Review

Genitourinary Syndrome of Menopause in Breast Cancer Survivors: Are We Facing New and Safe Hopes?

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Abstract

Breast cancer survivors (BCSs) often suffer from menopausal symptoms induced by systemic treatments, with a consequent negative effect on quality of life. Since the introduction of aromatase inhibitors as the standard therapy for hormone-dependent tumors, genitourinary syndrome of menopause (GSM) has become a main problem for BCSs. This new terminology refers to the wide range of vaginal and urinary symptoms related to menopause, which can be relieved by estrogen therapy. Unfortunately, systemic hormone therapy is contraindicated for BCSs and also vaginal estrogens at standard dosage might influence the risk of recurrence because they cause a significant increase of circulating estrogens. Nonhormonal vaginal moisturizers or lubricants are the first choice for BCSs but only have limited and short-term efficacy. New strategies of management of GSM are now available, including: (1) low-dose or ultra low-dose vaginal estrogens; (2) oral selective estrogen receptor modulators (ospemifene); (3) androgen therapy; (4) physical treatment with vaginal laser; and (5) psychosocial interventions. In this review we discuss and analyze these different options.

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Introduction

Breast cancer affects 1 of 8 women who live up to the age of 85 years in Western countries. The survival rate of breast cancer is 89% after 5 years from the time of initial diagnosis, and has significantly increased because of earlier diagnosis and advances in adjuvant treatment.[1] Every year, an increasing number of new breast cancers are diagnosed among women in reproductive age.[2] Many breast cancer survivors (BCSs), especially young women, suffer from menopausal symptoms, which result directly from cancer treatment with chemotherapy, tamoxifen, aromatase inhibitors (AIs), and ovarian suppression. Across all trials of adjuvant endocrine therapy, vasomotor symptoms are the most common side effects, affecting approximately 65% of BCSs.[3] Even vulvovaginal atrophy (VVA) is reported by many women receiving endocrine therapy for breast cancer, particularly those using AIs, because of the deep estrogenic depletion induced by these drugs.[4-8] Despite the well established efficacy of adjuvant treatments, up to 20% of BCSs consider stopping or actually cease endocrine therapy because of menopausal symptoms.[9] In contrast to vasomotor symptoms, VVA tends to worsen rather than improve with advancing age,[10] being present in 25% to 50% of postmenopausal women 4 to 5 years after the menopause.[11,12] The vagina has a stratified squamous, nonkeratinized epithelium, which is sensitive to estrogen deprivation. Estrogen depletion results in vaginal epithelium thinning, dryness, inflammation, and alkalinization with a reduction of vaginal Lactobacilli and an increase of coliforms, with a subsequent risk of urinary and vaginal infections.[13] The reduction of fluid secretion and the progressive loss of vaginal elasticity predispose to trauma and pain during intercourse. In BCSs vaginal dryness has been reported by 19% to 23% and 42% to 70% of pre- and postmenopausal patients, respectively, whereas dyspareunia has been reported by 10% to 16% and 27% to 39%, respectively.[14,15] These symptoms are relevant to the overall sexual response (low sex drive,

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poor arousal, and sexual satisfaction),[16-18] and they might affect quality of life.[19,20]

Recently, the new terminology, genitourinary syndrome of menopause (GSM) has been proposed instead of VVA, to describe more accurately the constellation of symptoms and signs associated with menopause.[21] The syndrome includes genital symptoms such as dryness, burning, and irritation; sexual symptoms such as lack of lubrication, discomfort, and pain; and urinary symptoms such as urgency, dysuria, and recurrent urinary tract infections. Management of GSM in BCSs is an unsolved problem during and after adjuvant therapy. Lubricants and moisturizers are the first-line therapy,[11] but they provide only poor benefit. Much debate is ongoing on the safety of prescription of vaginal estrogens, even for a short period of time, and available guidelines do not help physicians and women to make a decision.[8,22] At present, many trials have explored the safety of very low dose vaginal estrogens that use new delivery modalities. Some hope might derive from new drugs and/or physical therapy that were not previously available. Herein, we aim to provide an overview on pharmacologic and physical interventions, and put risks and benefits into perspective.

