

BREAST CANCER

Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study

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Abstract

The study aim is to evaluate the efficacy and safety of two low-dose vaginal estrogen treatments (ETs) and of a non-hormonal vaginal moisturizer in postmenopausal breast cancer survivors with urogenital atrophy. Eighteen patients receiving estriol cream 0.25 mg ($n = 10$) or estradiol tablets 12.5 μ g ($n = 8$) twice/week for 12 weeks were evaluated and compared with eight patients treated with polycarbophil-based moisturizer 2.5 g twice/week. Severity of vaginal atrophy was assessed using subjective [Vaginal Symptoms Score (VSS), Profile of Female Sexual Function (PFSF)] and objective [Vaginal Health Index (VHI), Karyopycnotic Index (KI)] evaluations, while safety by measuring endometrial thickness and serum sex hormones levels. After 4 weeks, VSS and VHI were significantly improved by both vaginal ETs, with further improvement after 12 weeks. PFSF improved significantly only in estriol group ($p = 0.02$). Safety measurements did not significantly change. Vaginal moisturizer improved VSS at week 4 ($p = 0.01$), but score returned to pre-treatment values at week 12; no significant modification of VHI, KI, PFSF was recorded. Both low-dose vaginal ET are effective for relieving urogenital atrophy, while non-hormonal moisturizer only provides transient benefit. The increase of serum estrogens levels during treatment with vaginal estrogen at these dosages is minimal.

Keywords: Low-dose vaginal estrogens, urogenital atrophy, vaginal moisturizer, breast cancer survivors

Introduction

Symptoms resulting from vaginal atrophy are frequently reported by breast cancer patients. Adjuvant chemotherapy can either worsen pre-existing symptoms in postmenopausal women or even induce premature ovarian failure in the younger patients. Also endocrine adjuvant therapy is associated with vaginal symptoms: vaginal discharge is frequently reported by women using tamoxifen, while vaginal dryness and dyspareunia are common side effects of aromatase inhibitors (AIs) [1].

The issue of estrogen deficiency in breast cancer survivors has recently received increasing attention. Antoine et al. [2] interviewed 206 breast cancer survivors by postal questionnaire: 62.3% suffered from hot flashes, which were graded as severe in up to 50% of the cases, and current users of AIs complained

of sexual disorders, with unsatisfactory sexual life, vaginal dryness and decreased libido. Symptoms of atrophic vaginitis have a negative effect on quality of life in breast cancer patients and might affect cancer treatment compliance [3]. In a survey on 250 breast cancer patients treated at our Department [4], vaginal dryness and loss of sexual desire were more frequent in premenopausal as compared to postmenopausal women at the time of diagnosis and were classified as severe by more than two-thirds of the younger women. It has been recently pointed out that, given the complexity of female sexual dysfunction, this issue deserves both a psychosocial approach and a specific genital treatment [5].

Estrogen treatment (ET), administered either vaginally or systemically, is the therapeutic standard for moderate to severe vaginal atrophy in healthy postmenopausal women [6]. Unfortunately, the safety

of systemic estrogens in breast cancer survivors has been seriously questioned. Two European prospective placebo-controlled trials (HABITS and Stockholm trial) have been prematurely stopped because a significant higher recurrence rate in breast cancer patients who received systemic hormone replacement therapy compared to women treated with placebo [7,8]. Recently, also the LIBERATE trial, comparing tibolone *versus* placebo in postmenopausal breast cancer survivors, has been stopped because of a higher recurrence rate in treated patients [9].

Also the use of vaginal ET in women with a history of breast cancer is controversial, due to the theoretical increase of the risk of recurrence in case of systemic absorption of estrogens [10]. Moisturizers or lubricants products are thus recommended as first-line treatment for women with a history of hormone-dependent cancers [5,10]. Nevertheless, the efficacy of non-hormonal vaginal products is limited; in a double-blind clinical trial on breast cancer patients, vaginal moisturizers were no more effective than placebo in relieving urogenital symptoms and the benefits were perceived only during the first two weeks of treatment [11].

Vaginal tissues show a prompt response to local ET, probably due to the direct perfusion or lymphatic absorption of estrogens through the vaginal epithelium [12]. Several types of estrogens can be administered vaginally [conjugated equine estrogens (CEE), promestriene, estradiol (E2) and estriol (E3)], through different pharmaceutical formulations (creams, tablets, rings and pessaries) at variable doses, and may be more effective than systemic estrogens to treat symptoms of urogenital atrophy [13].

