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REVIEW

Vaginal estrogen products in hormone receptor-positive breast cancer patients on aromatase inhibitor therapy

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Abstract Atrophic vaginitis represents a major barrier to compliance with aromatase inhibitor (AI) therapy in breast cancer (BC) survivors. While local estrogen therapy is effective for postmenopausal vaginal dryness, the efficacy of such therapies has not been evaluated systematically in hormone receptor-positive (HR+) BC patients on AI therapy. Furthermore, the potential risk of breast cancer recurrence with vaginal estrogen therapy represents a long-term safety concern for the patients with HR + BC. Unfortunately, there is no standardized assay to measure very low concentrations of estradiol (E2) in these women being treated with AI therapy. This makes it difficult to evaluate even indirectly the potential risk of BC recurrence with vaginal estrogen therapy in HR + BC patients on AI therapy. In this review, we describe available assays to measure very low concentrations of E2, discuss the Food and Drug Administration-approved vaginal estrogen products on the market, and summarize published and ongoing clinical trials evaluating the safety and efficacy of vaginal estrogen in HR + BC patients on AI therapy. In the absence of any randomized controlled clinical trials, this review serves as a summary of available clinical data and ongoing studies to aid clinicians in selecting the best available option for their patients.

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Introduction

As the second leading cause of cancer-related deaths in the United States, breast cancer (BC) is estimated to cause around 40,290 deaths in women living in the United States in 2015 [1]. Approximately, 70 % of all BC patients express estrogen receptors (ER) and/or progesterone receptors (PR), collectively named hormone receptors (HR) [2]. Typically, HR-positive (HR+) BC is less aggressive than HR-negative BC. Endocrine treatments targeting HR pathways are very commonly utilized in HR + BC. Although proven to be very effective, endocrine therapies cause a host of side effects which may greatly affect patients' quality of life and, hence, compliance with therapy. The standard of care for postmenopausal women with HR + BC includes aromatase inhibitor (AI) therapy (e.g., anastrozole, letrozole, or exemestane). AI's are very effective in reducing circulating plasma estradiol (E2) levels from extra-ovarian sources in postmenopausal women [3]. Because of substantially lower E2 levels in postmenopausal women on AI therapy, vaginal toxicities including vaginal dryness, irritation, pruritus, and dyspareunia are very common. Greater than 60 % of postmenopausal BC survivors report experiencing vaginal dryness yet describe this symptom as the most poorly addressed of their side effects [4, 5]. Side effects from AI therapy have been reported to result in compliance rates to be as low as 50 % after several years of use [6].

While first line treatment of vaginal side effects includes non-estrogen containing vaginal lubricants for BC patients,

they are typically not effective in relieving symptoms in most patients [7]. Local estrogen therapy, on the other hand, is proven to be effective for postmenopausal atrophic vaginitis, but the efficacy of this therapy has not been evaluated systematically in HR + BC patients on AI therapy [8]. Furthermore, a major concern of prescribing local estrogen therapy in HR + BC patients is the risk of systemic absorption of estrogen, which may facilitate the growth of these tumors [9, 10].

Within BC survivors, studies have been conflicting regarding oral hormone replacement therapy (HRT). Two randomized, controlled trials have attempted to answer this important question: The Stockholm trial [11] and the HABITS trial [12]. The Stockholm trial found no increased risk of BC recurrence in the HRT arm compared to the placebo [Hazard Ratio = 0.82, 95 % Confidence Interval (CI) 0.35–1.9] [11]. Whereas, the HABITS trial from Scandinavia found a higher risk of BC events with HRT compared to placebo (Hazard Ratio = 2.4, 95 % CI 1.3–4.2) [12]. While the difference in the results could be attributed to different tumor characteristics (more lymph node-positive patients in the HABITs trial) and management protocol (type of progesterone and its regimen), the management of vaginal symptoms in BC survivors on AI therapy remains unclear.

Although studies evaluating local vaginal estrogen products have not investigated the long-term risk of BC recurrence, some studies have evaluated plasma E2 concentrations with some vaginal estrogen products in HR + BC patients on AI therapy. In this review, we describe available assays to measure very low concentrations of E2, discuss the Food and Drug Administration (FDA)-approved vaginal estrogen products on the market, and summarize published and ongoing clinical trials evaluating the safety and efficacy of vaginal products in HR + BC patients on AI therapy.

