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To cite this article: R. E. Nappi, L. Tiranini, E. Martini, D. Bosoni, C. Cassani & L. Cucinella (2023): Different local estrogen therapies for a tailored approach to GSM, *Climacteric*, DOI: 10.1080/13697137.2023.2218998

To link to this article: <https://doi.org/10.1080/13697137.2023.2218998>



Published online: 15 Jun 2023.



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REVIEW

Different local estrogen therapies for a tailored approach to GSM

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ABSTRACT

Local estrogen therapy (LET) is the mainstay of treatment for vaginal dryness, dyspareunia and other urogenital symptoms because it may reverse some pathophysiological mechanisms associated with decreasing endocrine function and increasing aging. Over the years, several vaginal products including different formulations (tablets, rings, capsules, pessaries, creams, gels and ovules) and molecules (estradiol [E2], estriol [E3], promestriene, conjugated equine estrogens and estrone) have been used with superimposable therapeutic results. Low-dose and ultra-low-dose LET is the gold standard due to its minimal systemic absorption, with circulating E2 levels persistently remaining in the postmenopausal range. In healthy postmenopausal women, preference among the various products is presently the main driver and dissatisfaction with LET seems high, namely because of the delayed use in those with severe symptoms of genitourinary syndrome of menopause (GSM). Specific concerns remain in high-risk populations such as breast cancer survivors (BCS), especially those under treatment with aromatase inhibitors. Based on the multitude of symptoms under the umbrella of GSM definition, which includes vulvovaginal atrophy (VVA), it is mandatory to investigate specific effects of LET on quality of life, sexual function and genitourinary conditions by conducting studies with a patient-tailored focus.

ARTICLE HISTORY

Received 2 April 2023
Revised 21 May 2023
Accepted 23 May 2023
Published online 15 June 2023

KEYWORDS

Local estrogen therapy; estradiol; estriol; promestriene; efficacy; safety; genitourinary syndrome of menopause; vulvovaginal atrophy; breast cancer survivors

Introduction

Estrogens play a pivotal role in several areas of women's health and profoundly affect urogenital and sexual health [1,2]. Vulvovaginal atrophy (VVA) is part of the genitourinary syndrome of menopause (GSM) and is mostly due to the decline of estrogen production by the ovaries [3]. Even androgens, along with the aging process of urogenital tissues, contribute to some components of GSM [4]. Given the significant overlap among sexual symptoms with menopause [5] and their biopsychosocial etiology [6], a thorough evaluation is essential to provide an effective treatment [7,8]. Indeed, women over age 40 years reported clusters of urogenital and sexual symptoms potentially underlying different determinants [9] with a significant impact on quality of life [10]. Therefore, health-care providers (HCPs) should be aware that the umbrella term of GSM embraces a variety of clinical manifestations not only resulting from endocrine changes associated with menopause [11]. On the other hand, replacing the word VVA with this new terminology seems suitable to overcome the vaginal 'taboo' and facilitate individualized counseling [12].

Addressing the issue of sexual health at menopause is a fundamental step to identify the best strategy to manage the most common symptoms associated with GSM [13]. Being a non-life-threatening condition, the treatment of GSM is a

shared decision and motivations should be the relief of distressing subjective symptoms rather than the sole evidence of objective signs [14].

Local estrogen therapy (LET) is the mainstay of treatment for vaginal dryness, dyspareunia and other GSM-associated urogenital symptoms because it may reverse some pathophysiological mechanisms of this common chronic clinical condition [15]. When non-hormonal over-the-counter symptomatic relief products fail and no other menopausal symptoms are present, expert recommendations indicate the use of LET with Level A evidence [16–18]. Also, systemic menopause hormone therapy (MHT) improves symptoms of GSM in most menopausal women, but its risk–benefit profile is acceptable for this purpose when other indications, mainly vasomotor symptoms or prevention of osteoporotic fractures, represent the main reasons for prescription [16,18]. Combination of MHT and LET may be required initially for women with severe symptomatology [18]. A subset of patients – that is, breast cancer survivors (BCS) – display contraindications to MHT and treatment of GSM remains an unmet need, unless LET is prescribed with an individualized approach [19].

In this article, we report a brief narrative overview of the available LET pointing to efficacy and safety of this class of drugs. In addition, we will discuss peculiarities of various LET in the treatment of GSM besides the class effect.