Vaginal administration of estrogens at standard dosage increases serum levels of E2 and estrone (E1). The current vaginal therapies include tablets containing 25 µg of micronized E2, creams containing 0.3–1.25 mg of CEE or 0.5 mg of E3, ovules containing 3.5 mg of E3, while vaginal rings are not yet available in Italy. Lower estrogen doses are sufficient to control local symptoms and associated with minimal systemic absorption. Recent data suggest that low-dose vaginal ET (10 µg of E2 as tablet or cream preparation twice a week) improves vaginal symptoms in the majority of treated women [14,15], with plasma E2 levels remaining in the range of postmenopausal levels. Data are lacking about the absorption and the efficacy of low-dose vaginal ET in breast cancer survivors; theoretically, if systemic absorption of estrogens is minimal, any increase of breast cancer recurrence should be unlikely. On the other hand, local ET could be particularly contraindicated in patients receiving AIs. These drugs cause a profound estrogen depletion by inhibiting the enzyme aromatase that promotes the peripheral conversion of androgens to estrogens in post menopausal women. Therefore, it has been

suggested that even a small increase in systemic serum estrogens, such as those associated with vaginal ET, may have a detrimental effect on the risk of recurrence [16].

The current study aims to evaluate the efficacy and safety of two low-dose vaginal estrogen preparations in postmenopausal breast cancer patients with symptoms and signs of urogenital atrophy. A comparison has also been performed between local ET and a vaginal moisturizer.

Methods

Postmenopausal breast cancer patients seeking advice at the Menopause Clinic of our Institute for symptoms of urogenital atrophy were recruited for the study. All women were postmenopausal and had been submitted to surgery, radiotherapy and chemo/hormonotherapy.

Menopausal status was defined according to one of the following criteria: previous bilateral oophorectomy; amenorrhoea since one year and follicle-stimulating hormone (FSH) > 30 IU/l; ovarian suppression by gonadotropin-releasing hormone (GnRH) analogs. Women with vaginal bleeding of unknown origin, genital prolapse (grade II or III) or disease recurrence were excluded. Any previous or concomitant adjuvant chemotherapy, or concurrent tamoxifen ± GnRH analogs, was allowed, while women on AIs were excluded from the treatment with vaginal estrogens.

The standard approach at our Institute is to offer these women, after a thorough discussion about risks and benefits, a treatment with low-dose vaginal estrogen [either 0.25 mg of E3 cream (Colpogyn, Angelini[®]) or 12.5 µg of micronized hemihydrate E2 tablets (Vagifem, Novo Nordisk[®])], both administered twice a week for 12 weeks. Symptomatic women who either refuse hormonal therapy or are taking AIs, are treated with a polycarbophil-based vaginal moisturizer (Replens, Mipham[®]) at the dosage of 2.5 g twice weekly for 12 weeks.

Informed consent to treatment and to data collection for research purposes is obtained from all patients. No additional investigations beyond those commonly prescribed at the Menopause clinic for breast cancer survivors have been performed. The study has been conducted according to the ethical regulations of the Institution.

The patients were divided into three groups according to the different treatment prescribed (estriol, estradiol or moisturizer), the latter group being used as non hormonal comparator.

The severity of vaginal atrophy was assessed using both subjective and objective evaluations. A questionnaire [Vaginal Symptoms Score (VSS)] was submitted to all women regarding the presence and severity of urogenital symptoms including vaginal

dryness, itching or burning, vaginal discomfort, dyspareunia, leucorrhoea, urinary incontinence, urgency and frequency. Symptoms severity was graduated on a scale from 0 to 4; higher scores indicate more severe symptoms. The questionnaire was filled in at baseline, after 4 weeks and after 12 weeks of treatment.

Sexual function was evaluated adopting the specific tool Profile of Female Sexual Function (PFSF) that analyzes different domains of sexual function (sexual desire, arousal, orgasm, sexual pleasure, sexual concerns, sexual responsiveness and sexual self image). PFSF was submitted to patients at baseline and after 12 weeks. Every domain was scored by women with a five-point category rating scale, with 'poor' corresponding to 1 and 'excellent' to 5. All the scores were summed up and linearly transformed into a 0–100 metric score, with 100 indicating the most favourable (best sexual function) and 0 the least favourable (worse sexual function) condition [17,18].