Discussion

Systemic Hormone Therapy

Hormonal supplementation is the most effective strategy in reducing menopausal symptoms in healthy postmenopausal women.[11,20] Unfortunately, the safety of systemic estrogen-progestogen combinations in BCSs has been seriously criticized after the results of randomized controlled trials. In the HABITS (hormonal replacement therapy after breast cancer — is it safe?) trial,[23] the hazard ratio (HR) for recurrence in women who received hormone therapy (HT) at a median follow-up of 2.1 years was 3.5 (95% confidence interval [CI], 1.5-8.1); the increase of the risk was not significant for hormone-negative tumors. On the contrary, in the Stockholm trial,[24] started in 1997, at a median follow-up of 4.1 years, the risk of recurrence was not associated with HT (HR, 0.82; 95% CI, 0.35-1.9). Because of slow recruitment in both trials, a joint analysis of the data was decided, showing that the risk of breast cancer recurrence was significantly increased in patients who received HT compared with the control group (HR, 1.8; 95% CI, 1.03-3.1). As a result, both trials were prematurely stopped in December 2003.[23] An updated analysis of the data of the 2 trials, after a longer follow-up period, yielded the same results, with a significant increase of recurrence in patients in the HABITS trial (HR, 2.4; 95% CI, 1.3-4.2)[25] and no excess of the risk in the patients in the Stockholm trial (HR, 1.3; 95% CI, 0.9-1.9).[26]

Alternative to conventional HT, tibolone is a compound that displays estrogenic, progestogenic, and androgenic properties. On the basis of its chemical and clinical profile,[27] it was tested versus placebo in the LIBERATE (Livial Intervention Following Breast Cancer: Efficacy, Recurrence, and Tolerability Endpoints) trial, which started in June 2002.[28] After 1 year of treatment, a significant superiority of tibolone compared with placebo was observed in reduction of vasomotor symptoms and improvement in sleep quality, sexual behavior, mood, and attraction.[29] Unfortunately, the trial was prematurely stopped 6 months before the planned time, in July 2007, because of a significant increase of disease recurrence in women treated with tibolone compared with the placebo group. Even in the LIBERATE trial, the increase of the risk was not significant for hormone-negative tumors.

That notwithstanding, systemic HT in BCSs is contraindicated.[11,20]

Local Estrogen Therapy

Vaginal estrogen administration is now the preferred way of delivery when vaginal symptoms are the only complaint in postmenopausal women, because it is more effective than systemic estrogen administration in the relief of symptomatic VVA, with 80% to 90% of women who report a favorable response.[8] Furthermore, vaginal estrogens also alleviate sensory urgency and reduce the frequency of urinary tract infections.[20,30]

Several types of estrogens (conjugated equine estrogens [CEE], promestriene, estradiol, and estriol) with different pharmaceutical formulations and at variable doses are available; however, systemic absorption can occur with all of the conventional doses,[31,32] particularly in case of atrophic vagina.[33,34]

It is known that not all available estrogens have the same properties. Whereas estradiol and estrone can be reversibly metabolized into each other, estriol is an end product of estrogen metabolism. Estriol has a 10 times lower affinity to the nuclear receptor compared with estradiol and is considered a short-acting estrogen. Promestriene has a very low absorption after topical administration.[35] Even if estriol has a lower potency than estradiol, in a recent in vitro study on a comparison of the effect of estradiol and estriol on growth of human breast cancer cell lines, both estrogens triggered a robust estrogenic response in breast cancer cells, which suggests caution regarding the use of estriol by BCSs.[36]

Low-dose local estrogen therapy (LET) is considered to have a lower risk profile compared with standard doses because it produces very low serum levels when administered intravaginally. Several studies in healthy postmenopausal women demonstrated that low-dose LET improves vaginal symptoms in most treated women, with plasma estradiol levels remaining in the range of postmenopausal women[37-39] and no increased risk of endometrial hyperplasia or carcinoma.[40]

A recent analysis of data from 33 studies provided a definition of what constitutes low-, intermediate-, and high-dose LET.[41] Low-dose preparations include the 7.5 μg vaginal ring and the 10 μg estradiol tablet. The intermediate dose includes 25 μg estradiol or 0.3 μg CEE. The high-dose regimens include 50 to 2000 μg of estradiol or 0.625 to 2.5 mg of CEE. In this analysis, low-dose LET resulted in systemic absorption, but estradiol levels during long-term administration were < 20 pg/mL; intermediate doses resulted in plasma estradiol levels approaching or exceeding 20 pg/mL, and the higher doses resulted in premenopausal levels of estrogen.

