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Vaginal oestrogen therapy after breast cancer: Is it safe?

Riccardo Ponzone *, Nicoletta Biglia, Maria Elena Jacomuzzi, Furio Maggiorotto, Luca Mariani, Piero Sismondi

Academic Department of Gynaecological Oncology, University of Turin, Mauriziano Umberto I° Hospital of Turin & Institute for Cancer Research and Treatment of Candiolo, Largo Turati 62, Turin 10129, Italy

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Abstract

The increasing number of breast cancer patients who suffer from menopausal symptoms is mainly due to the extensive use of adjuvant treatments in the younger women. Both short and long-term side effects of oestrogen deficiency may severely impact on the quality of life of these women and should not be underestimated. Hormonal treatments are contraindicated in breast cancer survivors mainly due to the concern that dormant micrometastases may be stimulated to grow. Alternative non-hormonal remedies are now available to alleviate symptoms and to prevent chronic diseases associated with oestrogen deficiency. Urogenital atrophy is an important consequence of oestrogen deprivation that can be effectively treated by vaginal estrogens, although systemic absorption occurs with conventional doses. Preliminary data suggest that much lower doses of vaginal estrogens can alleviate urogenital atrophy without influencing serum estrogenic levels. Further research is warranted to confirm whether vaginal estrogens are safe in symptomatic breast cancer patients who are non-responsive to alternative treatments.

Keywords: Oestrogen; Vaginal; Breast cancer

1. Introduction

Menopausal symptoms are a major problem for an ever increasing number of breast cancer survivors of our society. In the year 2000 over a million women worldwide were diagnosed with breast cancer and this number is expected to almost double by 2050 [1].

The good news is that mortality has started to lower in developed countries for the first time in history since 1990. The persistence of this trend, with a stable 2.2% yearly decrement in the mortality rate, and the dramatic increase of lung cancer incidence, account for the fact that lung cancer has overtaken breast cancer as the leading cause of cancer death in the female US population. Nevertheless, breast cancer still represents 32% of all female cancers and longer survivals translate into higher overall numbers of women experiencing treatment-related side effects [2]. Furthermore, since the first release of the Oxford overview, the number of patients undergoing hormonal and/or cytotoxic treatment has been steadily increasing both in the pre- and in the post-menopausal age [3]. The diffusion of adjuvant treatments, together with longer survivals, has undoubtedly determined an increase of short and long-term side effects, some of which are directly related to oestrogen deficiency.

Since hormonal therapy (HT) is currently contraindicated in breast cancer patients, alternative remedies have been developed to alleviate systemic (hot flashes) and local (mainly urogenital atrophy) acute effects of oestrogen deprivation. In particular, the vaginal administration of estrogens is very effective for preventing and treating urogenital atrophy. Nevertheless, even this route of administration may cause systemic absorption of estrogens and thus its safety in breast cancer patients

* Corresponding author. Tel.: +39 11 5082682; fax: +39 11 5082683.
E-mail address: rponzone@mauriziano.it (R. Ponzone).

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is debated. In order to clarify this issue, both the relevance of menopausal symptoms and the evidence for and against vaginal HT in breast cancer survivors will be reviewed in the light of personal experience and from the available literature data.

2. Sex hormones and breast cancer

The crucial role of sex hormones in the pathogenesis and progression of breast cancer is sustained by a large body of epidemiological, biological and clinical data. Apart from age and family history, endogenous and exogenous sex hormones account for the majority of established risk factors for breast cancer. Both early menarche and late menopause increase breast cancer risk due to the widening of the "estrogenic window" during which the breast is exposed to the action of sex hormones. In postmenopausal women, the levels of estrogens in the serum are positively correlated with breast cancer risk, with an overall increase in relative risk of 1.29 [95% confidence interval (CI) 1.15–1.44; $p < 0.001$] for every doubling of oestradiol (E2) concentration [4]. Accordingly, higher estrogenic levels in overweight women due to peripheral conversion of androgens in the fat tissue, may account for their higher breast cancer risk as compared to lean women [5]. Also *in vitro* and animal models are widely available providing strong evidence that the development of breast cancer is oestrogen-dependent and that estrogens are required for tumour growth and distant spread [6].

The publication of the Women's Health Initiative (WHI) trial, which showed a relative risk (RR) of 1.26 (95% CI 1.0–1.59) of developing breast cancer for postmenopausal women on oestrogen plus progestin combination, created a somehow frenzy reaction in the media and a diffuse ostracism against it both in the medical community and in the lay public [7]. The WHI trial did not provide unexpected data, as the increase of breast cancer risk associated with HT use had been already recognised, as well as the biological mechanism behind it. Actually, in 1997 the Collaborative Group on Hormonal Factors in Breast Cancer published a reanalysis of 51 epidemiological studies, showing that long term ($\geqslant 5$ years) HT use increases breast cancer risk by 35% [8]. Nevertheless, such an increase is small in absolute terms and it is also comparatively lower than that conferred by the persistence of a premenopausal condition. Indeed, it has been estimated that HT increases the risk of developing breast cancer by about 2.3% per year for current users, while the risk increases by about 2.8% for each additional year that a woman remains premenopausal [8]. This finding could be related to the fact that HT users show intermediate levels of serum E2 as compared to premenopausal women and postmenopausal non-HT users (170 pmol/L in women on HT *vs.* 500 pmol/L in premenopausal women *vs.* 25 pmol/L in postmenopausal women) [9].

