contains 0.625 mg of conjugated estrogens (0.5 mg is bioequivalent to ~100 µg of estradiol)	Initial: 0.5 g of cream intravaginally once a day for 2 weeks Maintenance: 0.5 g of cream twice a week	Dose may be adjusted according to patient's symptoms and clinical response

An updated Cochrane systematic review compared the efficacy and safety of intra-vaginal estrogenic preparations for the treatment of vaginal atrophy symptoms in postmenopausal women. Patients with a history of breast cancer were excluded. The review included 30 randomized studies using different estrogenic preparations administered intravaginally in postmenopausal women for at least 12 weeks. There was no evidence of a difference in efficacy between the various intravaginal estrogenic preparations (estrogen ring, cream, or tablets). All vaginal estrogen preparations improved the symptoms of vaginal atrophy compared to placebo.[6] A separate Cochrane review concluded that vaginal estrogen improves symptoms of urinary incontinence.[7] Relatively small randomized clinical trials have also demonstrated efficacy of vaginal estrogen for the treatment of post-menopausal women with recurrent urinary tract infections (defined as ≥2 infections in 6 months or ≥3 infections in 1 year).[8,9]

The measurement of serum estradiol level played an important role in many clinical studies evaluating the impact of hormones on several diseases. However, many assays lack sensitivity and specificity for the detection of low levels of estradiol. Mass spectrometry–based assays are more sensitive and specific for the detection of low levels of estradiol; however, they are costly and require highly trained personnel.[10] Several of these studies have evaluated the impact of low-dose vaginal estrogen use on systemic levels of estradiol. Vaginal estrogens minimally increase the levels of serum estradiol, significantly less than with systemic estrogen use. Mean estradiol levels in post-menopausal women measured at baseline in most of the studies of vaginal estrogens ranged from 2.9 to 4.9 pg/mL. The absorption of estrogen through the vaginal mucosa is dose-dependent, and several studies demonstrated that the estradiol levels decrease after several weeks of vaginal estrogen use, suggesting that estradiol absorption decreases as the vaginal wall thickness increases with treatment. The absorption of estradiol may also vary by the site of placement of estradiol in the vagina, with lower applications leading to lower estradiol absorption.[11] Of note, post-menopausal women on aromatase inhibitors are expected to have post-menopausal estradiol levels by assays commonly used in practice, and monitoring those levels while using vaginal estrogen would not provide reassurance.

One study evaluated the estradiol absorption of vaginal estrogen tablets containing either 10 μg (ultra-low dose) or 25 μg (low dose) administered once daily for 2 weeks, followed by twice weekly for 10 weeks in 58 post-menopausal women with vaginal atrophy. Blood samples were taken over 24 hours at baseline and days 1, 14, 82, and 83. The mean serum estradiol levels were at least 50% lower with the 10 μg tablets than with the higher dose (9.39 and 19.84 pg/ml on day 1; 6.56 and 18.29 pg/ml on day 14; 4.64 and 9.41 pg/ml on day 83 for the 10 μg and 25 μg doses, respectively). The estradiol levels in the first 2 weeks remained in the postmenopausal range with the 10 μg tablets but exceeded that range with the 25 μg dose. After 12 weeks, the estradiol level returned to baseline with the 10 μg dose and remained slightly higher with the 25 μg dose.[12]

Several other studies evaluated serum estradiol levels with different vaginal estradiol formulations. In general, estrogen is more easily absorbed with vaginal creams than with tablets, rings, or inserts. A study assessing serum estradiol levels in 24 post-menopausal women using a vaginal estrogen ring containing either 7 or 20 μg/day demonstrated that

the device may release a higher dose of estradiol in the first 24 hours of use. The median serum estradiol levels rose within 2 h to 233 pmol/l (range 108-583) with the 7 µg/day ring, and to 354 pmol/l (range 267-851) with the 20 µg/day ring. However, after an initial peak, the serum estradiol levels over 3 months of treatment were unchanged compared to pretreatment values with both delivery rates.[13]