Ultra-low doses of LET have been recently investigated in postmenopausal healthy symptomatic women. A new 0.005% estriol vaginal gel delivered daily at 50 μg per application has shown a very favorable safety profile and good efficacy, with negligible plasma levels after 21 days of administration.[42] A study that evaluated the efficacy and safety of this new estriol formulation administered daily for 3 weeks and then twice weekly up to 12 weeks showed the superiority of estriol in improving vaginal dryness compared with placebo.[43] In a prospective,

placebo-controlled study, 436 postmenopausal women with VVA were treated with pessaries containing either 0.2 mg or 0.03 mg estriol or with placebo for 12 weeks. Superiority of estriol-containing pessaries over placebo was shown and the same efficacy and safety was achieved in the treatment of VVA symptoms with very low-dose estriol formulations (0.03 mg).[44]

Systemic absorption of LET can be relevant especially for women with contraindication to hormonal treatments, such as BCSs.[45] In particular, BCSs who receive AIs, which completely deprive the female body of estrogens, even a small increase in systemic serum levels might have a detrimental effect on the risk of recurrence. Because results of many in vitro studies suggest that long-term estradiol deprivation causes an upregulation of the amount of estrogen receptors alpha and of growth factor pathways with consequent cancer cells' hypersensitivity to low concentrations of estrogens, serious concern exists.[46] Only few studies have been performed in BCSs (Table 1) to investigate whether low-dose LET can alleviate urogenital symptoms associated with VVA, without an increase of serum levels of estrogens.[47-53] In a study that included only 6 postmenopausal BCSs treated with AIs who received estradiol tablets at a standard dose (25 μg), serum estradiol levels increased from baseline levels < 5 pmol/L to a mean of 72 pmol/L

Table 1 Studies on LET in BCSs

Reference	Type of Study	Study Population	Main Outcome	Treatment	Study Period	Results
O'Meara et al, 2001[48]	Retrospective case-control study	43% (75 patients) of 174 BCSs using HRT (compared with 2581 BCSs not using HRT)	Recurrence and mortality	LET (CEE and dienestrol)	457 person-years	Risk of recurrence or mortality not increased
Dew et al., 2003[49]	Cohort study	69 BCSs treated for VVA (compared with 1403 BCSs who did not require treatment for VVA)	Recurrence	36 BCSs vaginal estriol creams and pessaries; 33 BCSs estradiol 25-mg tablets	1 year (median time; range, 0.1-5)	No increase in the recurrence rate
Kendall et al, 2006[47]	Prospective clinical study	7 Postmenopausal BCSs treated with AIs	Serum E2, FSH, LH levels	Vaginal estradiol 25 mg tablets	12 weeks	Serum E2 levels increase from baseline levels <5 pmol/L to a mean 72 pmol/L at 2 weeks; however, a decrease to a mean of 16 pmol/L was observed after 1 month; significant further increases were seen in 2 BCSs
Biglia et al, 2010[50]	Prospective clinical study	26 Postmenopausal BCSs using SERMs or AIs (BCSs receiving AIs were excluded from LET administration)	• Efficacy: improvement of VVA evaluated using the Vaginal Symptoms Score, Profile of Female Sexual Function, Vaginal Health Index, and Karyopycnotic Index • Safety: endometrial thickness and serum FSH, LH, E2, E1, TT and SHBG levels	10 Women, vaginal estriol cream 0.25 mg; 8 women, vaginal estradiol tablets 12.5 mg; 8 women, nonhormonal polycarbophil-based vaginal moisturizer (2.5 g)	12 weeks	• Efficacy: low-dose LET is effective for VVA relief, and nonhormonal moisturizer only provides transient benefit • Safety: minimal increase of serum hormone levels with LET
Wills et al, 2012[51]	Prospective study	48 Postmenopausal BCSs and women at risk of breast cancer during AI or SERM treatment	Serum E2 levels	24 Control participants (receiving AIs only); 14 women, intravaginal 25 mg estradiol tablet; 10 women intravaginal estradiol ring (7.5 mg/d)	≥3 Months	LET increases E2 levels, regardless of whether the preparation is by tablet or slow-release ring. Mean E2 levels before insertion and 12 weeks after insertion in BCSs who were using the ring were significantly greater than in control participants; levels before insertion for BCSs who were receiving tablets were not increased compared with control participants, suggesting that E2 increases with use of tablets might not be continuously sustained
Donders et al, 2014[52]	Phase I clinical study	16 Postmenopausal BCSs who were receiving AIs	Serum E1, E2, E3 levels	Ultra—low-dose estriol 0.03 mg and *Lactobacillus acidophilus* vaginal tablets	3 Months	Small and transient increase in serum E3 level, but not in E1 or E2 levels; VVA resolved or improved in all women
Pfeiler et al, 2011[53]	Prospective randomized clinical study	10 BCSs who were receiving AIs	Serum E2 or E3 levels	Vaginal 0.5 mg estriol	2 Weeks	Serum levels of E3 and E2 were not increased