At the screening visit, after 4 weeks and at the end of treatment, a gynaecological examination was performed and the vaginal health index (VHI) score was calculated. VHI evaluates the appearance of vaginal mucosa (elasticity, paleness, vaginal discharge, mucosal integrity, moisture) and vaginal pH [19]. Each of these factors was scored on a scale of 1 to 5 and then summed up to provide the VHI score. Only women with VHI < 14 at baseline were enrolled in the study. Vaginal smears with the evaluation of karyopyknotic index (KI) were obtained at study entry and after 12 weeks and assessed by the same cytologist in all cases.

A vaginal bacteriological examination was performed at screening evaluation; women with vaginal infections were treated and the test was repeated after 2 weeks; only women with normal bacteriological examination were included in the study.

Endometrial safety was assessed by measuring the endometrial thickness with transvaginal ultrasound scan at baseline and at the end of treatment.

Serum levels of FSH, Luteinizing Hormone (LH), E2, E1, Testosterone (T) and Sex Hormone Binding Globulin (SHBG) were measured before starting treatment and during the last week of treatment in a centralized laboratory. The detection limit of the radioimmunoassay used for measuring E2 levels was 5 pg/mL. E2 RIA was performed using a 3H-tracer purchased from Amersham International (Amersham, UK). Highly specific antisera against E2-6-CMO-BSA was kindly supplied by Dr. GF Bolelli (University of Bologna, Italy). Steroid standard for calibration curve was purchased from Sigma (St. Louis, MO, USA). E2 was measured by RIA after solid-phase extraction with diethyl-ether on Extrelut 1 columns (Merck, Darmstadt, Germany). The intra- and inter-assay coefficients of variation for this

assay ranged between 4.1 and 6.3 and 5.7 and 9.5, respectively.

Routine laboratory assessments were performed at baseline and after 12 weeks including haematology and blood chemistry (bilirubin, alkaline phosphatase, lactic dehydrogenase, gamma-glutamyltransferase, blood urea nitrogen, aspartate transaminase, alanine transaminase, creatinine, uric acid, glucose, total cholesterol and triglycerides).

Statistical consideration

Statistical significance was determined by using an alpha level of 0.05 and two-sided tests. Quantitative variables were compared using Pearson's chi-square test or Fisher's exact test. Kolmogorov–Smirnov test was adopted to confirm that the sample origins from a normal population. When normality of data was not confirmed, a non-parametrical analysis was used (Mann–Whitney U-test). The dependent-samples *t*-test was used to analyse data during the time and when non-normal distribution was proved, Wilcoxon signed-rank test was used. Statistical analysis was performed using a SPSS® statistical and data management package.

Results

Thirty-one postmenopausal women with a history of breast cancer and complaining of moderate to severe vaginal symptoms were enrolled in the study. Eighteen women were treated with vaginal low-dose estrogens and completed all the 12 weeks of therapy. Eight women, who either refused ET ($n = 2$) or started AIs as adjuvant treatment for breast cancer ($n = 6$), were treated with a polycarbophil-based vaginal moisturizer for 12 weeks. Five women who never started the prescribed treatment were excluded from the analyses.

No difference of patient and tumour characteristics was found between the two groups of ET and women receiving vaginal gel. The mean age of women in the two ET study arms was slightly higher (54.1 years) as compared to those receiving vaginal moisturizer (46.1 years), although not significantly ($p = 0.078$). More than 80% of the women enrolled underwent iatrogenic menopause as a result of chemotherapy or GnRH analogs use. Since estrogen and/or progesterone receptors were expressed by 72% and 87% of primary tumours in the ET and control groups, respectively, most of these patients had received adjuvant endocrine therapy, alone or after the completion of chemotherapy.

Vaginal signs and symptoms were similar at study entry in patients treated with ET and in those treated with the vaginal moisturizer. Endometrial morphology was linear in all women, with a mean thickness of 2 mm. No differences of sex-hormone serum levels

Table I. Baseline characteristics according to treatment with vaginal estrogens or vaginal moisturizer.

