



## EMAS clinical guide: Low-dose vaginal estrogens for postmenopausal vaginal atrophy

Margaret Rees<sup>a</sup>, Faustino R. Pérez-López<sup>b</sup>, Iuliana Ceasu<sup>c,d</sup>, Herman Depypere<sup>e</sup>, Tamer Erel<sup>f</sup>, Irene Lambrinou<sup>g</sup>, Karin Schenck-Gustafsson<sup>h</sup>, Tommaso Simoncini<sup>i</sup>, Yvonne T. van der Schouw<sup>j</sup>, Florence Tremollieres<sup>k,\*</sup>

<sup>a</sup> Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

<sup>b</sup> Department of Obstetrics and Gynecology, Universidad de Zaragoza, Facultad de Medicina, Hospital Clínico, Zaragoza, Spain

<sup>c</sup> Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania

<sup>d</sup> Department of Obstetrics and Gynecology, 'Dr. I. Cantacuzino' Hospital, Bucharest, Romania

<sup>e</sup> Breast Clinic and Menopause Clinic, University Hospital, De Pintelaan 185, 9000 Gent, Belgium

<sup>f</sup> Department of Obstetrics and Gynecology, Istanbul University, Cerrahpasa School of Medicine, Valikonagi Cad. No 93/4, Nisantasi, 34365 Istanbul, Turkey

<sup>g</sup> 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieio Hospital, GR-11528 Athens, Greece

<sup>h</sup> Department of reproductive medicine and Child Development, University of Pisa, Via Roma, 67, 56100 Pisa, Italy

<sup>i</sup> Department of Medicine, Cardiology Unit and Head Centre for Gender Medicine, Karolinska Institutet and Karolinska University Hospital, Thorax N3:06, SE 17176 Stockholm, Sweden

<sup>j</sup> Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>k</sup> Menopause and Metabolic Bone Disease Unit, Hôpital Paule de Viguier, F-31059 Toulouse cedex 09, France

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### ABSTRACT

Vaginal atrophy is common in postmenopausal women. This clinical guide provides the evidence for the clinical use of vaginal estrogens for this condition focussing on publications since the 2006 Cochrane systematic review. Use after breast cancer, before assessment of cervical cytology and prolapse surgery is also discussed.

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### 1. Introduction

Vaginal atrophy is common in postmenopausal women and adversely affects quality of life. Thus a cross-sectional analysis based on 98,705 women enrolled in the Women's Health Initiative studies between 1993 and 1997 using a self administered questionnaire found the following prevalence rates: 27.0%; irritation or itching, 18.6%; discharge, 11.1%; and dysuria, 5.2% [1].

The 'women's voices in the menopause' web based survey undertaken in 2009 in 4246 women aged 55–65 years living in Sweden, Finland, the United Kingdom, the United States and Canada reported higher rates with variation between countries [2]. Thus 39% of the postmenopausal women had experienced vaginal atrophy, with the prevalence varying from 34% in Canada to 43% in Finland and the United States. Attitudes towards symptoms also varied between countries. Symptoms were described as moderate

or severe by less than half of women from Finland and Sweden, compared with nearly two-thirds of women from the United States. However, vaginal atrophy was deemed to impact on quality of life by a higher proportion of women in Finland and Sweden ( $\geq 60\%$ ) than in the United Kingdom, the United States and Canada ( $\leq 50\%$ ).

Vaginal estrogens have been used for many years. Preparations include estradiol-containing tablets and rings; estriol pessaries, creams and ovules; promestriene and conjugated estrogens. As well as increasing the Vaginal Maturation Index, oestrogen lowers vaginal pH, increases subepithelial capillary growth, thickens the epithelium, raises the level of vaginal secretions, increases the transvaginal potential difference and reduces autonomic and sensory vaginal innervations density [3,4].

In 2006, a Cochrane systematic review [5] identified 19 good quality trials with 4162 women from a total of 37 trials. When comparing the efficacy of different estrogenic preparations (creams, pessaries, tablets and the estradiol-releasing vaginal ring) in relieving the symptoms of vaginal atrophy, results indicated significant findings favouring the cream, ring, and tablets when compared to placebo and non-hormonal gel. With regard to safety one trial

\* Corresponding author. Tel.: +33 567 771 185; fax: +33 567 771 184.

E-mail address: [tremollieres.f@chu-toulouse.fr](mailto:tremollieres.f@chu-toulouse.fr) (F. Tremollieres).

showed significant adverse effects of the cream (conjugated equine oestrogen) when compared to tablets (estradiol) which included uterine bleeding, breast pain and perineal pain (1 RCT; OR 0.18, 95% CI 0.07–0.50). Two trials showed significant endometrial overstimulation as evaluated by a progestogen challenge test with conjugated equine oestrogen cream when compared to the ring (OR 0.29, 95% CI 0.11–0.78). Although not statistically significant there was a 2% incidence of simple hyperplasia with the estradiol ring when compared to conjugated equine oestrogen cream and 4% incidence of hyperplasia (one simple, one complex) with conjugated equine oestrogen cream when compared to the estradiol tablet.

