

# Managing Genitourinary Syndrome of Menopause in Breast Cancer Survivors Receiving Endocrine Therapy

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Patients with breast cancer receiving antiestrogen therapy, specifically aromatase inhibitors, often suffer from vaginal dryness, itching, irritation, dyspareunia, and dysuria, collectively known as genitourinary syndrome of menopause (GSM). GSM can decrease quality of life and is undertreated by oncologists because of fear of cancer recurrence, specifically when considering treatment with vaginal estrogen therapy because of unknown levels of systemic absorption of estradiol. In this article, we review the available literature for treatment of GSM in patients with breast cancer and survivors, including nonhormonal, vaginal hormonal, and systemic hormonal therapy options. First-line treatment includes nonhormonal therapy with vaginal moisturizers, lubricants, and gels. Although initial studies showed significant improvement in symptoms, the US Food and Drug Administration recently issued a warning against CO<sub>2</sub> laser therapy for treatment of GSM until additional studies are conducted. In severe or refractory GSM, after discussing risks and benefits of vaginal hormonal therapy, the low-dose 10- $\mu$ g estradiol-releasing intravaginal tablet or lower-dose 4  $\mu$ g estrogen vaginal insert and intravaginal dehydroepiandrosterone (prasterone) are options for treatment, because studies show minimal elevation in serum estradiol levels and significant improvement in symptoms. The decision to offer vaginal estrogen therapy must be individualized and made jointly with the patient and her oncologist.

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## INTRODUCTION

In 2018, more than 3.1 million US women have a history of breast cancer. This includes women currently being treated and women who have finished treatment. The mainstay of treatment of hormone receptor–positive breast cancer for the last 50 years has been estrogen receptor–targeted therapy. Randomized clinical trials have demonstrated that antiestrogen therapies have a powerful impact on the natural history across the entire spectrum of hormone-responsive breast disease.<sup>1-3</sup> Postoperative therapy with the selective estrogen receptor modulator tamoxifen or aromatase inhibitors (AIs) reduces breast cancer recurrence and improves overall survival in women with estrogen receptor–positive early-stage breast cancer.<sup>4</sup> However, systemic treatments for patients with breast cancer often induce genitourinary symptoms attributable to urogenital or vulvovaginal atrophy. These symptoms include vaginal dryness, itching, irritation, dyspareunia, dysuria, and frequent urinary tract infections and are collectively termed as genitourinary syndrome of menopause (GSM). Several studies have suggested deterioration in quality-of-life scores due to these symptoms.<sup>5,6</sup> This may lead to early discontinuation of therapy or poor compliance, which may ultimately have an impact on breast

cancer–related outcomes. Many oncologists struggle with prescribing vaginal estrogens to breast cancer survivors receiving antiestrogen therapy because of concerns about potential systemic absorption of estrogen. A recent study found that 41% of breast oncologists refer breast cancer survivors to gynecologists for treatment of vulvovaginal atrophy, and 35% manage it independently. Seventy-one percent of oncologists mentioned that the main reason not to prescribe vaginal estrogen therapy is the probability of increased cancer recurrence.<sup>7</sup> In this article, we review the biology of antiestrogen therapy; discuss available data for nonhormonal, topical estrogen, hormone precursors like vaginal dehydroepiandrosterone (DHEA), and systemic estrogen options in treatment of GSM; and make recommendations on additional management of GSM in breast cancer survivors receiving antiestrogen therapy. All the studies are summarized in [Table 1](#).

## BACKGROUND: ANTI-ESTROGEN THERAPY

Tamoxifen and AIs exhibit antiestrogen activity within the breast and in breast cancers but exhibit different effects in urogenital tissue. Tamoxifen is a nonsteroidal triphenylethylene derivative that binds to the estrogen receptor. It is pro-estrogenic on uterine epithelium, thus increasing risk of endometrial carcinoma.

### ASSOCIATED CONTENT

See accompanying commentaries on pages 371 and 373

Author affiliations and support information (if applicable) appear at the end of this article.

