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Topical estrogens and non-hormonal preparations for postmenopausal vulvovaginal atrophy: An EMAS clinical guide

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A B S T R A C T

Introduction: Vulvovaginal atrophy (VVA) is a chronic condition caused by estrogen deficiency. It affects around 50% of postmenopausal women, reducing their general and sexual quality of life as well as the quality of their personal relationships.
Aim: The aim of this clinical guide is to set out an individualized approach to the management of VVA with topical estrogens and non-hormonal preparations.
Materials and methods: Literature review and consensus of expert opinion.
Summary recommendations: An individualized approach is required for the management of VVA. Topical low-dose estrogens are effective and also alleviate urinary incontinence and prevent recurrent urinary tract infections. Women should not be denied long-term use of topical estrogens as long as they feel that this treatment is of benefit to them, because the safety data are reassuring.
Non-hormonal preparations (lubricants and moisturizers) should be the first-line treatment for VVA in women taking adjuvant endocrine therapies for cancers considered to be hormone-dependent. They can be used over the long term.

1. Introduction

Vulvovaginal atrophy (VVA), a component of genitourinary syndrome of menopause (GSM), is caused by estrogen deficiency. It is characterized by symptoms of dryness, burning, itching and dyspareunia [1]. It is well established that it has a negative impact on a woman's general and sexual quality of life as well as the quality of her personal relationships [2]. VVA is also associated with urinary tract problems, such as frequent urination, urge incontinence and recurrent urinary tract infections. GSM includes both genital and urinary symptoms [1]. Here, we focus on genital symptoms and consequently discuss the management of VVA.

Symptoms of VVA are common after the menopause, although they may also occur in pre- and perimenopausal women. Epidemiological data have shown that about 50% of postmenopausal women over 60 years of age experience symptoms of VVA as a natural physiological consequence of hypoestrogenism [3,4]. Premenopausal women may develop local symptoms of hypoestrogenism during lactation [5], and in

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association with hypothalamic amenorrhea and hyperprolactinemia [6]. Furthermore, cancer treatment, including radiation, chemotherapy and adjuvant endocrine therapies such as tamoxifen and aromatase inhibitors, commonly induce symptoms of VVA [7].

The initial diagnosis of VVA is often symptom-based, as clinical examination may be painful. Clinical examination should nevertheless be undertaken if symptoms do not respond to treatment or if there is abnormal bleeding or suspicion of pathology. The clinical signs of VVA include flattening of folds or thinning, dryness, pallor, friability and presence of petechiae of the vaginal mucosa. Vaginal pH greater than 5 and wet mount microscopy showing predominantly immature vaginal epithelial cells (parabasal cells) and a reduced number of lactobacilli support the diagnosis. Differential diagnoses include infection, inflammation, lichen sclerosis and neoplasia [8,9].

The symptoms reported to be most bothersome are vaginal dryness and dyspareunia [10]. In addition, many studies have shown that VVA can have a major impact on interpersonal relationships and quality of life, especially in sexually active women [2,4,11]. However, despite the condition's high prevalence and impact on women's lives, it is under-reported and underdiagnosed, and therefore undertreated or treated late [12,13].

In 2012, EMAS published recommendations regarding the use of low-dose vaginal estrogens for postmenopausal vaginal atrophy [14]. This 2021 clinical guide takes into account the 2012 recommendations and new research, and aims to provide an overview of topical estrogen and non-hormonal treatment options for VVA. However, it does not include topical androgens, ospemifene, oxytocin, laser treatment or complementary and alternative medicines. Specific advice for treatment of women after breast cancer, gynecological cancer and cardiovascular disease is given. Note that the availability of individual preparations discussed in the guide varies worldwide. It must not be forgotten that postmenopausal VVA is a chronic condition and symptoms will recur on cessation of therapy. Thus, a long-term strategy is required, with no arbitrary limits regarding the duration of use of topical therapies. They can be used for as long as the woman feels the benefits outweigh the risks for her. Decisions must be made on an individual basis so that women do not suffer in silence.

2. Methods

A PubMed search was undertaken for English-language publications through to April 11, 2021 using the following search terms: vulvovaginal atrophy, vaginal dryness and dyspareunia in combination with topical estrogen, vaginal estrogen, non-hormonal vaginal treatment, vaginal lubricants and vaginal moisturizers. This strategy was also used for specific patient populations, i.e. breast cancer, endometrial cancer, ovarian cancer, cervical cancer and women at increased risk of venous thrombosis and cardiovascular disease. The literature search focused on systematic reviews and meta-analyses, randomized controlled trials (RCTs) and previous position statements.