A randomized trial with 72 post-menopausal women evaluated serum estradiol levels with 4, 10, or 25 µg estradiol inserts once a day for 2 weeks followed by twice a week for 10 weeks. Patients who received the 4 µg insert had no significant difference in serum estradiol levels compared to patients who received placebo. Patients who received the 10 µg dose had an increase in estradiol on day 1 (10.9 versus 6.6 pg/mL in patients with placebo) but not on day 14. Patients who received 25 µg had higher levels on both day 1 (29.8 pg/mL) and day 14 (15.7 pg/mL) than the placebo group. Estradiol concentrations on day 84 were similar to baseline and placebo for the 4, 10, and 25 µg dose groups.[14]

Most studies evaluating the absorption of estradiol creams are older and therefore used a higher dose of estradiol than currently used.[10] In a study with 20 post-menopausal women with atrophic vaginitis who were treated with 0.3 mg of conjugated estrogens vaginally 3 nights per week for 6 months, there were no significant changes in serum estrogen levels.[15] However, it is important to note that conjugated estrogens contain several estrogen compounds, and serum estradiol levels may not reflect the entire estrogenic activity.[11]

Most patients experience some improvement of GSM symptoms in the first 2 weeks of treatment. The treatment duration should be individualized depending on each patient's degree of GSM symptoms. Adverse effects of vaginal estrogen include vaginal irritation or pruritus, vaginal bleeding, vulvovaginal candidiasis, and breast pain.

A large prospective cohort study utilizing data from participants of the Women's Health Initiative Observational Study aimed to determine the association between vaginal estrogen use and risk of several diseases, including breast cancer. More than 45,000 women without a history of breast cancer were included in the analysis, and the median duration of vaginal estrogen use was 2 years. With a median follow-up of 7.2 years, the study found that the risk of breast cancer was not significantly different between women who used vaginal estrogen compared to non-users.[16]

Although vaginal estrogen is an effective treatment for GSM symptoms, its use in patients with a history breast cancer has been historically avoided due to a concern of possible increase in the risk of breast cancer recurrence, despite limited data. For several decades, low-dose vaginal estrogen carried the same black box warning as systemic hormonal therapy for the risk of primary breast cancer. However, in November 2025, the US Food and Drug Administration (FDA) advised manufacturers to remove the black box warning related to breast cancer from low-dose vaginal estrogen products.[17] Most recent data suggest that vaginal estrogen may be safe for many patients with a history of breast cancer.

The purpose of this Consensus Statement was to review the data regarding the efficacy and safety of vaginal treatment options for GSM symptoms in patients with a history of

breast cancer and establish a consensus regarding their use among clinicians in the Dana-Farber Cancer Institute's Breast Oncology Center (BOC) group.

Development of the Consensus Statements

The Dana-Farber Cancer Institute's Breast Oncology Center (BOC) held a multidisciplinary meeting on 02/08/2023 to discuss recommendations for the use of vaginal estrogen in patients with a history of breast cancer. Additional relevant data were reviewed to address the questions in this document as noted below. The gathered evidence was presented for discussion to a multidisciplinary group, which included Dana-Farber physicians, nurses, clinical investigators, lab investigators, translational researchers, administrators, and patient advocates. The discussion and suggestions for improvements continued via email exchanges following the meeting. The final consensus statements were consolidated in March of 2026.

The consensus statements can be subject to future variations and periodic updates, based on emerging evidence and new reports from ongoing clinical studies. Therefore, the information provided in this document should not be considered as being complete or inclusive of all proper assessments, treatments or methods of care or as a statement of the standard of care. This information does not mandate any particular course of medical care and is not intended to be a substitute for the independent professional judgment of a health care provider. The document is based on the opinion of a multidisciplinary team at Dana-Farber but does not represent the official institutional position and overall must be considered as a consensus based on the positions and ideas of the Dana-Farber providers.

Clinical Questions

This document summarizes the discussions and consensus among the Dana-Farber BOC group regarding the following clinical questions:

1. **What is the first-line therapy for genitourinary syndrome of menopause (GSM) in patients with a history of breast cancer?**
2. **Can vaginal estrogen be used in women with a history of HR-negative breast cancer?**
3. **Can vaginal estrogen be used in women with a history of HR-positive breast cancer who are taking tamoxifen or aromatase inhibitors?**
4. **Should other medications be used for the treatment of GSM symptoms in women with a history of breast cancer?**

1. What is the first-line therapy for genitourinary syndrome of menopause (GSM) in patients with a history of breast cancer?