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**TABLE 1.** Summary of Studies and Their Outcomes

First Author	Product Name	Route of Administration	Dose	Outcome
Bygdeman <sup>8</sup> Nachtigall <sup>9</sup>	Replens	Vaginal moisturizer	Nonhormonal	Temporarily relieves symptoms of GSM
Hickey <sup>10</sup> Lester <sup>11</sup>	K-Y Jelly Astroglide	Vaginal lubricant	Nonhormonal	Temporarily relieves symptoms of GSM
Chen <sup>12</sup> Jokar <sup>13</sup>	Hyaluronic acid (Hyalofemme [MEDintim, Abano Terme, Italy])	Vaginal gel	Nonhormonal	Temporarily relieves symptoms of GSM
Salvatore <sup>14</sup> Filippini <sup>15</sup> Salvatore <sup>16</sup> Pagano <sup>17</sup>	MonaLisa Touch	Fractional laser microablation	Nonhormonal	Improvement in symptoms and quality of life at 12 weeks after treatment (three sessions)
Kendall <sup>18</sup>	Vagifem	Vaginal tablet inserted into lower third of vagina	25 µg daily for 14 days then two times weekly	Temporary increase in serum estradiol levels (5 to 72 pmol/L), decreased to 35 pmol/L after 4 weeks Not available in United States
Chollet <sup>19</sup> Eugster-Hausmann <sup>20</sup>	Vagifem	Vaginal tablet inserted into lower third of vagina	10 µg daily for 14 days then two times weekly	Overall lower serum estradiol concentration when compared with 25 µg Vagifem (14-22 pmol/L v36-73 pmol/L)*
Simon <sup>21</sup>	Vagifem	Vaginal tablet inserted into lower third of vagina	10 µg daily for 14 days then two times weekly	Postmenopausal patients (N = 205) with no history of breast cancer; at 62 weeks of therapy, two events of hyperplasia or carcinoma (incidence of 0.52% per year)
Wills <sup>22</sup>	Estring	Vaginal ring	7.5 µg daily for 90 days	Statistically significant increase in serum estradiol levels (to 30 pmol/L) up to 60 days after insertion
Melisko <sup>23</sup>	Testosterone cream	Vaginal testosterone cream	5,000 µg three times weekly	Persistent estradiol elevation in 12% of women
Witherby <sup>24</sup>	Testosterone cream	Vaginal testosterone cream	150 µg or 300 µg daily	No significant elevation in serum estradiol (< 30 pmol/L)*
Barton <sup>25</sup>	Prasterone Intrarosa	Vaginal DHEA moisturizer	3.25 mg or 6.5 mg daily	No significant symptom improvement when compared with placebo (plain moisturizer) at 12 weeks. Mean estradiol levels remained < 18.35 pmol/L.
Holmberg <sup>26</sup>	Oral estrogen-progestogen tablet	Oral estrogen-progestogen tablet	Estradiol hemihydrate and norethisterone	In breast cancer survivors, an increased risk of new breast cancer events and adverse events were observed after 2 years of therapy.
von Schoultz <sup>27</sup>	Oral estrogen-progestogen	Oral estrogen-progestogen tablet	2 mg estradiol for 21 days with addition of 10 mg medroxyprogesterone acetate for last 10 days; or 2 mg estradiol for 84 days with 20 mg medroxyprogesterone acetate for last 10 days; or 2 mg estradiol valerate daily	No increased risk of breast cancer recurrence; trial was closed early.

Abbreviations: DHEA, dehydroepiandrosterone; GSM, genitourinary syndrome of menopause.

\*Serum estradiol levels in study reported in pg/mL, multiplied by 3.671 for conversion to pmol/L, for consistency.

Premenopausal women treated with tamoxifen may have elevated serum estrogen levels related to the treatment.<sup>28</sup> The ATAC (Arimidex, Tamoxifen Alone or in Combination) and Breast International Group studies have shown that AIs are the preferred adjuvant therapy for postmenopausal women with hormone receptor–positive early-stage breast

cancer because of improved outcomes when compared with tamoxifen.<sup>29,30</sup> AIs exert their activity by inhibiting the enzyme aromatase. Aromatase promotes the peripheral conversion of adrenal androgens into estrogen and is the predominant source of estrogen in postmenopausal women. AIs inhibit the enzyme by more than 95% and reduce plasma estradiol levels from 20 pmol/L to 3 pmol/L or less.<sup>5</sup> Because the ovaries produce the vast majority of estrogen before menopause, AIs can only be used for premenopausal patients in combination with ovarian function suppression. The use of vaginal estrogens may be appropriate for women with urogenital symptoms who use tamoxifen, because the competitive interaction with the estrogen receptor prevents mild serum estradiol elevations from increasing risk of breast cancer.<sup>31</sup>