Abbreviations: AI = aromatase inhibitor; BCS = breast cancer survivor; CEE = conjugated equine estrogens; E1 = estrone; E2 = estradiol; E3 = estriol; FSH = follicle-stimulating hormone; HRT = hormone replacement therapy; LET = local estrogen therapy; LH = luteinizing hormone; SERM = selective estrogen receptor modulator; SHBG = sex hormone-binding globuline; TT = testosterone; VVA = vulvovaginal atrophy.

at 2 weeks; however, a decrease to a mean of 16 pmol/L was observed after 1 month.[47] Interestingly, O'Meara reported that the risk of recurrence in BCSs treated with LET was not increased, regardless the total amount used.[48] Dew and colleagues reinforced the concept of safety because they showed no increase in the recurrence rate in BCSs who used LET after diagnosis.[49]

Previous published data from our department assessed the efficacy and safety of 2 low-dose vaginal estrogen treatments (estriol cream 0.25 mg or estradiol tablets 12.5 μg) and of a nonhormonal polycarbophil-based vaginal moisturizer (2.5 g) administered twice a week for 12 weeks in postmenopausal BCSs with urogenital atrophy. Estradiol levels increased by a mean of 3.5 pg/mL in women who received vaginal estriol cream and by a mean of 2.7 pg/mL in the group treated with micronized estradiol tablets. Similar modifications were found for serum estrone levels, and follicle-stimulating hormone values remained stable.[50]

The effects of 2 vaginal estrogens on serum estradiol levels when administered for ≥ 3 months in postmenopausal BCSs receiving AIs or tamoxifen have been evaluated in a recent study.[51] Forty-eight women were recruited: 24 control participants who received AIs only, 14 who used intravaginal estradiol tablets at the standard dose (25 μg/d), and 10 women who received an intravaginal estradiol ring (1 ring every 90 days, which delivered 7.5 μg/d); serum samples were drawn after at least 3 months of LET. LET increased serum estradiol levels, regardless of whether the preparation was tablet or slow-release ring. Mean estradiol levels before insertion and 12 weeks after insertion in BCSs who used the ring were significantly greater than in control participants; in contrast, levels assessed before insertion for BCSs who received tablets were not increased compared with control participants, which suggests that serum estradiol increases with tablets might not be continuously sustained.