Twenty years ago progestins were believed to act as anti-mitogens and to contrast the proliferative stimulus of estrogens on the breast [10]. Their inclusion in the so-called "combined HT" was thought to prevent the carcinogenic effect of estrogens on the breast, similarly to what had been observed for endometrial cancer. Since then, a large body of laboratory and clinical data have accumulated suggesting that progestins exert instead a proliferative effect on the breast. Accordingly, several observational studies showed that the yearly incremental RR of breast cancer for estrogens alone is in the range of 1–3% as opposed to 7–9% for combined HT [11]. The WHI [7,12] was the first study to provide randomised evidence that progestins increase the risk of breast cancer beyond that attributable to estrogens when used as HT in postmenopausal women. Actually, the recent publication of the oestrogen only component of this study suggested that estrogens alone may even decrease breast cancer risk as compared to placebo (RR 0.77; 95% CI 0.59–1.01), although the authors warned that further studies were necessary before drawing any conclusion on this specific issue [12].

Hormonal remedies for menopausal symptoms have always been considered with great concern in breast cancer patients because estrogenic deprivation is a key element of the armamentarium for breast cancer treatment. Clinical evidence on the role of estrogens in breast cancer progression was provided as early as in 1886 by Sir Beatson who demonstrated that surgical oophorectomy was able to provide tumour regression in patients with locally advanced breast cancer [13]. This pivotal observation and the discovery of oestrogen receptors [14] were instrumental for the development of many endocrine treatments over the last 50 years, among which tamoxifen has been the most successful [15].

On the other hand, several clinical observations do not support the view that exogenous estrogens are necessarily detrimental in breast cancer patients. As a premise, it may be useful to point out that high-dose estrogens, including diethylstilbestrol, ethinyl oestradiol and conjugated estrogens have been successfully used for breast cancer treatment [16]. Other reassuring indications may be derived from the so-called "natural experiments". The outcome of breast cancer diagnosed in women taking oral contraceptives or HT is similar to that of never oestrogen users. Furthermore, although during gestation serum levels of estrogens may increase by 1000 times, pregnancy related breast cancer does not appear to have a worse prognosis provided that cases and controls are matched for age and stage [17]. There is now also compelling evidence that the outcome of breast cancer patients is not impaired by subsequent pregnancies. Most of the studies show that breast cancer

patients who get pregnant fare actually better, although the existence of an "healthy mother effect" (i.e., patients with the best prognosis are more likely to get pregnant) is very difficult to exclude. [18,19]. Clearly, these data cannot be extrapolated and directly applied to HT for breast cancer survivors, yet they serve to underline the complexity of the relationship between estrogens and breast cancer and speak against the adoption of any dogmatic position on this subject.

3. Systemic HT after breast cancer

The relief from menopausal symptoms is a major issue for breast cancer patients. The disease has a high incidence around the age of 50 years when menopausal symptoms are most common. Furthermore, adjuvant treatments exacerbate symptoms of oestrogen deficiency. On the average, tamoxifen increases the incidence of hot flashes by 20%, while analogs of the gonadotrophin releasing hormone (Gn-RH) produce amenorrhoea in all pre-menopausal patients and chemotherapy in about half of them, depending on age.

According to an extensive survey conducted in the US among breast cancer survivors, hot flashes are the prevailing menopause-related symptom (71% of post-menopausal patients). Furthermore, having had a transition into menopausal status during the treatment for breast cancer is associated with worse hot flash severity [20]. For comparison, in a survey that we recently conducted in Italy among 250 breast cancer survivors, hot flashes were reported by, respectively, 90% and 54% of pre-menopausal and post-menopausal patients undergoing chemotherapy plus hormonotherapy. Among pre-menopausal and post-menopausal patients who expressed interest on the possibility of taking HT (34% and 22%, respectively), the main reason was for vasomotor symptoms relief (53% and 50% respectively) [21]. The relevance of vasomotor symptoms is confirmed by our own experience at the Menopause clinic of the Institute for Cancer Research and Treatment in Turin where this is the main motivation to seek medical advice among breast cancer survivors (Fig. 1).

Over the last 15 years, several case-series of breast cancer survivors who received HT for the relief of menopausal symptoms have been published. Most of these studies suffer from several limitations as far as their design (uncontrolled retrospective series), size (less that 1000 patients undergoing HT overall), selection of patients (patients with more favourable prognosis more likely to receive HT) and duration of follow up are concerned [22]. A consensus conference was held at the end of 1997 in Charlottesville on the subject, stating that HT should be used only in those women who do not respond to other treatments or if they make specific request of HT, for short treatment periods, at low oestrogen dosage and preferably within controlled clinical trials [23].