Systemic loss of estrogen results in physiological and structural modifications within the genital structures and vaginal mucosa. Changes include reduced cervical gland secretions, deterioration of tissue, decrease in blood flow, loss of elasticity, thinning of tissue and epithelium, and increased pH.<sup>32-34</sup> These changes are responsible for symptoms of vaginal dryness, dyspareunia, irritation, and soreness, which together are known as vulvovaginal atrophy symptoms or GSM. There is also a decrease in glycogen content in the vaginal mucosa, which subsequently causes a decrease in lactobacilli.<sup>32</sup> This causes the vaginal pH to become more alkaline, thus predisposing women to urinary tract infections.

Ospemifene is an oral selective estrogen receptor modulator that has been approved by the US Food and Drug Administration (FDA) for the treatment of vulvovaginal atrophy due to menopause, including dyspareunia. Several studies, including placebo-controlled randomized phase II trials, have shown favorable outcomes of ospemifene on atrophic vaginitis in postmenopausal women.<sup>35,36</sup> Two large multicenter randomized phase III studies (N = 826) and (N = 605) compared 30 mg or 60 mg/day of ospemifene with placebo.<sup>37,38</sup> Results were consistent and showed ospemifene was superior to placebo in achieving increase in vaginal epithelial cells, improvement in vaginal maturation index, decrease in pH at both the 30-mg and 60-mg dose, and improvement in vaginal dryness or dyspareunia at the 60-mg dose only.<sup>37,38</sup> Although ospemifene is not contraindicated in Europe for breast cancer survivors who have completed treatment, it has not been approved by the FDA for use in the United States in women with breast cancer. Although data supporting use of ospemifene are favorable in postmenopausal women, additional studies are needed before ospemifene can be safely used in breast cancer survivors receiving AI therapy.

In addition, fulvestrant is a competitive estrogen receptor antagonist, acting as an estrogen receptor downregulator, which is used in patients with metastatic breast cancer. Because of its mechanism of action, rates of GSM may be less when compared with aromatase inhibitors.<sup>39</sup> Similar to fulvestrant, tamoxifen behaves as an estrogen antagonist in the breast. However, because tamoxifen is a mixed

estrogen antagonist and agonist, it can be either an antagonist or agonist in the reproductive tract, and therefore patients could experience fewer adverse effects of GSM.

### NONHORMONAL THERAPIES: VAGINAL MOISTURIZERS, LUBRICANTS, GELS, AND LASER THERAPY

Currently, the mainstay of treatment of breast cancer survivors receiving antiestrogen therapy is nonhormonal products. When breast oncologists were surveyed on treatment of vulvovaginal atrophy, 71% prescribed nonhormonal treatments.<sup>7</sup> Nonhormonal therapies are not able to reverse atrophy once it occurs but can help alleviate symptoms by increasing vaginal moisture. Vaginal moisturizers are intended to replace normal vaginal secretions, although they must be used on a regular basis to be effective.<sup>28</sup> Vaginal moisturizers have been found to be more effective than vaginal lubricants in relieving symptoms. A small randomized clinical trial and observational study found that Replens, a polycarbophil-based vaginal moisturizer, was as effective as a vaginal estrogen preparation in relieving vaginal dryness, itching, and dyspareunia and restoring normal vaginal pH.<sup>8,9</sup>

In addition to using moisturizers on a regular basis, vaginal lubricants can be used during intercourse to reduce friction and to decrease irritation. Lubricants are either water-soluble products (K-Y Jelly, Johnson & Johnson, New Brunswick, NJ), silicone based (ID Millennium, ID Lubricants, Santa Ana, CA), or glycerin based (Astroglide, BioFilm, Vista, CA). Lubricants only provide temporary relief and do not have any impact on improving long-term vaginal moisture.<sup>10,11</sup>