Estradiol vaginal tablets are now available at a lower dose (10 μg), with similar symptom relief and less systemic absorption after initial and chronic use.[38] A prospective trial with this dosage in BCSs receiving AIs is ongoing.[54]

Results of a small phase I clinical study with ultra-low dose 0.03 mg estriol and Lactobacillus combination vaginal tablets in 16 BCSs with VVA have been recently published.[52] After 3 months of treatment (initial treatment every day for 4 weeks followed by maintenance therapy of 3 vaginal tablets weekly for 8 weeks) compared with baseline, serum estrone and estradiol did not increase in any of the women at any time after vaginal application. Serum estriol transiently increased after the first application in 15 of 16 women, with a maximum of 168 pg/mL 2 to 3 hours after insertion; after 4 weeks serum estriol was slightly increased in 8 women. Vaginal dryness and quality of sexual life continuously improved during the study period.[55]

In a prospective, randomized study of 10 postmenopausal BCSs using AIs it was found that the daily use of 0.5 mg estriol for 2 weeks did not result in increased serum levels of estriol or estradiol.[53]

Promestriene is a diethyl-ether of estradiol available as vaginal cream or ovules. In a small study on 17 women with gynecologic cancer who received 10 mg of vaginal promestriene daily for 1 month, the levels of circulating estrone sulfate were not significantly affected, but a wide range was noted before and after treatment in individual patients.[56]

Currently, it is not possible to determine the safety of vaginal estrogens in BCSs, because the small available studies only report the effect of these treatments on estrogen circulating levels. The North America Menopausal Society stated that there are few reports regarding the safety of LET in BCSs and that BCSs who do not respond to nonhormonal therapies might discuss the risks and benefits of low-dose LET with their oncologist.[11]

Vaginal Moisturizers and Lubricants

Nonhormonal vaginal moisturizers and lubricants are recommended as first-line treatment for women with a history of hormone-dependent cancer.[45,57] Moisturizers are used chronically to replace normal vaginal secretions, whereas lubricants are used to reduce friction during sexual intercourse.[58,59] Studies in BCSs showed that vaginal moisturizers are effective in relieving urogenital symptoms within 2 weeks of treatment, but their efficacy is not statistically different from that of placebo and has been consistently lower compared with vaginal estrogens in randomized trials.[34,60] Our experience with a nonhormonal polycarbophil-based vaginal moisturizer in BCSs with VVA showed only a transient benefit and after 12 weeks of treatment the level of atrophy had returned to basal level.[50]

In a randomized double-blind study that compared vaginal topical pH-balanced gel (gel with lactic acid, pH of 4) and placebo (gel without lactic acid, pH of 7.2) in 98 BCSs with VVA, vaginal pH-balanced gel was significantly superior to placebo (gel without lactic acid, pH of 7.2) in the relief of vaginal symptoms.[61]

Ospemifene

Another alternative to hormonal treatment for VVA in postmenopausal women is the novel selective estrogen receptor modulator (SERM), ospemifene. Ospemifene is a new oral compound that was originally developed as a treatment for postmenopausal osteoporosis. It has been approved by the US Food and Drug Administration[62] and recently also by the European Medicines Agency[63] for the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidates for LET.

Several clinical studies have been performed to evaluate whether ospemifene is a safe and effective treatment to improve dyspareunia in postmenopausal women with VVA.[64-67] A phase III randomized double-blind clinical study on 826 postmenopausal symptomatic women showed that ospemifene at 30 or 60 mg/d for 12 weeks was more effective than placebo for the treatment of VVA, with a favorable safety profile.[64] The long-term safety evaluation arm of this study on 180 women, showed only few treatment-emergent adverse events after 52 weeks of treatment with ospemifene and showed no significant endometrial changes during the 1-year treatment period.[65] No clinically significant adverse changes in breast or endometrial safety assessments were observed in any treatment group. In an additional 12-month safety assessment of the same study on 426 patients of ospemifene 60 mg/d arm, its tolerance and efficacy were confirmed and no woman was diagnosed with breast or endometrial cancer.[67]