Local estrogen therapy

LET includes a range of vaginally administered estrogen products approved with the indication to treat symptomatic VVA because GSM is a novel heterogeneous clinical entity [20]. Subjective rating scales of the most bothersome symptoms (dryness, soreness, irritation, pain with intercourse and bleeding after intercourse) and objective measurements, including vaginal pH (>5, in the absence of bleeding or infection) and vaginal cytology (Vaginal Maturation Index with <5% superficial cells or more than 75% parabasal cells), are useful tools to evaluate response to LET [21]. Trophic effects of LET are mostly evident on the vaginal epithelium and blood flow; however, distribution of estrogen receptors is also present at lower urinary tract level and to a lesser extent in the vulvar area [22].

Availability of specific vaginal products (Figure 1) varies worldwide and includes many formulations (tablets, rings, capsules, pessaries, creams, gels and ovules) and molecules (estradiol [E2], estriol [E3], promestriene, conjugated equine estrogens and estrone) which have been tested over the years [16,17]. At present, low-dose and ultra-low-dose LET is the first choice in order to minimize systemic absorption, with circulating E2 levels persistently remaining in the postmenopausal range [19]. Indeed, by using accurate methodologies, low-dose/ultra-low-dose products do not increase E2 into the circulation above the mean level (from undetectable to 10.7 pg/ml) measured in normal, untreated postmenopausal women [23].

Different formulations are typically used daily for 2 weeks, followed by twice per week administration (ring is replaced every 90 days) [15]. Estrogenic absorption is dose-dependent, and the formulation, positioning in the vagina as well as thickness of the epithelium may influence systemic exposure, especially in the first 12 weeks of treatment [23].

Estradiol

E2, the main ovarian estrogen during fertile life, has been available at different dosages in several formulations (tablet, ring, cream, soft gel insert), but ultra-low doses, ranging from 4 to 10 µg E2, are currently the most used [23]. Indeed, they significantly improve the proportions of vaginal superficial

and parabasal cells and vaginal pH, and decrease the severity of GSM-associated symptoms as compared with low-dose 25 µg E2 [24,25], increasing circulating E2 to a lower extent [26,27]. Interestingly, it has been calculated that the treatment of women with 10 µg E2 tablet intravaginally (once daily during the first 2 weeks, then twice weekly for an additional 50 weeks) results in an annual E2 exposure of only 1.14 mg [28]. In addition, the same dose of E2 is less systemically absorbed when soft-gel vaginal capsules are placed without an applicator as compared with vaginal tablets inserted with an applicator [29]. The placement of LET in the inner third of the vaginal canal increases the amount of E2 delivered to the uterus and periurethral areas [30].

Estriol

E3, an estrogen of placental origin, is a final metabolite of estrogen synthesis and a short-acting molecule that is very efficient when used intra-vaginally [31]. Potential advantages of E3 include a greater relative affinity for estrogen receptor-β than for estrogen receptor-α, which leads to fewer extra-vaginal effects [32].

Efficacy and safety have been established over time in postmenopausal women (age range 44–87 years) with symptomatic VVA [33]. E3 is available at different dosages, usually 0.5 mg, in several formulations (cream, ovule, pessary, gel) [33], including an ultra-low dose of 0.03 mg combined with lyophilized, viable *Lactobacillus acidophilus* KS400 [34] that have been tested with promising results in BCS [35]. Even a low dose of 0.05 mg E3 in a highly hydrating gel has been investigated in BCS showing positive results against placebo, with negligible systemic absorption [36]. Moreover, a small dose of E3 vaginal gel (25 µg) applied to the vulvar vestibule daily for 3 weeks and then twice weekly for up to 12 weeks is effective to relieve postmenopausal dyspareunia, likely by reducing sensory vestibular innervation [37].

Promestriene

Promestriene is a synthetic estrogen widely used as cream or insert at 10 mg dose [36]. Being minimally absorbed, it has a superficial activity on the vaginal mucosa and is considered a safer option in women with severe atrophy [38] and in

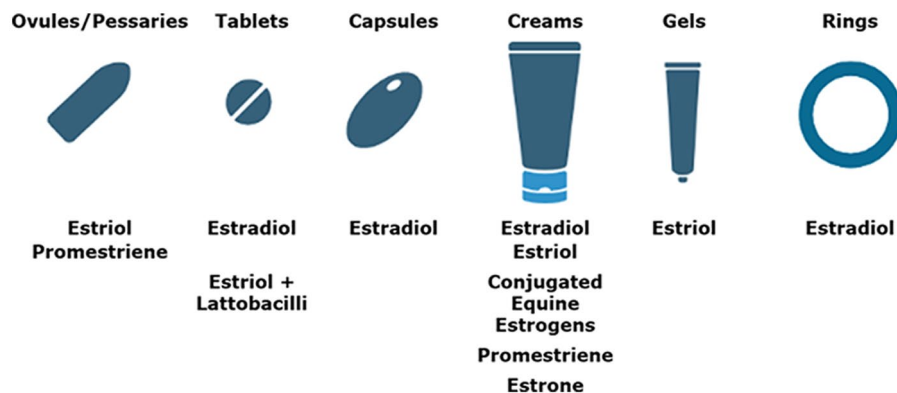


Figure 1. Main formulations of local estrogen therapy (LET) available worldwide. Created in BioRender.com.

estrogen-sensitive cancer patients displaying good efficacy on urogenital signs and symptoms [39].