A randomized, double-blind, placebo-controlled trial using vaginal pH-balanced gel in postmenopausal breast cancer survivors suffering from atrophic vaginitis was conducted in 2011. A total of 88 breast cancer survivors were randomly assigned to receive either pH-balanced gel (with lactic acid pH 4 to 7.2) or placebo. The treatment was used three times per week for 12 weeks. This study showed statistically and clinically significant improvement in vaginal dryness and dyspareunia in the pH-balanced gel group ( $P < .001$ ) compared with placebo, as well as reduction in vaginal pH, and enhanced vaginal maturation index.<sup>40</sup>

Another nonhormonal option is hyaluronic acid vaginal gel. The gel contains a derivative of hyaluronic acid, which releases water molecules into the tissue, thus alleviating the dry state of the vagina without irritating the vaginal mucosa. It also plays a role in tissue repair. Recent randomized controlled trials compared hyaluronic acid with estrogen cream in postmenopausal women and found that both significantly improved symptoms of vaginal atrophy.<sup>12,13</sup> Specifically, Jocar et al<sup>13</sup> found that improvement in urinary incontinence, dryness, maturation index, and composite score of vaginal symptoms was better in the hyaluronic acid group than those in estrogen cream group; this may be due to longer duration of treatment than in the prior study.

A newer form of therapy for vaginal atrophy is CO<sub>2</sub> laser therapy (MonaLisa Touch, DEKA Laser, Calenzano, FL). During this procedure, a fractional microablative CO<sub>2</sub> laser is used to deliver a small amount of thermal injury to the vaginal tissue. This causes the development of new cells and formation of a new collagen and extracellular matrix. Another form of laser therapy is the nonablative vaginal erbium laser, which has been shown to improve stress urinary incontinence and vaginal prolapse and improve vaginal dryness and dyspareunia. Three different observational studies have shown statistically significant ( $P < .001$ ) improvement in sexual function and quality of life at 12 weeks after treatment (three sessions) with the CO<sub>2</sub> laser, as a measure of the Female Sexual Function Index, in addition to improvement in vulvovaginal atrophy assessed subjectively with a 10-point visual analog scale and objectively using the Vaginal Health Index.<sup>14-16</sup> In addition, a retrospective study by Pagano et al<sup>17</sup> assessed 26 patients with breast cancer who had undergone chemotherapy and antiestrogen therapy followed by three treatments with MonaLisa Touch and found significant improvement in vulvovaginal atrophy symptoms ( $P < .001$ ). No clinically significant adverse reactions were observed.<sup>17</sup> A randomized controlled trial (N = 45) compared treatment with fractional CO<sub>2</sub> laser alone, laser therapy with topical estrogen, and topical estrogen alone in postmenopausal women with vulvovaginal atrophy. Laser therapy and laser therapy with topical estrogen groups showed significant improvement in dryness and dyspareunia. The laser therapy with topical estrogen group showed significant improvement in total Female Sexual Function Index, whereas the laser therapy alone group showed significant worsening of pain domain in the Female Sexual Function Index.<sup>41</sup> Fractional microablative CO<sub>2</sub> laser treatment is an option for patients with breast cancer suffering from vulvovaginal atrophy; however, the cost for three treatments is \$1,800 to \$3,000. It is also a procedure that is not yet widely performed by gynecologists, and thus access may be limited by a patient's geographic location. This treatment is not approved by the FDA for treatment of GSM, and the agency recently issued a warning about marketing laser and radiofrequency for vaginal rejuvenation,<sup>42</sup> so additional study is warranted in this space before such therapy is widely adopted for management of GSM.

### SYSTEMIC ESTROGEN THERAPY

In 2003, the pivotal HABITS study (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?) by Holmberg et al<sup>26</sup> addressed the question of whether systemic hormone replacement therapy is safe for women with a history of breast cancer. A total of 434 women who had completed treatment of stage 0 to II breast cancer with symptoms of menopause were randomly assigned to receiving cyclic or continuous combination hormonal therapy (HT) with estrogen-progestogen, most commonly estradiol