The available clinical data for ospemifene support a neutral effect in the breast; however, the small size and the short duration of clinical trials do not permit any conclusion about the safety of ospemifene on breast cancer. As a class, SERMs appear to have

antiestrogenic or neutral effects on the breast and preclinical data in experimental models that used ospemifene are promising.[62,68-74] In vitro studies showed that ospemifene induced a moderate, dose-dependent growth inhibition of estrogen-dependent MCF-7 cells.[68] In a ductal carcinoma in situ mouse model, cell proliferation was reduced significantly with use of ospemifene and tamoxifen.[69] In immunologically intact mice, the average breast tumor volumes were significantly larger in control mice than in those treated with ospemifene. Furthermore, a significantly longer survival was observed in the ospemifene group.[72] In a chemically induced mouse mammary carcinoma model, ospemifene was comparable to tamoxifen in preventing the development of breast tumors, which suggests that ospemifene might be effective as a breast cancer chemopreventive agent.[73]

These observations allow the belief that ospemifene might be proposed as a likely safe treatment option for BCSs suffering from VVA in the near future. However, at present any extrapolation of preclinical animal models to humans must be done with caution.

Androgen Therapy

Vulvovaginal tissues also express androgen receptors and their density shows a good correlation with the vaginal maturation index, which is lower in cases of vaginal atrophy.[75]

Very few data are available on intravaginal testosterone treatment after breast cancer. In a small phase I/II trial, 21 postmenopausal BCSs with symptomatic VVA who received AIs were treated with intravaginal testosterone gel (10 women at 300 μg/d, 10 women at 150 μg/d, and 1 at a dose not evaluable) for 28 days. A significant improvement of atrophy and dyspareunia in the absence of increased estradiol or estrone serum levels was observed.[76]

Very promising data for BCSs have been recently published on use of dehydroepiandrosterone vaginal ovules. Although still in phase III clinical trials, and not studied in women with a history of malignancy, available data suggest efficacy on many symptoms associated with VVA, including sexual dysfunction, without induction of a change in sex steroid levels.[77]

Barton et al randomized 133 cancer survivors to placebo or systemic testosterone and found no significant effect of testosterone over placebo on sexual frequency, mood, vitality, sexual function, and sexual pleasure.[78] There are concerns regarding possible aromatization of androgens to estrogen in women with breast cancer,[57] thus systemic testosterone use in BCSs still remains experimental.

Vaginal Laser

The nonsurgical laser procedure has been proposed to treat vaginal relaxation syndrome in postpartum women,[79] because it is known that it acts to induce the production of new collagen and elastic fibers. Because of the long-term experience with laser treatment as safe and effective on many body districts such as the skin of the face, neck, and chest, more recently it has been tested on ex vivo vaginal specimens without damage or side effects.[80] On the basis of these preliminary experiences, a pilot study was designed to assess the efficacy and feasibility of fractional CO_2 laser in the treatment of VVA symptoms in postmenopausal women.[81] Vaginal dryness, vaginal burning, vaginal itching, dyspareunia, and dysuria were significantly improved at the 12-week follow-up with minimal discomfort experienced after 3 applications of laser treatment; a significant improvement of sexual function and satisfaction with sexual life in postmenopausal women with VVA symptoms was also documented.[82] However, the long-term effects of fractional CO_2 laser treatments associated with VVA remain to be elucidated.

Psychosocial Interventions

The North American Menopausal Society and The International Menopausal Society make recommendations on the essential role of clinicians in routine discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and managed appropriately, to preserve sexual function.[8,83]

In fact, data from the REVIVE (Real Women's Views of Treatment Options for Menopausal Vaginal Changes) study show that only 7% of women with symptoms of VVA reported that their health care practitioner initiated a conversation about this topic.[17] Dedication of a small amount of time in counseling cancer survivors about their vaginal health can reduce vaginal discomfort and increase adherence to recommended pelvic examinations.[59]

In most couples with breast cancer diagnosis the emotional intimacy and the sense of affection is improved, although physical and erotic intimacy might be affected. The longer the time is between surgery and intercourse, the higher the probability of sexual dysfunction. Patients and their partners should be reassured that there is no medical contraindication to sexual intimacy during breast cancer therapy and afterward.[84] Sexually active women report and show on pelvic examination fewer symptoms of VVA compared with nonactive women, because the coitus facilitates active blood flow to the vagina and increases vaginal lubrication.[85]