3. Topical Estrogens

Topical estrogens have been used for many years. Preparations include: estradiol-containing tablets, rings and capsules; estriol pessaries, creams, gels and ovules; promestriene; and conjugated estrogens. Availability of individual preparations varies worldwide. There is no need to add a progestogen for endometrial protection or to offer routine monitoring of endometrial thickness when low-dose topical estrogens are used [15]. The most common treatment schedule for topical estrogens is a two-week start period with daily administration, followed by twice-weekly administration. The exception is the vaginal ring, which is changed every three months.

In general, once a preparation has been selected that is acceptable to the individual woman, the initial dose offered should be the lowest available; the initial dose may then be changed according to symptom response [15]. With regard to duration of use, recommendations vary between preparations, but vaginal atrophy is a chronic condition and will recur on cessation of treatment. In 2020 the European Medicines Agency limited the use of high-strength creams, defined as containing 100 micrograms/gram (or 200 micrograms per dose) of estradiol, marketed in Europe, to a single treatment period of up to 4 weeks [16]. In contrast, the dose of estrogen in most current licensed vaginal preparations is very low, leading to minimal systemic absorption, with circulating estrogen levels remaining in the postmenopausal range (see below). Of note, the total administered vaginal dose per year of a preparation containing 10 micrograms of estradiol used twice weekly is similar to one single daily dose of systemic oral therapy (i.e., 1 milligram) [17].

As well as increasing the Vaginal Maturation Index score, estrogen lowers vaginal pH, increases subepithelial capillary growth, thickens the epithelium, raises the level of vaginal secretions, increases the transvaginal potential difference and reduces the density of autonomic and sensory vaginal innervations [18].

3.1. Efficacy

Low-dose vaginal estrogens are used alone when VVA is the only symptom of estrogen deficiency. They can be added to systemic menopausal hormone therapy (MHT) if VVA symptoms are uncontrolled by the latter [15].

Efficacy is dose-dependent and in experimental settings estradiol preparations are more potent than those containing estriol [19). However, a Cochrane systematic review of 30 RCTs concluded that there was no evidence of a difference in efficacy between the various intravaginal estrogenic preparations and all preparations improved the symptoms of VVA in postmenopausal women when compared with placebo [20]. In contrast, a 12-week RCT found that neither a 10 microgram vaginal estradiol tablet nor an over-the-counter vaginal moisturizer provided additional benefit over placebo vaginal tablet and gel in reducing postmenopausal vulvovaginal symptoms [21]. The study, however, has been considered to have several limitations, such as small sample size, short duration, study endpoints which excluded dyspareunia and use of a non-conventional placebo gel [22]. The lowest documented doses with proven efficacy are estriol 30 microgram [23] and estradiol 4 microgram [24], both administered twice weekly.

There is also evidence that topical estrogens may improve urinary incontinence and prevent recurrent urinary tract infections [25,26,27,28]. There are insufficient high-quality data to support the use of vaginal estrogens for stress urinary incontinence after the menopause. However, the evidence regarding local estrogens and overactive bladder in postmenopausal women is robust [26,29]. Meta-analysis indicates that the use of a local estrogen in the treatment of urge urinary incontinence and bladder overactivity is both safe and effective. In contrast, systemic MHT seems to worsen urinary incontinence. However, the evidence base consists mainly of large epidemiological studies primarily investigating the use of systemic MHT for the prevention of cardiovascular disease and osteoporosis, with urinary incontinence being investigated as a secondary outcome [25].

3.2. Safety

The rationale for topical administration is to deliver estrogen directly to the target tissue, and to minimize systemic absorption and, thereby, potential adverse effects. Initially, there may be minimal and transient systemic absorption with topical estrogens, as shown by a small increase in serum estrogen levels at the start of administration (when the vaginal lining is atrophic), which then falls to baseline levels as the vaginal mucosa thickens and during maintenance treatment twice weekly [24,30]. Absorption is dose-dependent, and for estriol products there is no conversion to the more potent estrogens, estradiol or estrone [19]. During this period, side-effects may occur, such as breast tenderness and

increased vaginal discharge, but vaginal bleeding is rare. Topical estrogen may also be associated with a greater frequency of vulvovaginal mycotic infections [17,31].