hemihydrate and norethisterone, for 2 years or best symptomatic treatment without receiving hormones.<sup>26</sup> The primary end point of the study was occurrence of any new breast cancer event. The results were reported in December 2003 for 345 women after 2.1 years of follow-up, with a hazard ratio of 3.5 (95% CI, 1.5 to 8.1) for risk of a new breast cancer event in the HT group versus non-HT group. Given the statistically significant increase in risk for a new breast cancer event in the HT group, the steering committee of HABITS decided to stop the trial prematurely and recommend that all patients receiving HT stop treatment. A total of 26 women in the HT group and eight in the non-HT group were reported to have experienced new breast cancer events. In the HT group, the events consisted of 11 local recurrences, five contralateral cancers, and 10 distant metastases. In the control group, two patients had local recurrences, one patient had a contralateral cancer, and five patients were found to have distant metastases. In addition, eight adverse events were reported in the HT group, including two rapidly progressing recurrences of breast cancer, one lung cancer, one pulmonary embolism, one deep venous thrombosis, one endometrial cancer, one suicide, and one thrombophlebitis. The HABITS study showed that breast cancer survivors who received HT had not only a higher risk of breast cancer recurrence but also a higher risk of adverse events compared with breast cancer survivors receiving best symptomatic treatment without hormones.

The Stockholm trial also studied breast cancer survivors (N = 378) randomly assigned to HT with cyclic estradiol and medroxyprogesterone acetate or estradiol valerate only or non-HT for symptoms related to lack of estrogen.<sup>27</sup> This study accrued patients during the same time frame as the HABITS trial. The Stockholm trial had a median follow-up of 4.1 years and did not find an increase in the risk of breast cancer recurrence with HT (hazard ratio, 0.82; 95% CI, 0.35 to 1.9). However, there was a statistically significant ( $P = .02$ ) heterogeneity in the rate of recurrence between the two studies, and the Stockholm trial investigators concluded HT may be associated with the recurrence of breast cancer. On the basis of these studies, HT is contraindicated in breast cancer survivors because of increased risk of breast cancer recurrence or new primary development.

### VAGINAL ESTROGEN, TESTOSTERONE, AND DHEA THERAPY

Because oral hormone therapy is contraindicated in breast cancer survivors, another option for treatment of vulvovaginal atrophy is local therapy. Local therapies include estradiol-releasing intravaginal tablets (Vagifem, Novo Nordisk, Plainsboro, NJ), low-dose estrogen vaginal inserts (Imvexxy, TherapeuticsMD, Boca Raton, FL), estrogen-based vaginal creams, and estradiol-releasing vaginal rings. All forms of vaginal estrogen therapies have similar rates of effectiveness but different levels of systemic absorption.

Kendall et al<sup>18</sup> measured serum estradiol levels in six women receiving adjuvant AI therapy for early breast cancer who used Vagifem 25- $\mu$ g tablets for severe symptoms of atrophic vaginitis. The tablets were prescribed daily for 2 weeks then twice weekly. Serum estradiol was measured at baseline, after 2 weeks, after 4 weeks, between 7 and 10 weeks, and more than 12 weeks after initiation of therapy. Serum estradiol increased significantly after 2 weeks of therapy, from initial levels of 5 pmol/L or less to a median of 72 pmol/L. By 4 weeks, the majority of women had a drop in estradiol levels to less than 35 pmol/L.<sup>17</sup> This increase in estradiol levels while using Vagifem raises concerns for the appropriateness of use in hormone receptor–positive breast cancer survivors, because the efficacy of aromatase inhibition depends on near-total suppression of estrogenic stimulation. Vagifem 25  $\mu$ g is no longer available in the United States. Vagifem 10  $\mu$ g and generic estradiol tablets 10  $\mu$ g are available. The newest, lowest dose of vaginal estradiol FDA approved for GSM is Imvexy vaginal inserts in a bio-adhesive coconut oil in 4- $\mu$ g and 10- $\mu$ g doses.