The use of non-hormonal moisturizers and lubricants is usually the first step in the treatment of GSM symptoms. Vaginal moisturizers are supposed to be used routinely (daily or every 2-3 days), and lubricants are intended to be used during sex to reduce friction and

dyspareunia. Moisturizers are typically bio-adhesive and mimic the vaginal natural secretion, and their effects last longer than those of the lubricants. Moisturizers usually contain water, a polymer, and other excipients; many contain hyaluronic acid, causing an increase in vaginal fluid content and acidity.[18] Examples of commercially available moisturizers include Hyalo Gyn©, Revaree© suppositories, Replens Long-Lasting Vaginal Moisturizer©, among others. Lubricants are water-based, silicone-based, mineral oil-based, or plant oil-based, and are useful during sexual activity. Products commercially available include Uber Lube©, K-Y Jelly Water Based Lubricant©, Astroglide Gel Lubricant©, among others.

There are relatively few studies evaluating the efficacy of non-hormonal moisturizers in the treatment of GSM symptoms. A study evaluated the efficacy of a vaginal moisturizer in comparison with a vaginal estrogen cream in 39 post-menopausal women with symptoms of vaginal dryness. Patients were randomly assigned to receive either Replens© one vaginal application 3 times a week for 12 weeks or Dienoestrol© vaginal cream 0.01% 0.5 mg daily during the first 2 weeks and 3 times a week thereafter. Both treatments were effective in reducing vaginal dryness, pruritus, irritation, and dyspareunia, with all women but 1 in each group reporting improvement of symptoms. There were no serious adverse events. When comparing both treatments, the estrogen cream was more effective in reducing vaginal dryness.[19]

A small study evaluated the efficacy and safety of 2 low-dose vaginal estrogen treatments and of a non-hormonal vaginal moisturizer in post-menopausal women with a history of breast cancer who had urogenital atrophy. Eighteen patients received either estriol cream 0.25 mg, estradiol tablets 12.5 μg twice a week for 12 weeks, or a polycarbophil-based moisturizer 2.5 g twice a week. Vaginal Symptoms Score (VSS) and Vaginal Health Index (VHI) significantly improved with both vaginal estrogen formulations, with further improvement after 12 weeks. The vaginal moisturizer improved VSS at week 4, but the score returned to pre-treatment values at week 12; there was no significant modification of VHI with the moisturizer.[20]

A single-arm study evaluated the effectiveness of a hyaluronic-containing vaginal moisturizer in patients with a history of HR-positive breast cancer treated with an aromatase inhibitor. The vaginal moisturizer was applied internally and externally daily for the first 2 weeks, then 3 times a week until weeks 12–14, with dose increase to 5 times a week for non-responders. Vulvovaginal health and sexual function significantly improved, but 75% of women required increase in frequency to 5 times a week. Although there was no decrease in pH in general, there was a decrease in severely elevated pH (6.5 of greater).[21]

The BOC group discussed their first-line therapy for GSM symptoms for patients with a history of breast cancer, including those taking endocrine therapy. Given the absence of hormones in their formulation with no concerns regarding increased risk of breast cancer recurrence, and taking into consideration their expected efficacy, the group agreed that moisturizers and lubricants should be the first step in treatment.

Based on the aforementioned considerations, the BOC group came to the following consensus:

Consensus Statement

It is recommended that women with a history of breast cancer who are experiencing symptoms of GSM, including those on endocrine therapy, are initially treated with non-hormonal moisturizers containing hyaluronic acid and lubricants. These products have some efficacy and do not have hormones in their formulation, with no impact on the risk of breast cancer recurrence.