With regard to safety, the Nurses' Health Study found that over 18 years of follow-up, after adjusting for covariates, the risks of cardiovascular disease, cancer and hip fracture were no different between users (n=896) and non-users (n=52901) of vaginal estrogen [32]. Other large observational studies and meta-analyses (detailed below) have been similarly reassuring with regard to cancer, cardiovascular disease and venous thromboembolism, but there have been no RCTs to date.

3.2.1. Risk of endometrial cancer

Although long-term clinical trial data (i.e., beyond one year) are lacking, there is no evidence of an increased risk of endometrial cancer with low-dose topical estrogens, which confirms that concomitant progestogens are not needed [33]. Recent systematic reviews based on both RCTs and observational studies confirm the endometrial safety of topical estradiol for up to 52 weeks of follow-up [34,35]. Likewise, a systematic review of topical estriol used for up to 52 weeks (0.5-1 milligrams per dose) [36] and a 30-week study with an ultra-low-dose estriol vaginal gel (30 micrograms per dose) [37] showed no treatment-related serious endometrial adverse events. Longer observational follow-up data, for example from the Women's Health Initiative Observational Study (45 663 women, median follow-up 7.2 years), also confirm endometrial safety, as no elevated risk was reported of endometrial cancer among vaginal estrogen users compared with non-users [38]. This was also found in the Nurses' Health Study, with 18 years of follow-up [32]. However, unscheduled vaginal bleeding in postmenopausal women treated with topical estrogen should always be investigated [15].

3.2.2. Risk of breast cancer

Large observational studies have shown no increased cancer risk in topical estrogen users compared with non-users. The Nurses' Health Study and the Women's Health Initiative Observational Study showed no increased risk of breast cancer with vaginal estrogen [32,38]. A meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (2019) based on 58 studies involving 568,814 women found no increased risk of breast cancer with vaginal estrogens [39].

3.2.3. Risk of venous thromboembolism and cardiovascular disease

Topical estrogen use is not associated with an increased risk of venous thromboembolism or cardiovascular disease as evidenced by observational data. Thus, the 2016 Cochrane review reported no increased risk of venous thromboembolism [20]. Furthermore, large observational studies such as the Nurses' Health Study, Women's Health Initiative and UK general practice databases [32,38,40] and a systematic review [35] showed no increased risk of venous thrombosis. The Women's Health Initiative Observational Study also found that topical estrogen users had a lower risk of coronary heart disease after adjustments for covariates [38]. Furthermore, a Finnish nationwide cohort study also showed reduced risk of cardiovascular mortality with vaginal estrogen [41]. However, in the Nurses' Health Study, users of vaginal estrogen had similar risks to non-users of all major cardiovascular outcomes [32]. So far, no clinical trial has addressed the effect of vaginal estrogen on cardiovascular events.

4. Non-Hormonal Lubricants and Moisturizers

Some women are unable to use topical estrogens, such as those taking adjuvant endocrine therapies for cancers considered to be hormone- dependent. Others may be reluctant to use estrogens or other hormone-based products. For these women, non-hormonal vaginal lubricants and moisturizers are an option. Lubricants are typically used episodically to correspond to sexual activity. They may be water, oil, silicone or hyaluronic acid based, and may also contain other ingredients, such as sea buckthorn oil, aloe vera and 18β-glycyrrhetic acid [42]. Lubricants, in general, give only temporary relief of symptoms; they must be applied frequently for more continuous relief and require reapplication before intercourse. Moisturizers are usually used on a regular basis, rather than episodically in association with sexual activity. They may contain a bioadhesive polycarbophil-based polymer, which attaches to mucin and epithelial cells on the vaginal wall and retains water. There is currently no evidence to contraindicate the use of lubricants and moisturizers by women taking either systemic or topical estrogens[15]. However, interactions with other locally applied vaginal treatments should be considered [17].

4.1. Efficacy

Vaginal lubricants and moisturizers improve mild to moderate symptoms of vaginal dryness and dyspareunia, although few large long-term studies have evaluated their efficacy [43]. However, there is no evidence to date that they improve urinary incontinence or prevent urinary tract infections. A randomized, double-blind study found that the use of lubricants was associated with higher ratings of sexual pleasure and satisfaction compared with no use [44]. The same study also showed that water-based lubricants were associated with fewer genital symptoms than silicone-based lubricants [44].