Assays to measure plasma estrogen

Detection of very low levels of plasma E2 concentrations has been challenging. Despite the availability of multiple mass spectrometry-based or immunoassay-based techniques, there is no gold standard method to measure ultra-low E2 concentrations [13].

Conventionally, E2 measurements have been performed by radioimmunoassay (RIA). However, since radioactive materials need special workplace protection and cost extra for special waste management, enzyme-linked immunosorbent assays have emerged to provide safer and less expensive approaches to measure estrogen [14]. To achieve accurate results, E2 needs to be separated from potential interfering compounds in the matrix, which may

cross-react with E2 anti-serum. Such separation, also known as an "indirect assay," may involve one to two steps of purification, sometimes with chromatographic approach. The most widely performed immunoassays are "direct assays," which omit the pre-purification steps to reduce cost and complexity while improving throughput. Such omission may introduce significant bias due to the matrix effect and cross-reactant. For determination of low levels of E2 in biological samples, procedures like diethyl ether extraction (DEE) is needed to achieve clinically useful results [15].

Mass spectrometry-based assays offer a new approach to solve this problem. Gas chromatography-tandem mass spectrometry (GC–MS/MS) has shown a greater advantage over RIA in terms of sensitivity and specificity at analyzing low levels of E2, even with additional steps of derivatization [16]. GC–MS/MS also can reduce interference and even further improve specificity compared to Gas chromatography-mass spectrometry (GC–MS). With the electrospray ionization technique, liquid chromatography-tandem mass spectrometry (LC–MS/MS) has been widely applied in biomedical research and in clinical laboratories [17]. LC–MS/MS does not need the derivatization step as in GC–MS/MS and can simultaneously quantify multiple steroids and their metabolites with one injection [18]. The main drawback of such assays is expensive instrumentation and the need for a trained operator for method optimization and analysis. Comparisons between mass spectrometry-based assay and immunoassays on steroid analysis have shown that immunoassays usually yielded higher measured values due to cross-reacting interference [19–21]. Because of this, the E2 concentration should not be compared across various platforms. Since none of these methods have been "standardized" for clinical laboratory use, only the relative changes in the E2 levels measured using the same assay should be considered for a given patient.

FDA-approved vaginal estrogen products

Five vaginal estrogen products are approved by the FDA for moderate to severe atrophic vaginitis associated with menopause. These are summarized in Table 1. Additional indications are moderate to severe vasomotor symptoms due to menopause for Femring® and atrophic vaginitis and kraurosis vulvae for Premarin®.

These estrogen products are available in various dosage forms including vaginal rings (i.e., Estring® and Femring®), vaginal creams (i.e., Estrace® and Premarin®), and a vaginal tablet (i.e., Vagifem®) (Table 1). The vaginal rings (2 mg for Estring® and 0.05–0.1 mg/day for Femring®) can be inserted every 90 days, while the creams have a tapered or a cyclic regimen. For example, Estrace®

Table 1 FDA-approved vaginal E2 products

Product	Dosage form	E2 dosing regimen	Cumulative E2 dose over 90 days	PK parameters for E2 (pg/ml)			Common ADRs (%)	Post-marketing experience
				C_{max}	C_{ss}/C_{avg}	T_{max}		
Estring®	Ring	2 mg E2 every 90 days	2 mg	63.2	48 h: 11.2; 4 wk: 9.5; 12 wk: 8.0	0.5–1 h	Headache (13 %)	TSS, B.Obst, RA, Vag erosion, hypersensitivity
Femring®	Ring	0.05 mg to 0.1 mg every 3 mo; taper or discontinue at 3- to 6-mo intervals	0.05–0.1 mg	1129[a]	40.6[a]– 76[b]	0.9 h[a]	Vag candidiasis (10.7 %), breast tenderness (10.7 %)	TSS, B.Obst, RA
Estrace®	Cream	0.2–0.4 mg E2/day for 1–2 wks; gradually reduce to 1/2 the initial dose for 1–2 wks, followed by a maintenance dose of 0.1 mg 1–3 times a wk; taper or discontinue at 3- to 6-mo intervals	3.1–11.4 mg	NR	NR	NR	None	Changes in vag bleeding/cervical excretions; breast tenderness/ discharge/cancer; clotting; rash and erythema; mood disturbances
Premarin®	Cream	0.313–1.25 mg E2/day cyclically (21 days on, 7 days off) OR 0.313 mg twice weekly (for dyspareunia)	7.5–19.68 mg	40 ± 40*	NR	7.7 ± 5.9	None	NR
Vagifem®	Tablet	10 mcg/days for 2 weeks; followed by 10 mcg twice weekly	0.34 mg	NR	Day 1: 10.9; Day 83: 5.5	NR	None	NR