2. Can vaginal estrogen be used in women with a history of HR-negative breast cancer?

In general, vaginal estrogen has a better safety profile than systemic hormonal therapy as its estrogen dose is significantly lower. However, there are no long-term randomized trials evaluating the safety of vaginal estrogen in patients with a history of breast cancer. In addition, the Cochrane review of local estrogen for treatment of vaginal atrophy excluded women with a history of breast or endometrial cancer.[6]

Several retrospective observational studies have evaluated the risk of breast cancer recurrence in patients with a history of breast cancer, but the majority focused on patients with a history of ER-positive disease. A cohort study evaluated 69 patients with a history of breast cancer who used vaginal estrogen (cream or tablets) and found no association of topical estrogen use and risk of recurrence. Patients with ER-negative breast cancer were included in this analysis, but information on receptor status was only available in 23% of the total database.[22] Another study (which enrolled from 1977 to 1994) explored the impact of hormonal replacement in patients with a history of ER-positive and ER-negative breast cancer; this study included patients receiving vaginal estrogen (the majority with conjugated estrogen). The relative risk of recurrence was low in both oral hormonal therapy and vaginal estrogen, with no increased risk compared to non-users, although this was an observational study and confounding factors are possible.[23]

Although there are insufficient data to confirm the long-term safety of vaginal estrogen in patients with a history of ER-negative breast cancer, there is no evidence that transitory increases in estradiol level impacts the risk of breast cancer recurrence in these patients. Therefore, the BOC group agreed that in patients with a history of ER-negative breast cancer who have GSM symptoms that are refractory to vaginal moisturizers and lubricants, a course of vaginal estrogen can be attempted. When using vaginal estrogen, the standard recommendations regarding dose and frequency should be followed as sub-optimal treatment will most likely result in lack of benefit.

Consensus Statement

Patients with a history of HR-negative breast cancer who have GSM symptoms that are refractory to vaginal moisturizers containing hyaluronic acid and lubricants can attempt a course of vaginal estrogen. When vaginal estrogen is used, the standard recommendations regarding application, dose and frequency should be followed as sub-optimal treatment will most likely result in lack of benefit.

3. Can vaginal estrogen be used in women with a history of HR-positive breast cancer who are taking tamoxifen or aromatase inhibitors?

The prevalence of GSM symptoms is high among patients with a history of ER-positive breast cancer taking endocrine therapy. Despite using vaginal lubricants and long-acting moisturizers, many patients continue to experience bothersome GSM symptoms.

A cohort study with nested case–control analysis using the United Kingdom General Practice Research Database (GPRD) included pre- and post-menopausal women with a history of breast cancer who received at least 1 tamoxifen or aromatase inhibitor prescription between 1998 and 2008, with a minimum of 1 year of follow-up. A total of 271 patients were treated with vaginal estrogen, most commonly vaginal cream and tablets. With a median follow-up of 4.2 years, the study found no increased risk of recurrence in patients treated with tamoxifen or aromatase inhibitors concurrently with vaginal estrogen. Of note, the results were mainly driven by patients treated with tamoxifen as the group treated with aromatase inhibitors lacked statistical power.[24]

A nested case-control study using the Breast Cancer Database Sweden investigated the impact of vaginal estrogen on breast cancer mortality in women with early HR-positive breast cancer treated with adjuvant endocrine treatment. A cohort of 15,198 women diagnosed from 2006 to 2012 were included. Exposure to estrogen therapy was defined as at least 1 filled prescription of either estriol or estradiol at least 1 year before the index date. No statistically significant difference in breast cancer mortality was seen in patients using vaginal estrogen concurrent with endocrine therapy with either tamoxifen or aromatase inhibitor. Of note, there was no difference in mortality regardless of the duration of therapy with vaginal estrogen. Although it was not possible to distinguish the pharmaceutical form of estrogen therapy in the study, systemic hormone therapy after breast cancer was contra-indicated in Sweden, and the authors presumed that the vast majority of estrogen therapy was vaginal estrogen.[25]

A Danish observational cohort study evaluated the risk of breast cancer recurrence and mortality with vaginal estrogen use and menopausal hormone therapy in patients with a history of breast cancer. Data from a national cohort of post-menopausal women aged 39-95 years in Denmark was analyzed. The cohort included women who were diagnosed with early ER-positive breast cancer from 1997 through 2004 and were included in the Danish Breast Cancer Group clinical database. Patients could have received no endocrine therapy, 5 years of tamoxifen, 5 years of aromatase inhibitor, or both treatments in sequence. Patients who received both an aromatase inhibitor and tamoxifen were

categorized as aromatase inhibitor users from the date of initiation of treatment with the aromatase inhibitor. Data from the Danish National Prescription Database was collected, and patients who had redeemed at least 2 prescriptions after the diagnosis of breast cancer were included; patients who had used vaginal estrogen or menopausal hormone therapy prior to the breast cancer diagnosis were excluded. The median follow-up was 9.8 years for recurrence and 15.2 years for mortality.[26]