In 2001, Col and colleagues [24] performed a systematic review of the studies on HT in breast cancer survivors. During a mean follow-up of 30 months, recurrences were lower (although not significantly) among HT users as compared to non-users (4.2% *vs.* 5.4% per year), and HT did not seem to affect breast cancer recurrence risk (RR 0.64, 95% CI 0.36–1.15). Since then, none of the following case-controlled studies has demonstrated any increase of breast cancer recurrence among HT users [25,26] and several randomised trial have been going on in Sweden, UK and in the US [27].

In 2004, somehow unexpectedly, great concern was caused by the early termination of the randomised Hormone Replacement Therapy after Breast Cancer Diagnosis—Is It Safe? (HABITS) trial from Sweden. In this study, HT was found to increase the risk of breast cancer events (26 *vs.* 7, RR 3.5, 95% CI 1.5–8.1) as well as serious adverse events (8 *vs.* 4) compared with no HT after a median follow-up of just 2.1 years. Soon after, a similar study in Stockholm was stopped although it

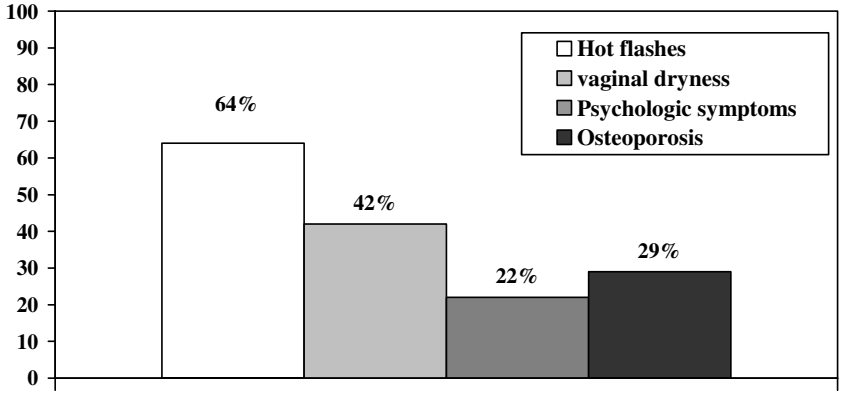

Fig. 1. Motivation to seek medical advice for menopause-related problems among breast cancer survivors. Data from the Menopause clinic at the Institute for Cancer Research and Treatment (IRCC) of Candiolo, Turin, Italy.

found a different trend (RR 0.82, 95% CI 0.35–1.90), and a pooled analysis of both studies showed significantly increased overall hazard for breast cancer with hormone therapy [28].

A detailed analysis of the controversy who took place in the scientific community after the publication of this study is beyond the scope of this review. As a matter of fact, a position statement of the North American Menopause Society was very timely released, suggesting that "*ERT/HRT is contraindicated in women with a history of hormone-sensitive cancer*" [29]. Accordingly, the Editor of Obstetrical and Gynecological Survey wrote that *"...the HABITS study might not be the definitive study on the subject of hormone therapy effects after breast cancer, but likely will be the last one"* [30]. In contrast, the LIBERATE study, a large international randomised trial aimed to investigate safety and efficacy of tibolone in women with climacteric symptoms and a history of breast cancer, has not been stopped and first results are expected in 2007 (Kenemans P, personal communication, 4th Amsterdam Menopause Symposium (AMS), Amsterdam 2–4 October 2004).

4. Vaginal HT after breast cancer

4.1. Efficacy of vaginal HT

Urogenital atrophy is a relevant problem in postmenopausal women. Non-hormonal vaginal moisturiser are effective in relieving urogenital symptoms within two weeks of treatment, but their efficacy is not statistically different from that of placebo and has been consistently lower as compared to vaginal estrogens in randomised trials [31]. The mucosal and stromal tissues in the vagina, vulva, urethra, and trigone of the bladder all contain oestrogen receptors and undergo atrophy when oestrogen deficiency occurs. The consequent decrease in vaginal tissue elasticity and fluid secretion predisposes to trauma and pain during intercourse; furthermore, oestrogen deficiency favours an elevation of vaginal pH ranging from 5.5 to 6.8 which in turn increases the risk of urinary tract infections.

Two out of three (vaginal dryness, dyspareunia and hot flashes) of the most frequently reported symptoms related to oestrogen deficiency are amenable of local therapy. This simple observation suggests the possibility of providing substantial benefit via the administration of vaginal estrogens, although the relevance of other variables unrelated to hormonal levels, such as psychosocial factors for sexual function, is well recognised [32]. Vaginal estrogens are often more effective for relieving urogenital symptoms than oral preparations, at least in part due to the avoidance of hepatic metabolism and to the prompt response of vaginal tissue. A meta-analysis of oestrogen therapy in the management urogenital atrophy in postmenopausal women showed that the vaginal route of administration correlated with better patient reports of symptom-relief, greater improvement in cytologic findings and also significantly higher serum E2 level as compared to the oral route [33]. Nevertheless, the precise mechanism for the vaginal absorption of estrogens has not been clearly defined and there is not a direct relationship between improvement of vaginal symptoms and estrogenic levels obtained in the serum after therapy. This has led to the speculation that the improvement in vaginal health might derive from direct perfusion or lymphatic absorption of the local estrogens through the vaginal epithelium [34].