ADR adverse drug reactions; *B.Obst* bowel obstruction; *E2* beta-estradiol; *FDA* Food and Drug Administration; *h* hour; *mcg* microgram; *mg* milligram; *ml* milliliter; *mo* month(s); *NR* not reported; *PK* pharmacokinetic; *pg* picograms; *RA* Ring Adherence to bladder/vaginal wall; *TSS* Toxic Shock Syndrome; *Vag* Vaginal; *wk* week

* C_{max} data was converted from pmol/l to pg/ml

[a] Reported for 0.05 mg/day

[b] Reported for 0.1 mg/day

2–4 g is applied daily for 1–2 weeks and then reduced to 1–2 g daily for 1–2 weeks, followed by a maintenance dose of 1 g up to three times weekly. It is then tapered or discontinued at 3–6 month intervals. The Vagifem® tablet (10 mcg) is inserted once daily for 2 weeks initially followed by a maintenance dose of one tablet twice weekly. On the other hand, Premarin® cream (0.5 g/day) is applied for 21 days followed by a 7-day off-period. For moderate to severe dyspareunia, Premarin® 0.5 g is applied twice weekly but for atrophic vaginitis or kraurosis the dose can be increased up to 2 g daily. The amount of E2 is different with application of various products, as is the cumulative dose of E2 over a 3-month period. This information is also described for the FDA-approved vaginal estrogen products in Table 1.

Although it is not known what threshold of E2 concentrations in the blood raise the risk of recurrence in HR + BC patients, it is believed that prolonged exposure to high E2 concentrations may be harmful, especially in women with breast cancer who are on AI therapy to reduce E2 production. Therefore, it is optimal to select a vaginal estrogen product that results in the lowest maximum and steady-state concentration (C_{max} and C_{ss}). Since the assays for E2 detection are not mentioned in the package inserts of various vaginal estrogen products, it is difficult to determine if these values can be compared directly. However, Premarin® and Estring® reported lower Cmax values compared to Femring®, and Estring® had the lowest Css reported compared to Vagifem®, which had a lower Css compared to Femring® (Table 1). This is despite the lowest

amount of cumulative E2 dose over a 90-day period with Femring® (Table 1).

Significant adverse drug reactions in more than 10 % of patients were only reported with the two vaginal ring products, Estring® and Femring®. Patients reported post-marketing experiences of toxic shock syndrome, bowel obstruction, ring adherence to the vaginal/bladder wall, and inadvertent ring insertion into the bladder with both Estring® and Femring®. In addition, Estring® caused higher rates of headache in patients, while Femring® was associated with vaginal candidiasis and breast tenderness.

Besides these FDA-approved products, several other estrogen and estrogen-derived products are being used in countries other than the United States. One tablet approved in Sweden and the Ukraine, Gynoflor®, contains 0.03 mg of estriol and at least 10,000 million viable Lactobacillus acidophilus. Gynoflor® is approved for atrophic vaginitis in postmenopausal women and is directed to be taken once daily for 12 days. The C_{max} was found to be 34.7 pg/ml 8 h after tablet insertion [22]. Significant adverse effects have not been reported. Another product, Ovestin® pessaries (oestriol 0.5 mg), is approved in Australia for vaginal atrophy and vaginal symptoms such as dyspareunia, dryness, and itching. Recommended dosing is 0.5 mg daily for 2–3 weeks followed by a reduction in frequency to 1 pessary (0.5 mg oestriol) once or twice weekly. Ovestin® was found to have a C_{max} of 100 pg/ml and a C_{avg} of 70 pg/ml within 1–2 h of insertion [23].