Several studies have shown effective relief of symptoms and improvement in vaginal mucosa with the use of vaginal estradiol in postmenopausal women. Multiple studies have shown improvement in symptoms, vaginal mucosa health, and vaginal pH with the low-dose 10- $\mu$ g estradiol vaginal tablet.<sup>19</sup> Vaginal tablets are inserted into the lower third of the vagina for optimal effect and to minimize endometrial stimulation. Eugster-Hausmann et al<sup>20</sup> conducted a study in which 58 postmenopausal women received either 10- $\mu$ g or 25- $\mu$ g estradiol vaginal tablets to study the pharmacokinetics. Average serum estradiol levels were 9.39 and 19.84 pg/mL (to convert to pmol/L, multiply by 3.671) on day 1, 6.56 and 18.29 pg/mL on day 14, and 4.64 and 9.41 pg/mL on day 83 for the 10- $\mu$ g and 25- $\mu$ g doses, respectively.<sup>20</sup> This study showed at least a 50% reduction in estradiol concentrations within 24 hours after dosing with the 10- $\mu$ g estradiol tablet compared with the 25- $\mu$ g tablet. The overall estradiol absorption with the 10- $\mu$ g tablet was less when compared with the 25- $\mu$ g tablet. In addition, after 1 year of treatment with the 10- $\mu$ g vaginal tablet, levels of estrogen in the body were within the menopausal range (2.44 to 12.08 pg/mL), indicating minimal absorption. Simon et al<sup>21</sup> performed a randomized, double-blind, placebo-controlled trial (N = 205), in which postmenopausal patients with no history of breast cancer received 10- $\mu$ g estradiol vaginal tablet or placebo for 52 weeks. Endometrial biopsies performed at week 62 showed two events of hyperplasia and carcinoma, which is an incidence rate of 0.52% per year.<sup>21</sup> The 10- $\mu$ g vaginal estradiol tablet can potentially be a safe alternative in breast cancer survivors receiving AI therapy, although no formal randomized clinical trials have been completed yet. A 17 $\beta$ -estradiol–releasing vaginal ring (Estring, Pfizer, New York, NY) has been shown to reduce vaginal symptoms in postmenopausal women with little increase in serum estradiol levels.<sup>43</sup> However, increases in serum estradiol up to 60 days

after insertion were observed in postmenopausal women at high risk or with a history of hormone receptor–positive breast cancer.<sup>22</sup> The Estring releases 7.5  $\mu$ g of estradiol daily and is inserted into the upper vagina every 90 days.

Vaginal testosterone cream has also been shown to improve GSM in postmenopausal women taking AIs.<sup>24</sup> Melisko et al<sup>23</sup> conducted a randomized, open-label, single-institution phase II trial evaluating the safety and efficacy of intravaginal testosterone cream or a vaginal ring for 12 weeks in postmenopausal women (N = 69) with hormone receptor–positive breast cancer receiving AI therapy who had symptoms of vulvovaginal atrophy. The intervention was considered unsafe if more than 25% of patients had persistent elevations in serum estradiol, defined as greater than 10 pg/mL and at least 10 pg/mL above baseline after treatment initiation.<sup>23</sup> Patients were either instructed to insert 5,000  $\mu$ g of testosterone cream vaginally daily for 2 weeks then 5,000  $\mu$ g three times a week for the remaining 12 weeks or insert Estring once. Estradiol levels were measured at baseline and at 4 and 12 weeks after initiation of therapy. At baseline, mean serum estradiol levels were 26.8 pg/mL (95% CI, 14.5 to 39.1 pg/mL) for the vaginal ring and 9.0 pg/mL (95% CI, 5.1 to 12.9 pg/mL) for patients receiving intravaginal testosterone ( $P = .04$ ).<sup>23</sup> Baseline estradiol was elevated in 37% of patients (19 of 40) with the vaginal ring and in 25% of patients (nine of 36) with intravaginal testosterone cream. Persistent estradiol elevation was observed in no women with vaginal ring and in 12% of women (four of 34) with intravaginal testosterone. It is unclear why baseline serum estradiol levels were elevated in patients receiving AI therapy; the study postulates that patients may have been taking supplements/skin-enhancing creams that contain estrogen or were possibly nonadherent to AI therapy. Overall, both interventions met the primary safety end point and improved vaginal atrophy, sexual interest, and dysfunction for all patients. This study supports the efficacy and safety of using intravaginal testosterone or estradiol-releasing vaginal ring in patients with breast cancer receiving AI therapy to treat vulvovaginal atrophy. However, persistent estradiol elevation seen in the intravaginal testosterone group suggests that a lower dose of testosterone cream can be used. A prior study by Witherby et al<sup>24</sup> in 2011 supported the safety of vaginal testosterone (150  $\mu$ g or 300  $\mu$ g daily) for treating vulvovaginal atrophy in patients (N = 21) with breast cancer receiving AI therapy. This study did not show any significant elevation in serum estradiol levels (remained less than 8 pg/mL) at either dose of testosterone at 4 weeks of therapy.<sup>24</sup>