4.2. Different types of vaginal HT

Several types of estrogens can be administered vaginally (conjugated equine estrogens, promestriene, oestradiol and oestriol) through different pharmaceutical formulations (creams, tablets, rings and pessaries) and variable doses. In a recent systematic review of the Cochrane Collaboration on the efficacy, safety and acceptability of local estrogens for vaginal atrophy in postmenopausal women, 16 trials were examined including a total of 2129 women treated [35]. The efficacy of estrogenic preparations in relieving the symptoms of vaginal atrophy resulted significantly superior when compared to placebo and non-hormonal gels, whereas no difference was reported for urinary symptoms. As far as safety was regarded, there were no significant differences between oestrogen *vs.* placebo for the occurrence of endometrial hyperplasia assessed by endometrial biopsy or endometrial thickness assessed by transvaginal ultrasound. Nevertheless, a comparison of different pharmaceutical formulations revealed that vaginal tablets of E2 were less likely to cause uterine bleeding, breast pain and perineal pain when compared to vaginal creams of conjugated equine estrogens (CEE) [odds ratio (OR) 0.18, 95% CI 0.07–0.50], while a vaginal ring releasing E2 reduced the incidence of uterine bleeding measured by the progestagen challenge test when compared to E2 vaginal tablets (OR 0.29, 95% CI 0.11–0.78). Accordingly, there were significant higher serum E2 levels, although remaining within normal menopausal range, in the tablet *vs.* ring as well as in the cream *vs.* tablet comparisons.

The Cochrane reviewers recommend additional progestagen protection for women with a uterus using vaginal estrogens "*if the dose used results in systemic estrogen absorption (usually associated with doses of estradiol greater than 0.5 mg/daily)*". With this regard, it is commonly believed that oestriol does not contribute to endometrial stimulation in the same way as E2. Vooijs and Geurts [36] in their meta-analysis of 12 studies examining 214 women who had been continually using oestriol vaginal cream, reported that a total of 337

post-baseline biopsies were classified as atrophic at varying stages of treatment, ranging from six months to two years after beginning oestriol use. Nevertheless, a case-control study from Sweden more recently showed a non-significant increase of the relative risk of endometrial cancer (OR 1.2, 95% CI 1.0–1.6) and endometrial atypical hyperplasia (OR 1.5, 95% CI 0.8–3.0) associated with the use of vaginal oestriol, and a much more pronounced one with 1–2 mg daily of oral oestriol (OR 3.0, 95% CI 2.0–4.4 and OR 8.3, 95% CI 4.0–17.4, respectively) [37].

4.3. Safety of vaginal HT in breast cancer patients

The availability of a safe and effective local treatment is of paramount interest for the case of breast cancer patients who experience one or more symptoms of urogenital atrophy. In the American survey already cited [20], the presence of vaginal dryness was reported by 23.4% and 70.8% of pre- and post-menopausal patients, respectively, and the corresponding figures for dyspareunia were 15.9% and 38.7%. For comparison, in our survey conducted in Italy vaginal dryness was reported by 19% and 42% of pre- and post-menopausal patients undergoing adjuvant treatments, respectively, and the corresponding figures for dyspareunia were 10% and 27% [21]. In addition, Ganz and colleagues [38] have clearly demonstrated that vaginal dryness is an important component determining the sexual health outcomes measured as sexual interest, sexual dysfunction and sexual satisfaction among breast cancer survivors.

The issue of blood absorption of vaginal estrogens is particularly relevant for women with contraindication to hormonal treatments, such as breast cancer survivors. Actually, if the vaginal dose can be reduced to one which does not increase plasma levels of estrogens, but still effectively treat the urogenital atrophy, these patients may be relieved from their symptoms without influencing their risk of cancer relapse. However, the precise assessment of plasma E2 levels in postmenopausal patients is complex. Recent studies generally adopt direct analytical approaches, consisting in immunoassays on serum or plasma that has not been subjected to pre-treatments that extract the E2 from the sample. It has been reported that this can lead to inaccurate results, with a fivefold variation of mean E2 levels reported by different laboratories (6–28 pg/ml). Conversely, the adoption of pre-treatments with organic extractants, leads to more precise estimates, with mean E2 levels of approximately 7 pg/ml (or 25 pmol/l) [39]. Another important point is represented by the variability of systemic absorption of vaginal estrogens according to the duration of treatment; although it has been reported that vaginal absorption of E2 [40] and oestriol [41] decreases as the vaginal epithelium matures within two weeks after the start of vaginal treatment, this has not been confirmed by other studies [42,43].

As already discussed, most of the increase of breast cancer risk attributed to systemic HT in postmenopausal women could derive from the association of progestins to protect the endometrium [7,12]; such association would not be required if vaginal estrogens do not stimulate the endometrium. On the other hand, if systemic absorption occurs, another possible pitfall of vaginal estrogens unopposed by progestins would be represented by the risk of causing endometrial hyperplasia and/or endometrial cancer. As already discussed, the available studies on the endometrial safety of vaginal estrogens unopposed by progestins are reassuring, whereas data from 30 case-control studies and seven cohort studies suggest that the risk of endometrial cancer among ever users of oral/transdermal estrogens alone is increased by approximately 2.8-fold (95% CI: 2.6–3.0) over that of never users [44].