Baseline characteristics	Mean + SD (range)		<i>p</i> -value	Mean + SD (range)		<i>p</i> -value
	Estrogen therapy (<i>n</i> = 18)	Vaginal moisturizer (<i>n</i> = 8)		Estriol (Colpogyn) (<i>n</i> = 10)	Estradiol (Vagifem) (<i>n</i> = 8)	
VSS	15.5 ± 5.7 (6–26)	15.7 ± 3.1 (12–22)	0.91	13.8 ± 4.5 (6–17)	15.7 ± 6.7 (10–26)	0.37
VHI Score	12.8 ± 1.6 (10–14)	13.5 ± 0.5 (13–14)	0.26	13.2 ± 1.7 (10–14)	12.4 ± 1.5 (11–14)	0.46
Vaginal pH	5.3 ± 0.1 (5–5.5)	5.3 ± 0.4 (4.7–6)	0.66	5.3 ± 0.1 (5.1–5.5)	5.3 ± 0.2 (5.0–5.5)	0.87
Karyopycnotic Index (KI) (%)	0.1 ± 0.2 (0–1)	0.1 ± 0.3 (0.1)	0.25	0.1 ± 0.3 (37–188)	0.1 ± 0.2 (0–2)	0.54
Endometrial thickness (mm)	2 ± 0.5 (1–2.5)	2.3 ± 1.3 (1–4)	0.54	1.7 ± 0.6 (1–2.5)	2.2 ± 0.5 (1.5–2.5)	0.26
Estradiol (pg/ml)	16.9 ± 8.0 (2–26)	27.5 ± 19.4 (14.7–64)	0.14	14.4 ± 5.3 (9.13–22.1)	19.4 ± 10.0 (2.0–26.0)	0.35
Estrone (pg/ml)	16.5 ± 12.1 (0.8–41.8)	27.1 ± 4.0 (23.2–31.2)	0.41	13.5 ± 6.00 (4.6–17.8)	19.5 ± 16.9 (0.9–41.8)	0.53
FSH (mIU/ml)	48.3 ± 33.8 (5.2–109.5)	23.3 ± 24.2 (1.8–58.9)	0.13	34.5 ± 20.6 (5.24–54.5)	62.0 ± 40.9 (29.8–109.5)	0.21
LH (mIU/ml)	27.9 ± 18.0 (0.1–54.7)	10.5 ± 19.4 (0.1–48.7)	0.90	25.3 ± 19.5 (0.1–49.0)	30.5 ± 18.3 (13.5–54.7)	0.67
Testosterone (ng/ml)	0.2 ± 0.8 (0.1–0.7)	0.5 ± 0.1 (0.4–0.7)	0.50	0.2 ± 0.1 (0.1–0.4)	0.6 ± 0.3 (0.2–0.9)	0.34
SHBG (nM/l)	29.2 ± 35.5 (21.1–99.2)	50.3 ± 1.4 (40–67.4)	0.27	16.0 ± 27.9 (21.1–66.0)	42.5 ± 40.2 (37–99.2)	0.26

were found in the groups of women assigned to vaginal estrogens, with baseline E2 values below 20 pg/mL. Mean basal serum E2 and E1 levels were higher and FSH and LH lower in women candidate to receive the vaginal moisturizer, but the difference did not reach statistical significance (Table I).

Measures of efficacy, indicated as average scores, are listed in Table II. The VSS improved in both groups of women treated with ET, with a significant reduction of 7.2 ± 4.1 points for estriol ($p = 0.02$) and of 3.4 ± 4.8 points for estradiol ($p = 0.01$) after 4 weeks of therapy; during the following two months of treatment a further improvement of the score was reported in both groups, with a score decrement of 13 ± 2.6 and 10.6 ± 6.9 points, respectively.

Also the objective evaluation of vaginal health showed a beneficial effect of the two ET. The VHI score increased during the first month as compared to pre-treatment values to a similar extent both in women receiving estriol ($+ 6.8 \pm 3.3$; $p = 0.01$) or estradiol ($+ 5.0 \pm 2.7$; $p = 0.02$); during the following 8 weeks of therapy a further increase of the score was found in both groups ($+ 10.5 \pm 2.4$; $p = 0.01$ and $+ 7.0 \pm 3.9$ respectively; $p = 0.02$).