A total of 1,957 patients who used vaginal estrogen were included in the Danish cohort study; the median age was 61 years. Vaginal estrogen treatment included Estring© (estradiol vaginal ring), Ovestin© (estriol cream, not available in the US), and Vagifem© (estradiol tablets). Women who received vaginal estrogen had an adjusted risk of recurrence similar to never-users (HR = 1.08, 95% CI = 0.89 to 1.32). However, after stratifying by adjuvant endocrine therapy, the use of vaginal estrogen among patients who received an aromatase inhibitor was associated with an elevated risk of recurrence (HR = 1.39, 95% CI = 1.04 to 1.85). The use of tamoxifen was not associated with an elevated risk of recurrence (HR = 0.64, 95% CI = 0.39 to 1.06). The adjusted hazard ratio for overall survival (OS) for users of vaginal estrogen compared with never-users was 0.78 (95% CI = 0.71 to 0.87). Importantly, there was no increased mortality with the use of aromatase inhibitors (adjusted HR = 0.94, 95% CI = 0.70 to 1.26). The absolute 10-year OS among users of vaginal estrogen was 79.5% compared to 73.8% among never-users.[26]

A recent meta-analysis evaluated 6 retrospective observational studies of patients on adjuvant endocrine therapy for breast cancer who used vaginal estrogen, including the Danish cohort study. A total of 1,805 women were included, with a median follow-up of 7 years for recurrence and 10 years for mortality. There was no statistically significant difference in recurrence among breast cancer survivors on adjuvant endocrine treatment with exposure to vaginal estrogen. When separated by type of endocrine therapy, exposure to vaginal estrogen was not associated with an increased risk of recurrence in patients taking tamoxifen (RR = 0.95, 95 % CI = 0.54–1.69, P = 0.87), but there was an increased risk of recurrence in patients taking aromatase inhibitors (RR = 2.51, 95 % CI = 1.10–5.72, P = 0.03). There was no increase in mortality with vaginal estrogen, regardless of the type of endocrine therapy.[27]

The impact on mortality with the use of vaginal estrogen in patients with a history of breast cancer was also evaluated in a cohort study that included 2 large cohorts in Scotland and Wales with 49,237 women. The study found no evidence of higher breast cancer-specific mortality among patients who used vaginal estrogen therapy. When stratifying by type of endocrine therapy, there was no impact on mortality from vaginal estrogen in patients taking tamoxifen or aromatase inhibitors.[28]

Although there is some limitation to the above data given the lack of large randomized clinical trials in this setting, it is possible that a difference in mechanism of action between tamoxifen and aromatase inhibitors may explain the discrepancy in risk of recurrence with vaginal estrogen use. As tamoxifen blocks the estrogen receptor, it is unlikely that small elevations in serum estradiol levels will significantly impact the risk of breast cancer recurrence. However, small increases in estradiol may counteract some of the effects of decrease in estradiol production by aromatase inhibitors.

Based on the aforementioned considerations, the BOC group agreed that vaginal estrogen is likely safe in most patients taking tamoxifen, but that patients on aromatase inhibitors may be at increased risk of recurrence with the use of vaginal estrogen, although the above data showed no impact on mortality.

Consensus Statement

The BOC group agreed that a course of vaginal estrogen can be used for patients with a history of breast cancer on tamoxifen who have GSM symptoms refractory to non-hormonal based local treatment.

For patients with a history of breast cancer who are taking an aromatase inhibitor and have GSM symptoms refractory to non-hormonal based local treatment, the BOC consensus group recommended to decide on the use of vaginal estrogen on a case-by-case bases. A shared decision between the provider and the patient should take into consideration the possible increased recurrence risk, the lack of evidence of increase in mortality, and the severity of the GSM symptoms.