The consensus statement in Charlottesville regarding local estrogens for urogenital atrophy in breast cancer survivors concluded that: "*...Further studies are required to evaluate modifications of circulating estrogens with available compounds*" [23]. Actually, the available direct evidence on the safety of vaginal estrogens in breast cancer survivors is quite limited. O'Meara and colleagues [25] reported that the risk of recurrence in breast cancer patients who used vaginal estrogens was not increased (adjusted RR 0.46; 95% CI 0.21–1.01) irrespective of the total dose (2–4 tubes *vs.* $\geqslant$5 tubes of cream). More recently, Dew and colleagues reported that 69 patients, among a series of 1472 breast cancer patients with bothersome menopausal symptoms, were allowed to use vaginal estrogens in the form of cream or tablets. Again, no detrimental effect was shown in a Cox regression analysis using vaginal estrogens after diagnosis as a time dependent covariate (corrected hazard ratio for recurrence 0.57; 95% CI 0.20–1.58, $p = 0.28$) [45].

Vaginal E2 is generally prescribed at doses ranging from 100 to 500 μg/day which are associated to significant systemic absorption. These regimens may be considered adequate to reduce systemic side-effects of oestrogen deficiency like hot flashes, mood alterations or osteoporosis [46]. Conversely, if vaginal estrogens are only administered to alleviate urogenital symptoms, such doses are at least 10-fold higher than what may be necessary. Actually, the lowest dose of vaginal E2 reported to be effective for treating vaginal atrophy is 5–10 μg/day, delivered via a silastic ring [47]. The next lowest effective dose is a daily 10-μg vaginal tablet [48]. It must be underlined that the efficacy on urogenital symptoms may slightly change among different types of estrogens. As an example, it has been reported "low-dose" vaginal E2 (vaginal tablets 25 μg/daily or 2 times/weekly) is most efficacious as compared to "low dose"

Table 1
Studies on low dose vaginal estrogens: systemic absorption and endometrial effect

Study	Nr. of pts.	Type of study	Drug	Type of preparation	Dose	Duration	Mean E2 serum levels over 24 h (pg/ml)	Endometrial thickness (mm)
Simunic [43]	1612	Double blind placebo-controlled	17β-E2 *vs.* placebo	Vaginal tablets	25 μg/day for 2 wks; then 25 μg twice/wk	12 mo	Basal: 15.7 *vs.* 14.2 ($p = 0.346$) At 4 mo: 17.3 *vs.* 15.1 ($p = 0.456$) At 12 mo: 15.5 *vs.* 13.8 ($p = 0.322$)	Basal: 3.1 *vs.* 3.2 ($p = 0.432$) – At 12 mo: 2.9 *vs.* 3.0 ($p = 0.324$)[a]
Notelovitz [48]	58	Double-masked, randomized parallel group	17β-E2	Vaginal tablets	10 *vs.* 25 μg/day	12 wks	Basal: 7.0 *vs.* 7.6 ($p =$ ns) At 1 wk: 15 *vs.* 22 ($p =$ ns) At 12 wks: 11 *vs.* 23 ($p =$ ns)	
Santen [42]	7	Single-blind, single arm	17β-E2	Vaginal cream	10 μg/day for 3 wks; then 10 μg twice/wk	12 wks	Basal: 1–3 At 24 h, 3 & 12 wks: 3–5 ($p =$ ns)[b]	Basal < 5 mm At 12 wks < 5 mm
Dugal [49]	96	Randomised parall group, single blind	17β-E2 *vs.* Estriol	Vaginal tablets *vs.* vagitories	25 μg/day for 2wks; then 25 μg twice/wk *vs.* 0.5 mg/day for 2wks; then 0.5 mg twice/wk	24 wks	Basal: <30 with both treatments ($p =$ ns) At 2, 12 and 24 wks: <30 with both treatments ($p =$ ns)	Increased during the first 2 wks with both treatments (1.1 mm *vs.* 0.5 mm) but returned to baseline by the end of study ($p =$ ns)
Nilsson [40]	6	Single arm	17β-E2	Vaginal tablets	25 μg/day for 2wks; then 25 μg twice/wk	12 wks	Basal: 7.4 At 12 wks: 13.6 ($p =$ ns)	
Naessen [50]	60	Randomised, non-placebo controlled	17β-E2 *vs.* no treatment	Vaginal ring	7.5 μg/day	12 mo	Basal: 13.5 *vs.* 15.3 ($p =$ ns) At 12 mo: 15 *vs.* 15.38 ($p = 0.15$)	Basal: 1.08 *vs.* 1.36 ($p =$ ns) At 12 mo: 0.94 *vs.* 1.18 ($p = 0.54$)

Abbreviations. E2, estradiol; mo, months; wk, week; Nr, number; Pts, patients; and ns, not significant.
[a] Vaginal bleeding in 5 (0.6%) *vs.* 0 patients ($p =$ ns).
[b] Mean 2 pg/ml increase only during the first 4 h after administration.

vaginal oestriol (vaginal cream, 3.5 mg/weekly) according to patient report (estimate of the average treatment effect shown as effect size: +1.66 *vs.* +0.88, $p < 0.008$). On the other hand, vaginal E2 has a more significant effect on serum oestrogen levels as compared to vaginal oestriol (effect size: +0.71 *vs.* −0.06, $p < 008$) [33].