Compared to baseline, both vaginal estrogen preparations significantly lowered vaginal pH, from 5.3 to 4.5 and from 5.3 to 4.6 for women receiving E3 and E2 respectively. Both types of ET minimally influenced the maturation of the vaginal mucosa; we observed a trend towards an increase of superficial cell population during treatment, but the difference of KI as compared to pre-treatment values was not statistically significant.

At the end of the study period, sexual function measured by the PFSF scores was improved by estriol ($+9.2$; $p = 0.02$) and, to a lesser extent, by estradiol ($+8.7$; $p = 0.09$) as compared to basal

values. The details of sexual function evaluation are showed in Table III. Women on ET reported higher rates of sexual pleasure ($p = 0.001$), orgasm achievement ($p = 0.03$), sexual responsiveness ($p = 0.01$) and a 60% improvement of the global sexual satisfaction after 3 months of therapy.

Endometrial thickness did not significantly change during treatment, with a mean increase of 0.5 mm after 3 months of vaginal ET. We did not find any significant modification of hormone serum values at the end of the treatment period as compared to baseline; however, E2 levels increased by a mean 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 E1 levels, while FSH values remained stable. LH was slightly decreased as compared to baseline, particularly in women treated with estradiol (-10.6 IU/l; $p = 0.36$). No clinically significant changes were identified for any of the blood chemistry variables examined during the study period.

The VSS decreased significantly compared to baseline after the first 4 weeks of treatment also in women treated with the moisturizer gel (Table II). However, during the following 8 weeks, while women treated with estrogens continued to improve, women receiving vaginal moisturizer reported a worsening of symptoms, which returned to pre-treatment values. Similar findings were found with the objective evaluation of vaginal mucosa; the VHI was not significantly modified in women treated with the moisturizer gel during all the study period.

The major difference between estrogens and Replens was found for vaginal pH, which shifted to more acidic values in women treated with vaginal estrogens after the first 4 weeks of administration, but

Table II. Modification of efficacy and safety measures during the treatment period in women receiving vaginal estrogens or moisturizer.

Variables	Time interval	Score changes + SD			Score changes + SD			Colpogyn vs. Vagifem, <i>p</i> -value
		ET (<i>n</i> = 18)	<i>p</i> -value	Vaginal moisturizer (Replens) (<i>n</i> = 8)	ET vs. Replens <i>p</i> -value	Estriol (Colpogyn) (<i>n</i> = 10)	Estriol (Vagifem) (<i>n</i> = 8)	
VSS	Basal – 4 weeks	↓ 5.3 ± 4.7	0.00	↓ 6.3 ± 4.3	0.01	↓ 7.2 ± 4.1	↓ 3.4 ± 4.8	0.01
	Basal – 12 weeks	↓ 11.6 ± 5.2	0.00	↓ 1.3 ± 5.5	0.72	↓ 13.0 ± 2.6	↓ 10.6 ± 6.9	0.03
VHI score	Basal – 4 weeks	↑ 5.9 ± 3.0	0.00	↑ 3.0 ± 1.6	0.07	↑ 6.8 ± 3.3	↑ 5.0 ± 2.7	0.02
	Basal – 12 weeks	↑ 8.5 ± 3.6	0.00	↑ 2.0 ± 3.4	0.42	↑ 10.5 ± 2.4	↑ 7.0 ± 3.9	0.02
Vaginal pH	Basal – 4 weeks	↓ 0.5 ± 0.3	0.02	↑ 0.1 ± 0.2	0.62	↓ 0.6 ± 0.2	↓ 0.3 ± 0.4	0.13
	Basal – 12 weeks	↓ 0.7 ± 0.2	0.00	↑ 0.1 ± 0.4	0.82	↓ 0.8 ± 0.3	↓ 0.7 ± 0.3	0.00
KI (%)	Basal – 12 weeks	↑ 12.8 ± 21.8	0.10	↑ 2.0 ± 2.6	0.32	↑ 10.0 ± 9.9	↑ 15.0 ± 28.3	0.30
PFSF	Basal – 12 weeks	↑ 7.2 ± 5.4	0.03	↑ 2.1 ± 9.3	0.70	↑ 9.2 ± 4.03	↑ 8.7 ± 7.1	0.09
Endometrial thickness (mm)	Basal – 12 weeks	↑ 0.5 ± 0.6	0.07	↑ 0.3 ± 0.5	0.42	↑ 0.5 ± 0.6	↑ 0.5 ± 0.7	0.23
Estradiol (pg/ml)	Basal – 12 weeks	↑ 3.1 ± 8.7	0.98	↑ 1.4 ± 8.5	0.17	↑ 3.5 ± 5.1	↑ 2.7 ± 10.6	0.64
Estrone (pg/ml)	Basal – 12 weeks	↑ 5.3 ± 11.9	0.13	↓ 7.0 ± 8.5	0.4	↑ 1.1 ± 6.4	↑ 4.7 ± 12.1	0.16
FSH (mIU/ml)	Basal – 12 weeks	↓ 3.43 ± 30.2	0.33	↓ 12.84 ± 22.4	0.41	↓ 4.02 ± 6.9	↓ 2.64 ± 9.8	0.52
LH (mIU/ml)	Basal – 12 weeks	↓ 8.8 ± 16.1	0.19	↑ 0.1 ± 0.2	0.42	↓ 6.4 ± 13.8	↓ 10.6 ± 19.5	0.36
Testosterone (ng/ml)	Basal – 12 weeks	↓ 0.15 ± 0.7	0.35	↓ 0.18 ± 0.1	0.32	↑ 0.01 ± 0.1	↓ 0.04 ± 0.3	0.39
SHBG (nM/l)	Basal – 12 weeks	↓ 6.3 ± 19.7	0.46	↓ 5.2 ± 13.1	0.15	↓ 5.0 ± 8.5	↓ 7.6 ± 29.9	0.70