4. Should other medications be used for the treatment of GSM symptoms in women with a history of breast cancer?

Androgen receptors are present throughout the female genitourinary tract, including the vaginal mucosa, muscularis, and adventitial layers, as well as the labia majora, minora, vestibule, clitoris, urethra and bladder. Androgen sex steroid hormones include dehydroepiandrosterone (DHEA), androstenedione, androstenediol, testosterone, and 5α-dihydrotestosterone (5α-DHT). Androgens may have a direct effect on the genitourinary tissue and are also precursors of estrogen through the aromatization pathway.[29] Several androgen components have been evaluated in studies including patients with a history of breast cancer.

Vaginal DHEA (or prasterone) was evaluated in 3-arm randomized trial by the Alliance for Clinical Trials in Oncology including postmenopausal cancer survivors with vaginal symptoms. DHEA 3.25 mg and DHEA 6.5 mg were each compared to a plain moisturizer over 12 weeks. A total of 464 postmenopausal women with a history of breast or gynecologic cancer were included. The majority of patients were on tamoxifen or an aromatase inhibitor. Participants were instructed to insert 1 syringe of gel daily right before going to bed, after any sexual activity, every night for 12 weeks. Patients in all 3 arms had improvement in either vaginal dryness or dyspareunia. Both doses of DHEA were comparable to the plain moisturizer at 12 weeks, although DHEA at 6.5 mg was more effective than the plain moisturizer at 8 weeks. Importantly, vaginal DHEA 6.5 mg significantly improved sexual health compared to the other 2 arms ($p < 0.001$). There were no differences in clinician-graded toxicities among the 3 arms.[30] As prasterone is a precursor of androstenedione and testosterone, which undergo aromatization locally to form estrone and estradiol, its mechanism of action led to a concern that patients

applying vaginal DHEA could have an increase in estrogen levels. In a study with 989 postmenopausal women who received daily intravaginal administration of 6.5 mg of DHEA or placebo for 12 weeks, serum estradiol and estriol levels were higher than in the placebo arm but remained at normal postmenopausal levels at 12 weeks.[31]

Currently there are no FDA-approved topical testosterone products for women with GSM symptoms in the United States, but studies have shown some therapeutic efficacy. A small study evaluated the use of topical testosterone in 21 postmenopausal patients with a history of breast cancer being treated with an aromatase inhibitor. Participants applied a testosterone cream (300 µg or 150 µg) to the vaginal epithelium daily for 28 days. There was an improvement of GSM symptoms with both testosterone doses, but only the 300 µg dose was associated with improved pH level. Estradiol levels remained suppressed after treatment.[32] Another study compared the use of vaginal testosterone cream with vaginal estrogen ring in 75 women with a history of early breast cancer on an aromatase inhibitor who had symptoms of vaginal dryness or decreased libido. Premenopausal women on ovarian function suppression and postmenopausal women were included. Estradiol level was measured at baseline and weeks 4 and 12 using a commercially available liquid chromatography and tandem mass spectrometry assay. At baseline, estradiol level was above the postmenopausal range (>10 pg/mL) in 28 of 76 women (37%). Persistent estradiol elevation occurred in none of the patients with vaginal ring and in 4 of 34 women (12%) with vaginal testosterone. Transient estradiol elevation occurred in 11% of patients with a vaginal ring and in 12% with vaginal testosterone. Both treatments were effective, and vaginal atrophy, sexual interest, and dysfunction improved in all patients.[33]

Ospemifene is a selective estrogen receptor modulator (SERM) that acts as an estrogen agonist in the vagina and appears to have a neutral or anti-estrogenic effect on the breast. Several randomized studies have demonstrated the efficacy of oral ospemifene either at 30 mg or 60 mg daily for 12 weeks compared to placebo for the treatment of vaginal dryness or dyspareunia. Some of the side effects of ospemifene are similar to tamoxifen and include hot flashes, endometrial thickening, and thromboembolism.[34-36] No randomized studies with ospemifene have been done in patients with a history of breast cancer, and its safety in this population has not been established.

Based on the above data, the BOC group agreed that currently there are insufficient safety data to recommend DHEA, topical testosterone, or ospemifene in women with a history of breast cancer.

Consensus Statement

Although there are efficacy data on the treatment of GSM symptoms with vaginal dehydroepiandrosterone (DHEA), topical testosterone, and oral ospemifene, the BOC group agreed that currently there are insufficient safety data to recommend DHEA, topical testosterone, or ospemifene in women with a history of breast cancer.

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