Table 1 summarises a series of studies on the systemic absorption of low dose vaginal oestrogen therapy in postmenopausal patients measured as mean E2 serum levels over 24 h [49,50]. Overall, doses below 25 μg twice weekly of E2 or 0.5 mg twice weekly of oestriol are not associated with a significant increase of serum estrogens as compared to baseline levels, either after short (1–3 weeks) or long-term (3–12 months) treatments. This appears to be true irrespective of the pharmaceutical formulation (tablet, cream, ring) and even in the early phase (usually 2 weeks) of treatment when higher dose are usually applied (25 μg/day of E2 or 0.5 mg/day of oestriol). The twice weekly maintenance dose seems adequate to affect the vaginal and urethral epithelium, when judged by both cytology and clinical and subjective symptoms. The lack of gradual increase of serum E2 can be interpreted as proof of a stable situation during maintenance therapy and also implies that the risk of endometrial stimulation should be minimal [41]. Actually, endometrial effects resulting from systemic absorption of low dose vaginal E2 are not apparent when assessed by transvaginal ultrasound, or even by endometrial biopsies repeated before and during treatment [50,51].

The best experimental evidence on the possibility of relieving urogenital symptoms while preventing significant increases in serum E2 concentration may be found in a study conducted to evaluate the absorption of two low-dose vaginal tablets of 17β-E2 (25 μg and 10 μg/day) [48]. Forty-two postmenopausal women with atrophic vaginitis and serum E2 concentrations below 20 pg/ml at baseline were entered in the study. After 12 weeks of daily treatment, 74% in the 25-μg and 96% in the 10-μg groups had low systemic absorption of E2 defined as area under the curve over 24 h less than 500 pg/ml. The corresponding average over 24-h E2 concentration was 23 pg/ml in the 25-μg and 11 pg/ml in the 10-μg group. Furthermore, no patients in the low and only 3 patients in the higher dose arm showed FSH suppression to premenopausal levels (<35 mIU/ml) possibly related to significant systemic E2 absorption.

In order to establish the minimal effective dose of vaginal E2 for relieving urogenital symptoms without increasing E2 serum levels, Santen and colleagues [42] set up a de-escalating dose study and published the preliminary results on seven patients. A very important aspect of their study consisted in the adoption of a novel ultrasensitive bioassay for serum E2 with a level of sensitivity 50- to 100-fold greater than that of current radioimmunoassays (0.02 pg/ml *vs.* 10–20 pg/ml) to detect small increments in plasma E2 expected after low-dose oestrogen administration. The relevance of this technical advancement is evident when considering that basal postmenopausal levels of E2 range from 3 to 10 pg/ml. A starting dose of 10 μg daily was chosen, to be reduced to a frequency of twice weekly after 3 weeks of E2 administration. At 12 weeks, all predefined markers of efficacy (vaginal and urethral cytology, vaginal pH) showed statistical improvement and 82% of vaginal symptoms were cured or improved. Low E2 absorption was confirmed as the endometrium remained atrophic (assessed by endometrial biopsy) and circulating E2 levels remained within the postmenopausal range of 3–10 pg/ml. The same authors are now planning to administer lower E2 doses (5, 2.5, and 1.25 μg) to be given on the same schedule in order to prove if efficacy can be retained with an even safer serum E2 profile for breast cancer patients.

5. Conclusions

Urogenital symptoms of oestrogen deficiency develop in a high percentage of breast cancer patients after a few months from primary treatment. Oral or transdermal HT is currently contraindicated and systemic alternative remedies are poorly effective. Non-hormonal local therapies such as lubricant preparations (to be used only before intercourse) and hydratant preparations (to be used continuously) are available, but their efficacy is significantly lower as compared to vaginal estrogens.

Vaginal estrogens are very effective in relieving vaginal atrophy and dyspareunia. Systemic absorption is considerable with conventional doses, although no endometrial stimulation or atypia has been demonstrated in randomised controlled trials. The side-effect profile of E2 and oestriol appears to be safer as compared to that of CEE, although the issue of the dose is clearly of paramount importance and cross-comparison between different studies may not provide reliable data.

If vaginal HT is administered with the aim of improving urogenital symptoms, currently prescribed doses are greatly in excess as compared to the minimal effective dose and the association of a progestin is required to protect the endometrium. Vaginal E2 doses higher than 100 μg/day increase serum E2 levels above those conventionally considered as postmenopausal, although slightly lower as compared to those obtained with the same doses administered by transdermal patches [52]. Also vaginal E2 doses between 10 and 25 μg/day increase serum E2, although to such a small extent that can only be detected by means of ultrasensitive bioassay. Conversely, vaginal E2 doses <10 μg/day do not seem to increase serum E2, even if 3–10 pg/ml are taken as the true basal level in postmenopausal women.