Conjugated equine estrogens

Conjugated equine estrogens are a mixture of different metabolites with estrogenic properties exerting positive effects on climacteric symptoms including urogenital health [40]. At present, low-dose conjugated equine estrogen cream (0.625 mg active ingredient/g) is available for use with positive effects on subjective and objective measures of tissue atrophy [41]. Indeed, it increases the vaginal blood flow and improves some domains of sexual function [42].

Estrone

Estrone is a weak estrogen mainly produced by conversion of precursors in peripheral tissues, especially visceral adipose tissues in postmenopausal women [43]. It is available as a vaginal cream at the dose of 1 mg active ingredient/g for short-term use. Estrone treatment induces variable circulating E2 and, therefore, cannot be considered as safe as other low-dose and ultra-low-dose LET [16].

Efficacy and safety

The last Cochrane review in 2016 concluded that approved LETs are all similarly effective in relieving vaginal dryness and dyspareunia, thus the choice should take into account the patient's preference [44]. Side effects are minimal and consist of discharge, mycotic infection, bleeding and breast pain [16,18].

Other systematic reviews [45,46] confirmed that LETs were beneficial compared with placebo with similar efficacy and safety among various formulations. A recent prospective, open-label, randomized, parallel-group study comparing E2 10 µg vaginal tablets and promestriene 10 mg/g vaginal cream demonstrated that both treatments improved the Vaginal Health Index and decreased vaginal pH, but reduction of symptom intensity was greater with E2 [47].

In general, improvement in GSM symptoms occurs within a few weeks and LET shows maximum benefit following 12 weeks [16]. In some women, application of LET should be adjusted according to individual tolerability. Those women with more severe symptoms may benefit from starting with lower doses, eventually in cream or gel formulations, to take advantage of soothing and adhesive properties [16–18]. In addition, cream [48] or gel [37] products may be applied directly to the vulvar and vestibular tissues in order to relieve dyspareunia. LET should be continued for as long as needed to relieve symptoms and, if low/ultra-low doses do not relieve symptoms sufficiently, HCPs may consider increasing the dose or switching to other hormonal or non-hormonal options [16–18].

There are no signals of significant endometrial proliferation with LET [49,50]. Therefore, protection of the endometrium by the use of progestogens is not required [16–18].

Such recommendations are based on safety data from randomized controlled trials that do not exceed 52 weeks [51]. However, a prospective observational cohort study, using data from participants of the Women's Health Initiative Observational Study, showed cardiovascular and oncological neutrality of LET with a 7.2-year median follow-up [51]. That being so, long-term LET safety data are reassuring and HCPs should counsel postmenopausal women on the favorable risk–benefit profile of intravaginal therapies in the management of GSM [52]. It is worth mentioning that the class labeling of all estrogen products is frightening and GSM will be undertreated whilst the black box warning of low-/ultra-low-dose LET will remain the same as for systemic MHT [53]. On the other hand, HCPs should be aware that misuse or overuse of LET, more frequently occurring in the absence of pre-fixed doses, might induce safety concerns and require active surveillance [16]. Special considerations on the role of minimal estrogenic absorption are appropriate for patients with a history of hormone-sensitive malignancies in terms of recurrence risk, particularly BCS, who may present with severe symptoms associated with the use of anti-estrogenic therapies [54]. A recent review underlined the need for further studies in BCS [55] taking into account the strong anti-proliferative effects of aromatase inhibitors on vaginal tissues, which may allow LET systemic absorption [56]. Other populations of postmenopausal women may be not ideal candidates for LET, including those having problems performing vaginal insertion/application [57].