A 12-week RCT tested a lactate-containing gel (to maintain vaginal pH at about 4) in breast cancer survivors. Vaginal dryness and dyspareunia improved more in the lactate gel group than in the placebo group [45]. Furthermore, vaginal pH was reduced, and score on the Vaginal Maturation Index was increased. While vulvovaginal irritation and burning sensation were significantly more prevalent in the lactate gel group, all adverse events were mild or moderate in severity.

A non-randomized, single-arm study evaluated the efficacy and safety of hyaluronate-based vaginal pessaries for 12 weeks of treatment of VVA in 40 postmenopausal women [46]. The treatment showed improvements in both symptoms and signs of VVA without any severe adverse events.

Short-term RCTs have compared hyaluronic acid-based and estrogen-based products. One trial comparing the effect of hyaluronic acid vaginal tablets with estradiol vaginal tablets (25 micrograms per dose) for 8 weeks found that hyaluronic acid was better than no treatment but inferior to estradiol [47]. Similarly, Chen et al (2013) compared the efficacy and safety of a hyaluronic acid vaginal gel and a estriol cream (0.5 milligrams estriol per dose) in postmenopausal women in a 30-day randomized open-label study [48]. Both treatments improved symptoms of vaginal dryness, with no significant difference between the groups. Improvement rates were 84.44% and 89.42% in the hyaluronic acid gel and estriol cream groups respectively.

A systematic review with evidence from clinical trials as well as from prospective observational studies concluded that vaginal estrogen therapy is superior to non-hormonal treatments in improving symptoms of VVA [49]. There is a need for large randomized long-term studies.

4.2. Safety

Lubricants and moisturizers can in some cases cause vaginal irritation and increase susceptibility to infections such as candida and bacterial vaginosis [43]. Products differ in terms of their composition, osmolality and pH, and there are concerns about potential adverse effects on vaginal mucosal epithelial cells observed mainly with *in vitro* or animal models [50]. Furthermore, lubricants such as petroleum-based products and baby oil, can compromise the integrity of condoms. This is important when condoms are used for contraception and/or to prevent sexually transmitted infections [51]. There is a need for large long-term observational and/or randomized trial data similar to those available for topical estrogens.

5. Topical Therapies in Women Living with and Beyond Breast and Gynecological Cancer

5.1. Breast cancer

Vaginal dryness and other symptoms of VVA are commonly reported by women receiving adjuvant endocrine treatment and/or chemotherapy for breast cancer. It has been reported to affect 50-75% of such women [52]. Aromatase inhibitors are associated with more severe symptoms of VVA than tamoxifen; they can cause dyspareunia, difficulty with lubrication and urinary tract problems, and have a negative effect on quality of life [52]. The standard duration of treatment with aromatase inhibitors is five years; however, recently it was reported that extending treatment to 10 years prolongs survival compared with placebo [53].

Non-hormonal lubricants and moisturizers should be considered the first-line treatment because of concerns regarding systemic absorption from topical estrogen preparations [54,55]. Higher absorption was reported with higher vaginal estradiol doses (25 micrograms, 10 micrograms) than with the lowest available dose (4 micrograms) [54]. A study by Kendall et al examined the use of 25 micrograms [55]. Absorption is greater if the estrogen product is deposited higher in the vagina [54]. However, a meta-analysis of 11 studies concluded that vaginal estrogen administration in postmenopausal women with a history of breast cancer is not associated with systemic absorption of sex hormones after 8 weeks of treatment [56]. The preparations considered in the meta-analysis contained estradiol, estriol or testosterone. Furthermore, the Blissafe study in women taking aromatase inhibitors randomized to either vaginal estriol (0.005% estriol, 50 micrograms/application) or placebo for 12 weeks showed symptom benefit and no significant effect on gonadotropins, estradiol or estrone levels [57,58]. Gel was applied once daily for the first 3 weeks and then twice weekly for weeks 4 to 12. Women receiving 0.005% estriol vaginal gel had slightly increased estriol levels at weeks 1 and 3, with a subsequent reduction until normalizing at week 12; estradiol and estrone remained below the limit of quantitation in almost all samples [58].

With regard to recurrence, a nested case-control study using the United Kingdom General Practice Research Database found that, after 3.5 years of follow-up, treatment with a topical estrogen was not associated with an increase in breast cancer recurrence among women taking aromatase inhibitors or tamoxifen [59]. The cohort included women newly diagnosed with breast cancer who received at least one aromatase or tamoxifen prescription between January 1, 1998 and June 30, 2008. A total of 13,479 women were included in the study, of whom 2,673 received aromatase inhibitors and 10,806 received tamoxifen; a total of 271 of these women also received topical estrogen creams and tablets.