Lifestyle modifications such as regular coital activity, smoking cessation, and management of psychosocial distress might be useful.[33,58] In a randomized trial of a 6-week psychoeducational intervention in BCSs, those in the intervention group reported improvements in their relationship adjustment and communication and also increased satisfaction with sex compared with the control group, who received written information.[86]

Physical Therapies

To restore vaginal function, gentle stretching of the vagina with the use of lubricated vaginal dilators of graduated sizes and reinitiation of regular sexual activity when vaginal penetration is again comfortable will be helpful. Also, pelvic floor physical therapy, which leads to pelvic muscle awareness and control, can be useful.[8,59] Indeed, women with VVA might face hypertonicity of the pelvic floor as a consequence of entry dyspareunia and anxiety associated with the anticipation of a painful sexual experience.[87] However, pelvic organ prolapse (POP) associated with sensation of obstruction within the vagina and vaginal laxity might contribute to poor arousal, orgasm, and satisfaction.[88] In a recent randomized controlled trial, some women with POP reported a significant improvement of sexual function after pelvic floor muscle (PFM) training, which consisted of 3 sets of 8 to 12 repetitions of near maximal PFM contractions daily over 6 months.[89] Sensation of a "tighter" vagina and improvement of self-confidence with pelvic floor physical therapy could be useful even in BCSs but large randomized trials are lacking.

Table 2 Different Options for Genitourinary Syndrome of Menopause Treatment in BCSs

Pharmacological Intervention
Nonhormonal vaginal moisturizers and lubricants (first-line therapy; transient benefit, low compliance)
Low-dose vaginal estrogens (LETs) (for BCSs who do not respond to nonhormonal intervention, after discussion of risk and benefits; caution in women receiving AIs. Great efficacy, even at ultra-low doses)
Oral ospemifene (no clinical trials available in BCSs; in healthy women the efficacy is comparable with LETs, no endometrial or breast stimulation after 12 months of therapy)
Androgen therapy (experimental; concerns regarding possible aromatization of androgens to estrogen in BCSs)
Nonpharmacological Interventions
Vaginal laser (no clinical trials available in BCSs; short follow-up for evaluating its efficacy in healthy women)
Couple counseling
Management of psychosocial distress
Regular sexual activity
Need for larger clinical trials: • Vaginal dilators of graduated size • Pelvic floor physical therapy • Topical liquid lidocaine

Abbreviations: AI = aromatase inhibitor; BCS = breast cancer survivor; LET = local estrogen therapy.

A novel intervention (Olive Oil, Vaginal Exercise, and MoisturizeR) has been proposed to improve sexual problems after breast cancer treatment. In a recent trial, 25 BCSs with dyspareunia were instructed to perform PFM relaxation exercises twice per day, to apply a polycarbophil-based vaginal moisturizer 3 times per week to alleviate vaginal dryness, and to use olive oil as a lubricant during intercourse. This novel intervention was acceptable to patients with demonstrated efficacy in improving dyspareunia, sexual function, and quality of life.[90]

For coital pain, the application of topical liquid lidocaine to the vulvar vestibule before penetration seems to be effective for comfortable intercourse. This method was recently evaluated in a randomized controlled, double-blind trial on 46 BCSs with severe menopausal dyspareunia associated with atrophy and with increased sexual distress. Patients applied either saline or 4% aqueous lidocaine to the vulvar vestibule for 3 minutes before vaginal penetration. Users of lidocaine had less intercourse pain, more comfortable penetration, and less sexual distress.[91]

Conclusion

Symptoms of GSM are common among BCSs and can adversely affect quality of life and sexual health. Nonhormonal lubricants and moisturizers should be considered as first-line treatment. There are safety concerns about topical estrogen use at conventional doses in postmenopausal women who receive adjuvant AIs. Short-term topical estrogens at very low doses might be used after extensive discussion with symptomatic women who do not respond to nonhormonal interventions. New hopes could derive from ospemifene and laser treatment. Because a wide range of possible treatments is now available for BCSs (Table 2), GSM should no longer be considered an unsolved problem but an interesting area of further clinical research with the goal of helping BCSs to overcome the burden of urogenital symptoms.

Disclosure

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