Also the use of vaginal oestriol at conventional doses is associated with significant systemic absorption: it has

been calculated that 1 mg of intravaginal estriol results in serum levels equivalent to 10 mg of the orally administered hormone [53]. Since 0.5 mg/day of vaginal oestriol appears to significantly decrease FSH/LH levels, some metabolic activity is likely [54], whereas reliable data are lacking on lower doses. Although it is commonly believed that oestriol does not contribute to endometrial and breast proliferation in the same way as E2, further research is needed to assess which of the two compounds has a more favourable balance between efficacy and safety.

In conclusion, low dose vaginal estrogens can be discussed with breast cancer patients with bothersome urogenital symptoms as preliminary evidence is emerging that short and intermediate term treatments with very low doses ($\leqslant$10 μg/day) of E2 provide good local symptom control and virtually no elevation of serum E2 levels. Nevertheless, the data are both qualitatively and quantitatively insufficient to exclude that even minimal changes of circulating estrogens may be detrimental in patients with hormone sensitive cancers. The lack of reliable data are in part due the fact that measurements of serum E2 have been traditionally used to assess the reproductive function in premenopausal women, whereas the technical problems connected with the determination of low E2 concentrations of postmenopausal patients are relatively new [55]. Therefore, given the availability of effective non-hormonal remedies for many menopause related problems like osteoporosis (bisphosphonates), cardiovascular risk (statins) and vasomotor symptoms (selective serotonine reuptake inhibitors), vaginal estrogens should be reserved to breast cancer patients suffering from urogenital symptoms unresponsive to non-hormonal remedies.

Conflict of interest statement

None declared.

References

1. Parkina DM, Braya FY, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001, **37**, S4–S66.
2. Jemal A, Tiwari RC, Murray T, *et al*. Cancer Statistics, 2004. *CA Cancer J Clin* 2004, **54**, 8–29.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005, **365**, 1687–1717.
4. The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002, **94**, 606–616.
5. Hankinson SE, Willett WC, Manson JE, *et al*. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 1998, **90**, 1292–1299.
6. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol* 2001, **2**, 133–140.
7. Chlebowski RT, Hendrix SL, Langer RD, *et al*. for the WHI investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003, **289**, 3243–3253.
8. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997, **350**, 1047–1059.
9. Cuzick J. Is hormone replacement therapy safe for breast cancer patients? *J Natl Cancer Inst* 2001, **93**, 733–734.
10. Gambrell Jr RD. Role of progestogens in the prevention of breast cancer. *Maturitas* 1986, **8**, 169–176.
11. Santen RJ. Risk of breast cancer with progestins: critical assessment of current data. *Steroids* 2003, **68**, 953–964.
12. Anderson GL, Limacher M, Assaf AR, *et al*. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomised controlled trial. *JAMA* 2004, **291**, 1701–1712.
13. Stockwell S. Classics in oncology. George Thomas Beatson, M.D. (1848–1933). *CA Cancer J Clin* 1983, **33**, 105–121.
14. Jensen EV, Jordan VC. The estrogen receptor: a model for molecular medicine. *Clin Cancer Res* 2003, **9**, 1980–1989.
15. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
16. Muss HB. Endocrine therapy for advanced breast cancer: a review. *Breast Cancer Res Treat* 1992, **21**, 15–26.
17. Kroman N, Mouridsen HT. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *The Breast* 2003, **12**, 516–521.
18. Gelber S, Coates AS, Goldhirsch A, *et al*. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 2001, **19**, 1671–1675.
19. Blakely LJ, Buzdar AU, Lozada JA, *et al*. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. *Cancer* 2004, **100**, 465–469.
20. Crandall C, Petersen L, Ganz PA, *et al*. Association of breast cancer and its therapy with menopause-related symptoms. *Menopause* 2004, **11**, 519–530.
21. Biglia N, Cozzarella M, Cacciari F, *et al*. Menopause after breast cancer: a survey on breast cancers survivors. *Maturitas* 2003, **45**, 29–38.
22. Pritchard KI. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer and a review of possible alternatives. *Ann Oncol* 2001, **12**, 301–310.
23. The Hormone Foundation, Canadian Breast Cancer Research Initiative, National Cancer Institute of Canada, Endocrine Society, and the University of Virginia Cancer Center and Woman's Place. Treatment of estrogen deficiency symptoms in women surviving breast cancer. *J Clin Endocrinol Metab* 1998, **83**, 1993–2000.
24. Col NF, Hirota LK, Orr RK, *et al*. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol* 2001, **19**, 2357–2363.
25. O'Meara ES, Rossing MA, Daling JR, *et al*. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst* 2001, **93**, 754–762.
26. Decker DA, Pettinga JE, VanderVelde N, *et al*. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. *Menopause* 2003, **10**, 277–285.
27. Biglia N, Gadducci A, Ponzone R, *et al*. Hormone replacement therapy in cancer survivors. *Maturitas* 2004, **48**, 333–346.