Decreased VSS score means less symptoms, increased VHI score means healthier vaginal mucosa, increase of PFSF indicates better sexual function.

not in women receiving the moisturizer gel (Table II). During the 12 weeks of therapy with Replens, no modification of KI, endometrial thickness and serum hormone levels was found, with the exception of a non-significant reduction of FSH at the end of treatment. Accordingly, the moisturizer gel had no significant effect on sexual function (Table III).

Discussion

The preliminary results of this study show that low-dose vaginal ET, both with E3 cream or E2 tablets, is effective in relieving vaginal atrophy in postmenopausal breast cancer survivors. This effect is obtained without inducing significant changes in estrogens serum levels. However, the sample is small and the statistical power of the study is limited; therefore, the results must be interpreted with caution. On the contrary, no significant benefit was obtained with the use of a non-hormonal vaginal moisturizer on subjective and objective measures of vaginal health.

A large number of breast cancer survivors experience bothersome symptoms related to urogenital atrophy [20]. Vaginal administration of estrogens is effective in relieving symptoms of estrogen deficiency, but concerns exist for patients with breast cancer, because most recommended regimens markedly increase serum estrogens levels [10,21]. Higher circulating estrogens could theoretically stimulate the growth of occult metastases or increase the risk of a second breast cancer. Clinical trials investigating the impact of ET on breast cancer recurrence do not suggest a detrimental effect for topical estrogens, although they are limited by their observational nature [22].

Many trials have evaluated the absorption of vaginal estrogen preparations at conventional doses in postmenopausal women, showing that it is strictly dose-dependent and is maximal in the first days of treatment, when the vaginal mucosa is thin and atrophic [23–25]. Recent studies have suggested that it might be possible to lower the vaginal estrogen dose to one which does not significantly increase systemic levels of estrogens, but is still effective on

symptoms. Three studies have compared the systemic absorption of lower (10 µg twice per week) versus standard doses (25 µg twice per week) of vaginal E2 tablets [26,14,15] in postmenopausal women. In the study by Notelovitz et al. [26] 96% of the women receiving 10 µg showed low systemic adsorption of E2, defined as an area under the curve over 24 hours of less than 500 pg/mL. Santen et al. [15] measured E2 levels with an ultrasensitive bioassay in 7 postmenopausal women treated with 10 µg of vaginal estradiol cream twice per week; after 3 months of treatment, circulating E2 levels remained within the postmenopausal range of 3–10 pg/mL. Comparable results have been shown in the study by Bachman [14].

In our study, baseline E2 and E1 levels were under 20 pg/mL in women treated with estrogens and under 30 pg/mL in women who had received the vaginal moisturizer. Such a difference may be related to the younger age of the latter group of women. After 12 weeks of vaginal estrogens, systemic levels of E2 increased by 2.7 pg/mL in the group treated with estradiol tablets and by 3.5 pg/mL in women treated with estriol cream. The systemic absorption of vaginal estrogen preparations was demonstrated also by the decrease of FSH and LH as compared to basal value in both groups; these modifications were though minimal and did not reach statistical significance.