Vaginal dehydroepiandrosterone (DHEA), also known as prasterone, has been studied as a treatment of GSM. Barton et al<sup>25,44</sup> conducted a phase III randomized clinical trial that evaluated two doses (3.25 and 6.5 mg/d) of vaginal DHEA gel compared with plain moisturizer for the improvement of vaginal symptoms (dryness or dyspareunia) in postmenopausal women (N = 464) with a history of breast

(97%) or gynecologic cancer who could be receiving endocrine therapy (56%). All arms reported an improvement in symptoms using the Female Sexual Function Index. No statistically significant difference was observed between DHEA doses and moisturizer at 12 weeks (6.5 mg,  $P = .08$ ; 3.25 mg,  $P = .48$ ), although a significant difference at 8 weeks for 6.5 mg DHEA was observed ( $P = .005$ ).<sup>25</sup> Peripheral blood analysis (N = 345) showed that circulating dehydroepiandrosterone-sulfate and testosterone levels were significantly increased in patients receiving vaginal DHEA in a dose-dependent manner compared with moisturizer.<sup>44</sup> Estradiol was significantly increased in those receiving 6.5 mg/d DHEA, but not in those receiving 3.25 mg/d DHEA or AI therapy. Mean estradiol concentration remained less than 5 pg/mL in both DHEA arms.<sup>44</sup> Vaginal DHEA (prasterone Intrarosa, [AMAG Pharmaceuticals, Waltham, MA] 6.5 mg/d) is currently FDA-approved for treatment of GSM. Although this study shows that vaginal DHEA causes an increase in hormone concentrations, levels remain in the lowest half or quartile of the postmenopausal range.

In conclusion, GSM is a serious concern among breast cancer survivors receiving AI therapy. The fear of cancer recurrence among oncologists and patients is valid. The current recommendations by the American College of Obstetricians and Gynecologists (ACOG) are that non-hormonal approaches are the first-line choices for managing urogenital symptoms experienced by women during or after treatment of breast cancer.<sup>45</sup> If symptoms are unresponsive to nonhormonal remedies, ACOG recommends vaginal estrogen therapy; however, this decision should be made in coordination with a woman's oncologist.<sup>45</sup> Current data do not show an increase in cancer recurrence with local vaginal estrogen therapy; however, some studies do show concerns for elevated serum

estradiol levels with estradiol vaginal rings and creams, which may reverse the effects of AIs. There is confusion about what specific estradiol or estrone levels should raise concern for postmenopausal breast cancer survivors. In postmenopausal women not receiving hormone therapy, reported estradiol levels average  $14.1 \pm 0.9$  pg/mL and estrone levels average  $27.5 \pm 1.2$  pg/mL.<sup>46</sup> It is unclear if values in this typical postmenopausal range are sufficient to increase risk or if one needs to have levels that exceed the upper range of normal. CO<sub>2</sub> laser therapy has been promoted for GSM, because symptoms improve with few known adverse effects. However, both ACOG and the North American Menopause Society released position statements, and the North American Menopause Society released a consensus recommendation expressing the need for more robust, sham-controlled, and longer-term safety data.<sup>47-50</sup>

In our clinical practice, we use an individualized approach for each patient. In mild cases, treatment is initiated with vaginal moisturizers, lubricants, and gels. In severe or refractory GSM, after patients experienced treatment failure with nonhormonal options, we can consider treatment with hormonal options after a detailed discussion addressing risks and benefits of vaginal HT. The low-dose 10- $\mu$ g estradiol-releasing intravaginal tablet (Vagifem) or lower-dose 4- $\mu$ g estrogen vaginal insert (Imvexxy) are good options, as well as intravaginal testosterone cream and intravaginal DHEA (prasterone); the studies discussed show minimal elevation in serum estradiol levels and improvement in GSM. Vaginal estrogen creams and rings have elevated systemic absorption of estrogen, so we would recommend using caution in prescribing these therapies to patients with breast cancer receiving AI therapy.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JOP.18.00710>.

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