Clinical studies evaluating local estrogen therapy and outcomes

Four prospective clinical trials have evaluated the use of vaginal estrogen products for the alleviation of vaginal symptoms in postmenopausal women with estrogen receptor-positive (ER+) BC taking an AI. A total of 81 patients have been evaluated with median ages for the studies ranging between 52 and 68 years. Products evaluated include Vagifem® 25 mcg tablets, Estring®, Gynoflor® vaginal tablets, and Ovestin® (estriol 0.5 mg) vaginal tablets. While none of the studies evaluated long-term BC recurrences, their effects on serum E2 concentration and efficacy in relieving vaginal symptoms have been reported in these studies. These results are summarized in Table 2.

Wills et al. compared changes in E2 levels between BC patients taking Vagifem® 25 mcg ($N = 14$), those using Estring® 2 mg ($N = 10$), and a control group not taking any vaginal estrogen therapy ($N = 24$). Plasma E2 levels were evaluated in blood samples taken 12-h prior and 12-h post-Vagifem® tablet insertion as well as 24-h prior to and 30- and 60-days post-Estring® insertion using RIA following DEE. While the median serum E2 values remained the same pre- and post-Estring® insertion (4.09 pg/ml at both time points), Vagifem® use resulted in a substantial increase in the median serum E2 concentration (from <0.82 to 12.26 pg/ml). Efficacy of these products in relieving vaginal symptoms was not reported in this study [24].

Donders et al. evaluated E2 levels in patients taking Gynoflor® vaginal tablets (0.03 mg estriol, $N = 16$) while on AI therapy. Patients inserted 1 tablet daily for 4 weeks and then one tablet thrice weekly for 8 weeks. Serum E2 concentrations were evaluated at baseline and at 0.5 and 24-h post-insertion on days 1 and 28 using GC/MS. Lower limits of quantitation (LLOQ) were established to be 1.00 pg/ml for E2. E2 levels did not rise above the LLOQ in collected serum levels except for a single sample with a level of 1.19 pg/ml. Vaginal symptom relief was reported by 75 and 94 % of patients at Week 2 and after Week 4, respectively [25].

Pfeiler et al. evaluated serum E2 levels in patients applying vaginal Ovestin® (estriol 0.5 mg) tablets ($N = 10$) once daily for 14 days. Serum E2 levels were drawn at Day 0 and Day 15 and measured by either GC/MS or electrochemiluminescence immunoassay, with LLOQ of 10 pg/ml, which was significantly higher than most other methods. Because of this, interpretation of these data is challenging although the study reported that serum E2 levels in all patients were below the LLOQ. Women in this study reported overall vaginal symptom improvement and 3 of 5 (60 %) reported relief of dyspareunia after using the vaginal tablets for 2 weeks [26].

Kendall et al. observed E2 levels in women applying Vagifem® 25 mcg tablets ($N = 6$) once daily for 14 days and then twice weekly for the remainder of therapy. A seventh patient with metastatic BC used Premarin® vaginal E2 cream in addition to the Vagifem® tablets. Serum E2 levels were measured by RIA after DEE at baseline, after weeks 2 and 4, between weeks 7–10, and >12 weeks after initiating Vagifem® therapy. Six patients on either letrozole or anastrozole had baseline levels ≤0.95 pg/ml, while one patient taking exemestane had a baseline E2 level of 2.02 pg/ml. The maximum increase in the serum E2 concentration was seen at week 2 in six out of the seven patients, after which point the E2 levels decreased at subsequent time points in most patients. It has been postulated that this rise in estrogen levels in the first 2 weeks could be due to the vaginal atrophy in these women, and after the replenishment of the vaginal mucosal barrier, the absorption of E2 would decrease. Five out of six women (~83 %) reported symptomatic improvement with Vagifem® use [27].