Our study confirms that lower than standard doses of estrogens are associated with good results on objective and subjective markers of vaginal health, although the sample size is small. The VSS showed a significant improvement after 4 weeks of therapy in women receiving E2 tablets or E3 cream at low dose, without difference between the two preparations. A further improvement was seen at the end of 3 months of therapy. In women receiving vaginal moisturizer, although a transient benefit on symptoms related to vaginal atrophy was recorded after 4 weeks, thereafter the effect was lost. The objective assessment of vaginal health conducted by study investigators (VHI), evaluating the appearance of the vaginal mucosa, confirmed the favourable effect of the two

Table III. Changes in the PFSF in patients treated with vaginal estrogen therapy and vaginal moisturizer at the end of the treatment period as compared to baseline.

PFSF variables	Time interval	Vaginal estrogen therapy (%)	p-value	Vaginal moisturizer (%)	p-value
Sexual desire	Basal – 12 weeks	↑ 3.3	0.41	↓ 5.7	0.22
Sexual arousal	Basal – 12 weeks	0.0	1.00	0.0	1.00
Orgasm	Basal – 12 weeks	↑ 4.6	0.03	↓ 5.8	0.18
Sexual pleasure	Basal – 12 weeks	↑ 6.1	0.001	↑ 3.2	0.18
Sexual concerns	Basal – 12 weeks	↑ 2.1	0.17	↑ 5.7	0.42
Sexual responsiveness	Basal – 12 weeks	↑ 6.3	0.01	↓ 4.5	0.27
Sexual self-image	Basal – 12 weeks	↑ 11.7	0.05	↑ 33.3	0.47
Global 'satisfaction with sexuality'	Basal – 12 weeks	↑ 60.0	0.00	↑ 33.3	0.42

Arrows going upward indicate better sexual function.

low-dose regimens of vaginal estrogens, with a significant improvement after 1 month of therapy and a further improvement after 3 months. The benefit was comparable in the two ET groups; in contrast, no changes of the vaginal parameters were found in women receiving the non hormonal gel. Vaginal estrogen therapy restores vaginal pH to premenopausal levels by re-establishing the normal concentration of lactobacilli in the vaginal flora. Compared with baseline, both vaginal low-dose preparations significantly decreased vaginal pH: the difference was significant after 4 weeks and a further benefit was obtained at the end of the study period, while no changes were seen with the moisturizer gel. Similar results for pH have been found in other trials evaluating standard or low-dose vaginal ET [14,15].

In our study, women treated with both low doses ET had a 12% increase of KI after 12 weeks of therapy as compared to baseline, but without reaching statistical significance; no modification of KI was found in women treated with the moisturizing gel. Accordingly, other trials showed a positive effect on vaginal cytology with low-dose vaginal estrogens [15,26].

Our data are in accordance with other studies showing that vaginal dryness and dyspareunia appear to be alleviated by placebo preparations, although such a benefit is temporary. In the trial by Bachman et al. the VSS decreased after 2 weeks of treatment both in women treated with estrogens (standard and low-dose) and with a water-soluble placebo; however, at week 12, the score continued to decrease only in women receiving estrogens and remained constant in the placebo group [14].

Replens is a hydrophilic insoluble cross-linked polymer heavily saturated with water, which binds to the vaginal tissue and is eliminated with epithelial cell turnover. The beneficial effects on symptoms related to vaginal atrophy of this acidic product are likely related also to its buffering properties, which lead to a decrease of vaginal pH. Nonetheless, the efficacy on vaginal symptoms is lower as compared to ET in all the published trials [27,28]. In a study comparing the efficacy of Replens with a vaginal cream containing dienioestrol [29] both treatments resulted in significant increase in the vaginal dryness index, but the comparison between the two drugs was in favour of dienioestrol after the first weeks of treatment. The moisturizer gel was administered also to women with breast cancer in a randomized double-blind study and compared to a water-soluble lubricating placebo for 4 weeks [11], with similar results. Average vaginal dryness symptoms decreased by 64% after 4 weeks of the moisturizing gel and by 62% after 4 weeks of placebo ($p = 0.3$); furthermore, the reduction in patient-reported vaginal dryness and discomfort during intercourse seemed to be primarily contained within the first weeks of treatment in both groups and

there was no evidence of a statistically significant difference between symptoms score of the two agents at any point of the study period.