Thus, when non-hormonal products are ineffective, topical estrogen could be considered, but safety data are limited in breast cancer survivors. The less potent estrogen estriol could be preferred to estradiol, and the lowest available doses should be used. Individual decisions should be made in collaboration with the woman's oncologist and take into account uncertainties and whether benefits outweigh the risks for her.

5.2. Gynecological cancer

Management needs to be individualized, taking into account tumor type, stage and hormone dependence [60,61].

5.2.1. Endometrial cancer and uterine sarcomas

While most cases of endometrial cancer are diagnosed after the menopause, it can occur in younger women, such as those with Lynch syndrome or polycystic ovary syndrome or who are obese. The majority of endometrial cancers are diagnosed at an early stage (Federation of Gynecology and Obstetrics (FIGO) stage I–II) and so have a good overall prognosis, with a 5-year survival rate of over 85% [60]. Treatment usually involves hysterectomy and bilateral oophorectomy and/or radiation therapy, and may affect sexual function [62].

Although data are limited, there is no evidence of increased risk of endometrial cancer recurrence with topical estrogen [60,63]. In contrast, uterine sarcomas may be hormone dependent but there are no clinical trial data to inform practice in women whose tumors are steroid receptor negative [60].

5.2.2. Ovarian, fallopian tube and peritoneal cancers

The three major types of ovarian cancer are epithelial (accounting for 90% of cases), germ cell (3%) and sex cord-stromal (2%). As fallopian tube cancer, primary peritoneal cancer and epithelial ovarian cancer share the same genomic signature, the three are considered together. About 20% of women will be premenopausal at the time of diagnosis. Treatment usually involves hysterectomy and bilateral salpingo-oophorectomy, chemotherapy and radiotherapy. In general, estrogen administration does not appear to be associated with harm and does not appear to decrease overall or disease-free survival in women with non-serous epithelial ovarian cancer and germ cell tumors, although the evidence is limited [60]. Caution is required in women with serous and granulosa cell tumors because of their hormone dependence [64].

5.2.3. Cervical, vaginal and vulvar cancers

Given that none of these cancers are considered to be hormone dependent, there is no evidence to contraindicate the use of topical estrogen. As with endometrial cancer, sexual function may be impaired after surgery [65,66]. However, estrogen receptors are frequently (39%) expressed in cervical adenocarcinomas, even though their expression does not correlate with clinicopathological parameters and does not influence overall and disease-free survival [67,68]. In the limited studies available, no significant difference in recurrence rate or survival [60] has been linked with estrogen use after treatment for cervical squamous cell carcinomas. Currently no safety data are available in women exposed to diethylstilbestrol *in utero*, which is associated with an increased risk of clear cell cancers of the vagina and cervix [69].

6. Conclusion

An individualized approach is required for the management of VVA. Both low-dose topical estrogen and non-hormonal preparations are available. The latter should be the first-line treatment of VVA in women taking adjuvant endocrine therapies for cancers considered to be hormone-dependent. Postmenopausal VVA is a chronic condition and symptoms will recur on cessation of therapy. Women should not be denied long-term use of topical estrogens as long as they feel that this treatment is of benefit to them, as the safety data are reassuring. Topical estrogens not only improve symptoms of VVA but also are effective in alleviating urinary incontinence and recurrent urinary tract infections.

Contributors

Angelica Lindén Hirschberg prepared the initial draft, which was circulated to all other named authors for comment and approval; production was coordinated by Margaret Rees and Irene Lambrinoudaki.

Conflict of interest

1. Angelica Lindén Hirschberg in the past 3 years has received grant support from ITF Research Pharma for the Blissafe study

2. Johannes Bitzer in the past 3 years has served on advisory boards of Bayer AG, Merck, MSD, Teva, Theramex, Mithra, Actavis, Ava, Natural cycles, Böhringer Ingelheim, Effik, Lilly, Exeltis, Vifor, Libbs, Gedeon Richter and HRA; and has given invited lectures and received honoraria by Bayer Pharma AG, Merck, Johnson and Johnson, Teva, Mylan, Allergan, Abbott, Lilly, Pfizer, Exeltis, Libbs, HRA and Pierre Fabre.

3. Antonio Cano has received in the past three years consulting fees from Pierre-Fabre Iberica and Mitsubishi Tanabe Pharma; and speakers' honoraria from Shionogi.

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