A major limitation of these studies is a very small sample size. However, comparison of E2 levels within patients enrolled in these studies suggest that Gynoflor®

Table 2 Summary of prospective clinical studies evaluating vaginal estrogen products

Reference	PM patients	N	Median age (years)	Treatment arms (s)	E2 assay (LLOQ)	Median E2 concentration	Efficacy	Study location
Wills, *JOP*, 2012	ER + BC or at high risk of BC taking an AI or a SERM for ≥14 days with atrophic vaginitis	48	VE: 68 (53–79); Control: 60 (49–67)	Vagifem® 25 mcg tablets (N = 14) OR Estring® (N = 10) for ≥90 days	RIA after DEE extraction (0.82 pg/ml)	Median values: Control: <0.817 pg/ml (range <0.82–2.10 pg/ml); Vagifem® preinsertion (12 h prior): <0.82 pg/ml (range <0.82–1.34 pg/ml) and Vagifem® post-insertion (12 h post): 12.26 pg/ml (range 5.18–24.24); Estring® (24 h prior): 4.09 pg/ml (range <0.82–5.18 pg/ml) and Estring® (60 days post): 4.09 pg/ml (range <0.82–9.53 pg/ml)*	NR	London, UK
Donders, *Br Can Res Treat*, 2014	NSAIs for at least 6 months with symptomatic vaginal atrophy	16	Reported in mean age: 57 (52–63)–	Gynoflor® 1 tablet daily ×4 wks followed by 3 tablets per wk ×8 wks	GC/MS method (1.0 pg/ml)	<1.0 pg/ml at baseline and at 0.5 and 24 h post-insertion on D1 and D28 in all patients except 1 patient (1.19 pg/ml)	Improvement in symptoms: 75 and 94 % patients at Wk 2 and Wk 4, respectively	Antwerpen, Belgium
Pfeiler, *Climacteric* 2011	HR + BC who had been receiving AI for at least 1 year	10	65 (50–77)	Ovestin 0.5 mg tablets daily for 14 days	ECL OR GC/MS (10.0 pg/ml)	<10 pg/ml at baseline and 2 weeks of therapy	Improvement of vaginal dryness: 5 of 6 BC (83 %); Relief of dyspareunia: 3 out of 5 (60 %)	Vienna, Austria
Kendall, *Annals of Oncology*, 2006	On adjuvant AI therapy for early BC with severe atrophic vaginitis	7	52 (51–59)	Vagifem® 25 mcg tablets daily ×2 wks then twice weekly (N = 6); Premarin® cream (N = 1)	RIA after DEE (0.82 pg/ml)	Baseline: ≤1.362 pg/ml*; D14: 19.613 pg/ml (0.817–63.198)*; D28: 4.358 pg/ml (0.817–10.896)*; Wk 7–10: 4.631 pg/ml (<0.817–59.657)*; Wk > 12: <0.817 pg/ml* (for 2/7 patients)	Improvement in symptoms: 5 of 6 (83 %)	London, UK

AI aromatase inhibitor; *BC* breast cancer; *Br* Can Res Treat-*Breast Cancer Research and Treatment*; *d/D* day; *DEE* diethyl ether extraction; *E2* beta-estradiol; *ECL* Electro-chemiluminescence immunoassay; *ER+* estrogen receptor-positive; *GC/MS* gas chromatography-mass spectrometry method; *h* hour; *HR+* hormone receptor-positive; *JOP* Journal of Oncology Practice; *LLOQ* lower limits of quantitation; *mcg* microgram; *mg* milligram; *ml* milliliter; *N* number; *NR* not reported; *NSAI* non-steroidal aromatase inhibitor (letrozole or anastrozole); *NC* no control; *NR* not reported; *pg* picogram; *PK* pharmacokinetic; *PM* postmenopausal; *RIA* radioimmunoassay; *SD* standard deviation; *SERM* selective estrogen receptor modulator; *UK* United Kingdom; *VE* vaginal estrogen; *Wk* week

* Data was converted from pmol/l to pg/ml

vaginal tablets and Estring® may raise plasma E2 concentrations minimally in HR + BC patients simultaneously taking AI therapy. Gynoflor® vaginal tablets were effective in relieving the majority of women's postmenopausal symptoms, but the efficacy of Estring® has not been evaluated. Because of the high LLOQ (10 pg/ml) of the assay employed in the study by Pfeiler et al., the effects of Ovestin® (estriol 0.5 mg) tablets on the plasma E2 are difficult to interpret. However, patients benefited from this treatment in the relief of vaginal symptoms as well as dyspareunia. While Vagifem® 25 mcg tablets substantially increased E2 levels in some of the evaluated serum

samples, it is not known whether this is still the case with the currently marketed dose of 10 mcg tablets.