28. Holmberg L, Anderson H. For the HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer – is it safe?), a randomised comparison: trial stopped. *Lancet* 2004, **363**, 453–455.
29. North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004, **11**, 11–33.
30. The editor. HABITS (Hormonal Replacement Therapy After Breast Cancer-Is It Safe?): a randomized comparison trial stopped. *Obstet Gynecol Survey* 2004, **59**, 442–443.
31. Loprinzi CL, Abu-Ghazaleh S, Sloan JA, *et al*. Phase III randomised double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol* 1997, **15**, 969–973.
32. Laan E, van Lunsen RHW. Hormones and sexuality in postmenopausal women: a psychophysiological study. *J Psichosom Obstet Gynaecol* 1997, **18**, 126–133.
33. Cardozo L, Bachmann G, McClish D, *et al*. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: Second, report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998, **92**, 722–727.
34. Rigg LA, Hermann H, Yen SC. Absorption of estrogens from vaginal creams. *N Engl J Med* 1978, **298**, 195–197.
35. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. The Cochrane Database of Systematic Reviews volume 2004, 4, CD001500.
36. Vooijs GP, Geurts TBP. Review of the endometrial safety during intravaginal treatment with estriol. *Eur J Obstet Gynecol Reprod Biol* 1995, **62**, 101–106.
37. Weiderpass E, Baron JA, Adami HO, *et al*. Low-potency oestrogen and risk of endometrial cancer: a case-control study. *Lancet* 1999, **353**, 1824–1828.
38. Ganz PA, Desmond KA, Belin TR, *et al*. Predictors of sexual health in women after a breast cancer diagnosis. *J Clin Oncol* 1999, **17**, 2371–2380.
39. Dowsett M, Folkerd E. Deficits in plasma oestradiol measurement in studies and management of breast cancer. *Breast Cancer Res* 2005, **7**, 1–4.
40. Nilsson K, Heimerb G. Low-dose 17P-oestradiol during maintenance therapy – a pharmacokinetic and pharmacodynamic study. *Maturitas* 1995, **21**, 33–38.
41. Heimer GM, Englund DE. Estriol absorption after long-term vaginal treatment and gastrointestinal absorption as influenced by a meal. *Acta Obstet Gynecol Scand* 1984, **63**, 563–567.
42. Santen RJ, Pinkerton JV, Conaway M, *et al*. Treatment of urogenital atrophy with low-dose estradiol: preliminary results. *Menopause* 2002, **9**, 179–187.
43. Simunic V, Banovic I, Ciglar S, *et al*. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynaecol Obstet* 2003, **82**, 187–197.
44. Collins JA, Schlesselman JJ. Hormone replacement therapy and endometrial cancer. In Lobo RA, ed. *Treatment of the postmenopausal woman*. Philadelphia (PA)/Baltimore (MD), Lippincott/Williams & Wilkins, 1999. pp. 503–512.
45. Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climateric* 2003, **6**, 45–52.
46. Baker VL. Alternatives to oral estrogen replacement: transdermal patches, percutaneous gels, vaginal creams and rings, implants, and other methods of delivery. *Obstet Gynecol Clin North Am* 1994, **21**, 271–297.
47. Henriksson L, Stjernquist M, Boquist L. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol releasing vaginal ring (estring) in postmenopausal women with symptoms and signs of urogenital aging. *Am J Obstet Gynecol* 1996, **174**, 85–92.
48. Notelovitz M, Funk S, Nanavati N, *et al*. Estradiol absorption from vaginal tablets in postmenopausal women. *Obstet Gynecol* 2002, **99**, 556–562.
49. Dugal R, Hesla K, Sordal T, *et al*. Comparison of usefulness of estradiol vaginal tablets and estriol vagitories for treatment of vaginal atrophy. *Acta Obstet Gynecol Scand* 2000, **79**, 293–297.
50. Naessen T, Rodriguez-Macias K. Endometrial thickness and uterine diameter not affected by ultralow doses of 17β-estradiol in elderly women. *Am J Obstet Gynecol* 2002, **186**, 944–947.
51. Mettler L, Olsen PG. Long term treatment of atrophic vaginitis with low-dose oestradiol vaginal tablets. *Maturitas* 1991, **14**, 23–31.
52. Nash HA, Bracheb V, Alvarez-Sanchezb F, *et al*. Estradiol delivery by vaginal rings: potential for hormone replacement therapy. *Maturitas* 1997, **26**, 27–33.
53. Head KA. Estriol: safety and efficacy. *Alt Med Rev* 1998, **3**, 101–113.
54. Bottiglione F, Volpe A, Esposito G, *et al*. Transvaginal estriol administration in postmenopausal women: a double blind comparative study of two different doses. *Maturitas* 1995, **22**, 227–232.
55. Toniolo P, Lukanova A. The challenge of measuring circulating estradiol at low concentrations. *Breast Cancer Res* 2005, **7**, 45–47.