There are no literature data on the effect of low-dose vaginal estrogens on sexual function in breast cancer survivors. Several studies have demonstrated that breast cancer and its treatment can negatively impact a woman's sexual functioning [30,31]. Our preliminary data show an improvement of global sexual satisfaction in breast cancer patients treated with estrogens, but no difference in those receiving the moisturizer gel.

A major issue is whether even minor changes in serum E2 levels from vaginal absorption of topical estrogens might increase breast cancer risk. The detection limit for most RIA and other non-radioisotopic immunometric methods is 10–20 pg/mL. Basal levels of E2, when measured by the most sensitive RIAs, range from 3 to 10 pg/mL; consequently, assays of higher sensitivity are required to detect the small increments in plasma E2 that can be expected after low-dose estrogen administration. Santen et al. [15] estimated that approximately 3% of a vaginal preparations containing 10 μg of vaginal estradiol cream administered twice per week is absorbed systemically, resulting in minor increments of plasma E2 from 2 to 3 pg/mL for 4 hours following each dose. It is not likely that similar increases of plasma estrogens might exert a negative effect in women with breast cancer, especially if they receive concomitant tamoxifen, due to its competitive interaction with the estrogen receptor [21]. On the contrary, it cannot be excluded that even a small increase in systemic estrogens may be detrimental in women receiving AIs. AIs inhibit the activity aromatase by 95% and reduce plasma E2 levels from approximately 20 pmol/l to 3 pmol/l or less. There are no data on the use of low-dose vaginal estrogens in women receiving AIs, who have been excluded from our study. In the study by Kendall et al. [16], seven breast cancer survivors receiving AIs were treated with standard dose of E2 tablets; at day 14 there was a rise in E2 levels from a median of 3 to 72 pmol/l; at day 28 there was a drop in E2 levels to less than 35 pmol/l (median 16 pmol/l), reflecting the maturation of vaginal mucosa under the effect of the treatment. Kendall et al. suggest that the combination of vaginal estrogens and tamoxifen might provide a short term interval option for women wishing to treat severe atrophic vaginitis, followed by a return to their usual AIs therapy. Another alternative for women receiving AIs with severe symptoms of vaginal atrophy might be the use of ultra low-dose of vaginal estrogens (5 μg , 2.5 μg and 1.25 μg), although no data are available on the efficacy and the safety of these regimens [15].

Despite its efficacy, the acceptability of vaginal estrogen therapy among breast cancer survivors is not

high; in fact, 16% (5/31) of symptomatic women who had initially accepted to use estrogens, never started the treatment. The reasons more frequently reported for this decision were either the reluctance to assume estrogens for the fear that, even at low doses, may increase the risk of breast cancer recurrence, or the adverse opinion of a general practitioner or medical oncologist.

Both vaginal estrogens preparations were well tolerated and no patient discontinued study medications due to side effects. In particular, no patient complained of abdominal pain or vaginal discomfort, which are the most frequent side effects with higher doses. Some studies have reported better patient acceptability of vaginal tablets as compared with vaginal cream or ovules because of vaginal leakage and requirement for sanitary protection are less common with tablets [32]. In our study, the compliance of the two ET preparations did not differ, at least in the short-term period (3 months).

Conclusion

Low-dose vaginal estrogens are effective for relieving vaginal atrophy in breast cancer patients and are associated with a minimal increase of serum estrogens levels during treatment. Our results are consistent with literature data on postmenopausal women from the general population, but need to be confirmed on larger series of breast cancer survivors. Ultra low-dose vaginal estrogens are promising, but their efficacy has still to be proven. On the contrary, non hormonal gel may provide only a transient benefit on vaginal symptoms. Since safety is a major issue, ultra-sensitive assays of serum estrogens are required for a precise quantification of the systemic adsorption of these compounds [33]. Such assays will also be essential to test the safety of vaginal estrogens in breast cancer survivors treated with the newer AIs, who already represent the vast majority of breast cancer patients with endocrine sensitive disease.

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