Another limitation in the interpretation of the results from these studies is the range of variability in the plasma E2 concentrations between patients after administering local vaginal therapy. One potential factor, as discussed in the Kendall et al. trial, could be due to vaginal epithelium differences such as dryness and thinning of the vaginal mucosa and vaginal maturation with use of local vaginal estrogen therapy [27, 28]. These differences could correlate to the variation in observed plasma E2 levels after administration of therapy ranging from no elevation to a substantial elevation. Thus, circulating estradiol levels may have limited utility for individual patients. Future studies are necessary to determine which products will have long-term safety and efficacy in this population and to further compare individual estradiol monitoring versus population-based estradiol monitoring. Some of the ongoing trials are described below.

Ongoing clinical trials

To identify ongoing clinical trials, an initial search was conducted on November 16, 2015, via the U.S. National Institutes of Health's Clinical Trials website (www.clinicaltrials.gov). Out of the 10 studies that matched the search using the terms 'vaginal estrogen,' 'breast cancer,' and 'aromatase inhibitor,' 4 were excluded due to their evaluation of products that did not contain estrogen (E2 or estriol). An overview of the studies is provided in Table 3. All of the 7 relevant studies are being conducted in post-menopausal women on AI therapy who are experiencing vaginal symptoms. Six studies are conducted in patients older than 18 years of age, while one study NCT01370551 has completed accrual of patients between 52 and 75 years of age.

Two clinical trials are currently evaluating Estring® 2 mg inserted every 3 months (Table 3). One trial (NCT01984138) being conducted at Baylor College of Medicine is comparing Estring® 2 mg to Replens, a vaginal lubricant with no estrogen component, to assess improvement in patients' vaginal symptoms with secondary endpoints of assessing compliance to AI, plasma E2 concentrations, and 5-year BC recurrence risk. The other trial (NCT01923298) being conducted at the University of Arizona is primarily evaluating changes in serum estrogen after insertion and secondarily evaluating the patient-based assessment of improvement of vaginal dryness.

There are currently two ongoing clinical trials evaluating the use of Vagifem® 10 mcg in postmenopausal BC patients. Neither trial has a comparison arm. Inclusion criteria for these trials are similar (Table 3), but the NCT02528383 trial additionally requires calcium and vitamin D supplements given to the participants. Both studies have primary endpoints evaluating serum estrogen levels after using Vagifem® therapy and secondary endpoints evaluating patient quality of life.

One ongoing trial (NCT01370551) being conducted in Belgium and Germany is evaluating Gyneflor® vaginal tablets with all patients inserting a tablet once daily for 28 days followed by the maintenance dose of one tablet three times weekly for 8 weeks. The primary endpoint is change in serum estrogen concentrations. Secondary endpoints for this trial are listed in Table 3. Another trial (NCT02413008) being conducted by the Spanish Breast Cancer group is currently comparing vaginal 0.005 % estriol gel to a placebo to primarily assess changes in FSH levels. Secondary endpoints for this trial included evaluating adverse effects and changes in vaginal symptoms.

In summary, there are many ongoing prospective studies to evaluate the efficacy of vaginal estrogen products in BC survivors on AI therapy. Although all studies include vaginal E2 level monitoring, only one study proposes to follow patients long term to evaluate the risk of BC recurrence. This lack of analysis of long-term safety of vaginal estrogen products may be a major limitation of these ongoing studies.

Discussion

In summary, this review further highlights the need for additional clinical studies to answer the very important question of the long-term safety and efficacy of vaginal estrogen products in BC survivors on AI therapy as well as a standardized clinical assay to detect ultra-low plasma E2 levels. Because of some efficacy observed with vaginal estriol as well as vaginal estradiol in small studies described here, comparison of these two agents in alleviating vaginal symptoms without compromising long-term safety should be performed systematically in randomized controlled studies. Currently, there are many subjective questionnaires to assess atrophic vaginitis without a widely accepted standard [28]. To accurately assess the problem, objective measures such as vaginal pH should also be evaluated for its utility and incorporation into future clinical trials.