Toward a tailored approach with LET

Communication and education are key factors in overcoming barriers to the treatment of GSM with LET [58]. An open discussion with HCPs increases the use of GSM specific therapies [59], even though compliance remains low according to a recent systematic review [60]. The REVIVE survey conducted both in Europe [61] and in the USA [62] showed fears or dissatisfaction with available LET. Women might be not willing to adhere due to safety issues, concerns over the application procedures or other unwanted side effects, with potential interference in intercourse [63]. On the other hand, women had a poor knowledge of the chronic nature of GSM [12] and eventually discontinued treatments because of too high expectations [60]. Interestingly, the constellation of GSM symptoms are variably overlapping and an appropriate clinical assessment is crucial for an early and individualized therapeutic intervention [64]. Indeed, according to the European Vulvovaginal Epidemiological Survey (EVES), postmenopausal women with GSM receiving a specific treatment for symptom relief complained of more severe symptomatology as compared with those untreated [65], suggesting a possible delay in clinical diagnosis. Treatments might be initiated at any age [18] but in women with very severe symptoms or older than 60 years, efficacy was reduced [66]. In addition, following LET discontinuation, objective VVA/GSM signs mostly deteriorated within approximately 4 weeks, where subjective symptoms recurred within 3–6 months [67].

A critical appraisal of inadequate management of GSM should also include overall efficacy of LET on the constellation of symptoms or specific activities of different products [15], as well as the importance of reconsidering women's needs over time [68]. In postmenopausal women with moderate-severe symptomatology, a double-blind controlled randomized controlled trial over a 12-week study period showed a mild improvement in quality of life and sexual function domain measures with vaginal 10 µg E2 tablet plus placebo gel as compared with vaginal moisturizer plus placebo tablet or dual placebo [69]. Although positive effects of LET on typical signs and symptoms were quite rapid and evident on sexual pain [44], even with low-dose and ultra-low-dose of vaginal soft-gel capsule containing solubilized E2 [70] or ultra-low-dose E2 gel [71], the placebo effect was highly significant in women treated for female sexual dysfunction [72]. In postmenopausal women with pelvic organ prolapse, 6-week use of a cream containing 0.1 mg/g bioidentical E2 did not improve sexual function as compared with placebo [73]. A randomized placebo-controlled study showed that even the preoperative 6-week use of the same LET did not ameliorate prolapse-associated symptoms in postmenopausal women with symptomatic pelvic organ prolapse [74]. Longer follow-up may be needed to observe meaningful clinical results on sexual function [75]. In addition, evaluation of change in the individual most bothersome symptoms over time might be important [76]. When treating lower urinary tract symptoms, evidence of low-dose LET superiority was less robust versus placebo in comparison with vaginal dryness and dyspareunia [44]. However, LETs were associated with fewer episodes of recurrent urinary tract infections [77] and a Cochrane review of studies conducted in postmenopausal patients with different diagnosis of urinary incontinence showed an overall improvement with use of LET [78]. On the other hand, a silicone vaginal ring releasing a daily dose of 7.5 µg for 12 weeks in postmenopausal women with overactive bladder was similarly effective in decreasing the number of daily voids in comparison with a labeled drug such as oral oxybutynin [79]. That being so, the most recent position statement from the North American Menopause Society (NAMS) supported the use of LET in women with concomitant vulvovaginal and urinary symptoms considering evidence-based therapies for lower urinary tract symptoms in absence of a significant improvement following 3 months [16]. Finally, in dealing with symptoms of severe genital involution (i.e. vulvar adhesion), HCPs should consider a preferential prescription of LET in cream formulations [80].

Conclusions

Early LET use, alone or combined with MHT in postmenopausal women with high GSM symptom severity, is of paramount importance in the management of urogenital aging. The quality of life and sexual burden associated with GSM should be prevented with tailored LET depending on the profile of the patient, taking into account preferences and treatment goals. A class effect of LET has been documented over time, but different products may serve specific aims that

still need to be better explored according to age, type and severity of symptoms, and underlying clinical conditions. Poor compliance and treatment adherence are evident in LET users and may arise both from efficacy and safety issues. Based on the multitude of symptoms under the umbrella of GSM definition, it is mandatory to investigate specific effects of LET on quality of life, sexual function and genitourinary conditions conducting studies with a patient-tailored focus.

Potential conflict of interest R. E. Nappi had past financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Ely Lilly, Endoceutics, Merck Sharpe & Dohme, Palatin Technologies, Pfizer Inc., Procter & Gamble Co., TEVA Women's Health Inc. and Zambon SpA; at present, she has an ongoing relationship with Abbott, Astellas, Bayer HealthCare AG, Exceltis, Fidia, Gedeon Richter, HRA Pharma, Novo Nordisk, Organon & Co., Shionogi Limited, Theramex and Viatrix, outside the submitted work. The other authors report no conflicts of interest in this work.

Source of funding Nil.

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