To ensure compliance to AI therapy, it is critical for clinicians to identify the barriers including adverse drug reactions. A major barrier to AI compliance is the vaginal symptoms. With the increasing use of AI's now even in premenopausal women in combination with ovarian suppression, the incidence of vaginal symptoms in breast cancer patients are expected to increase. Therefore, the

Table 3 Summary of ongoing clinical trials

ClinicalTrials.gov identifier	Location	Postmenopausal BC patients	Treatment	Control	Primary endpoint	Secondary endpoint
NCT01984138	Baylor BCC, Texas	ER, sg I–III currently on AI therapy, current vsx	Estring® 2 mg Q3 mos	Replens (vag lubricant)	Improvement in vsx	AI compliance; BC recurrence, vaginal pH; sexual health; plasma E2 concentrations
NCT01923298	UA, Arizona	ER+, sg I–III on AI, vsx > 2 weeks, at least 1 prior tx for vsx	Estring® 2 mg Q3 mos	None	Change in serum estrogen levels	Vag dryness
NCT00984399	MSKCC, New Jersey and New York	sg I–III, on adjuvant AI for at least 3 mos, current vsx	Vagifem® 10 mcg tablet	None	Change in E2 and FSH from baseline to 12 weeks	Patterns of E2 and FSH levels; FSFI scores and menopause QOL questionnaire at baseline
NCT02528383	UCHC, Connecticut	sg I–III, AIs at least 3 mos, current vsx	Vagifem® 10 mcg tablet	None	Change in serum estrogen levels	Measure changes in bone health biomarkers to evaluate QOL
NCT01370551	Medinova AG, Belgium and Germany	NSAI therapy for at least 6 mos, vsx's, vag pH > 5.0, Karnofsky score ≥ 80 %	Gynflor® daily for 28 days then TIW for 8 weeks	None	SC of E1, E2, E3; calculation of AUC 0–24, intraindividual mean, C_{max} and T_{max}	Baseline/trough SC of E1, E2, E3, FSH, LH and SHBG; vag pH; vag maturation index; lactobacillary grade; bacterial vaginosis; AV score; presence of Candida hyphae or blastospores; global assessment of efficacy
NCT02413008	ITF Research Pharma, S.L.U., Texas	ER + sg I–IIIa, NSAI tx for at least 6 mos, vsx's	0.005 % estriol vaginal gel (50 mcg of estriol) daily for 3 weeks and then twice weekly for wk 4–12	Placebo	FSH serum levels	Serum FSH and LH levels, AEs, changes in FSFI, changes in vsx's

AE adverse effect; *AI* aromatase inhibitor; *AV* aerobic vaginitis; *BC* breast cancer; *BCC* breast cancer center; *E1* estrone; *E2* beta-estradiol; *E3* estriol; *ECL* Electro-chemiluminescence immunoassay; *Edu* educational; *ER* estrogen receptor; *ER+* estrogen receptor-positive; *FSH* follicle-stimulating hormone; *FSFI* female sexual function index; *fxn* function; *GC/MS* gas chromatography-mass spectrometry method; *LH* luteinizing hormone; *LLOQ* lower limits of quantitation; *mcg* microgram; *MDACC* M.D. Anderson Cancer Center; *mg* milligrams; *mos* months; *MSKCC* Memorial Sloan Kettering Cancer Center; *NSAI* non-steroidal aromatase inhibitor (letrozole or anastrozole); *NC* no control; *NR* not reported; *PK* pharmacokinetic; *PM* postmenopausal; *QOL* quality of life; *SC* serum concentration; *SD* standard deviation; *sg* stage; *SHBG* sex hormone-binding globulin; *TIW* three times weekly; *tx* treatment; *UA* University of Arizona; *UCHC* University of Connecticut Health Center; *vag* vaginal; *VE* vaginal estrogen; *vsx* vaginal symptoms; *Wk* week

clinicians treating breast cancer patients need to identify safe and effective approaches to manage this side effect without compromising efficacy of AI therapy. Until clinical trials report the long-term outcomes for patients treated with local estrogens, caution in the use of these products is indicated and treatment should be juxtaposed with the frequent monitoring of circulating estradiol with an appropriate methodology. In conclusion, this review serves as a summary of available treatment options, clinical data, and ongoing studies for the clinicians selecting best available option for their patients.

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