This guidance aims to summarise publications on topical estrogens since the 2006 Cochrane systematic review [5] as new preparations with lower doses have been evaluated and become available. Use after breast cancer, before assessment of cervical cytology and prolapse surgery is also discussed.

## 2. Estradiol

Twenty five microgram tablets were first introduced in 1988 and in 2009 the Food and Drug Administration (FDA) approved a 10 mcg dose formulation. Efficacy and safety have been assessed in three studies. A double-blind, parallel-group study, multi centre study undertaken in the USA randomised 230 postmenopausal women to 25 mcg or 10 mcg estradiol (E2) or placebo for 12 weeks [6]. The primary efficacy endpoint was the change in the composite score of three vaginal symptoms (dryness, soreness, and irritation). After 12 weeks, all women were switched to the open-label extension and received treatment with 25 mcg E2 up to a year. Both doses significantly relieved vaginal symptoms and efficacy was maintained in the open label extension study. While both doses were effective in the treatment of atrophic vaginitis, improvements were greater with 25 mcg than with 10 mcg E2.

This was followed by a study undertaken in the USA and Canada where 309 postmenopausal women ( $N=309$ ) were randomly assigned to 10 mcg E2 or placebo vaginal tablets for 52 weeks in a multicenter, double-blind study [7]. After 12 weeks the 10 mcg tablet significantly improved vaginal cytology and pH and the most bothersome urogenital symptoms score, and treatment effects were maintained at 52 weeks. One endometrial adenocarcinoma stage II, grade 2 was found in the active treatment group. However, as the baseline biopsy showed no tissue in that individual, it is uncertain whether there was a pre-existing tumour at trial entry. Furthermore she had a previous history of using a systemic unopposed oestrogen and methyltestosterone combination for approximately 2 years for hot flushes. Also one case of complex hyperplasia without atypia was diagnosed in a participant who discontinued the study prematurely after 9 days of trial drug exposure.

A European study treated 336 postmenopausal women with 10 mcg E2 for one year and endometrial histology was analysed at the start and the end of the study [8]. No cases of endometrial hyperplasia or cancer were detected.

An analysis of endometrial histology was undertaken combining the two one year studies [7–9]. Both trials generated a combined 10- $\mu$ g E2-treated population of 541 individuals and 443 women had a biopsy performed at week 52: 85.6% were categorised as “atrophic endometrium”, 12.6% had non-evaluable biopsy samples, 1.1% had polyps, and 0.2% were categorised as “weakly proliferative”. Thus the incidence rate of hyperplasia and carcinoma in two women with a total of 386 evaluable biopsy samples was 0.52% per year and is not increased compared to baseline [10].

With regard to estradiol absorption a 12 week pharmacokinetic study in postmenopausal women and levels quantified by gas

chromatography mass spectrometry found that 10 mcg tablets resulted in at least 50% lower mean E2 concentrations than with the 25 mcg dose within 24 h after dosing [11]. The 25 mcg but not the 10 mcg dose resulted in mean E2 levels exceeding the published reference range for postmenopausal women. Thus estradiol absorption is lower with 10 mcg tablets.

## 3. Estriol

Estriol preparations (pessaries, creams and ovules) containing a dose of 0.5 mg are available for the treatment of vaginal atrophy. A 12 week multicenter, randomised, placebo-controlled, double-blind study evaluated lower doses [12]. Thus 436 postmenopausal women with vaginal atrophy were treated with pessaries containing either 0.2 mg estriol ( $N=142$ ) or 0.03 mg estriol ( $N=147$ ) or a matching placebo ( $N=147$ ) for 12 weeks. Both doses were significantly more effective than placebo.

With regard to combined preparations, an uncontrolled study of 19 women evaluated the use of vaginal suppositories containing estriol (1 mg) and progesterone (30 mg) over 6 months [13]. The Vaginal Maturation Index, vaginal pH, and vaginal dryness rating improved significantly at 3 and 6 months compared with baseline and there were no cases of endometrial hyperplasia.

## 4. Promestriene

Promestriene is a diethyl-ether of estradiol available as a vaginal cream or ovule. In several small open-label studies, it was shown to significantly improve vulvovaginal trophicity and related symptoms in both naturally and surgically menopausal women with minimal absorption [14]. A study of 17 women treated for gynaecological cancer given promestriene 10 mg vaginal suppository for a month found that levels of circulating estrone sulfate were not significantly affected overall, but a wide range was noted pre and post treatment in individual patients [15].

## 5. Synthetic conjugated estrogens

A vaginal cream containing plant-derived synthetic conjugated oestrogen A has been evaluated in a randomised placebo controlled study involving 305 women for 12 weeks [16]. Synthetic conjugated estrogens A contains nine synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17 $\alpha$ -dihydroequilin sulfate, sodium 17 $\alpha$ -estradiol sulfate, sodium 17 $\beta$ -dihydroequilin sulfate, sodium 17 $\alpha$ -dihydroequilenin sulfate, sodium 17 $\beta$ -dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17 $\beta$ -estradiol sulfate. The active cream was significantly more effective than placebo and the preparation was approved by the FDA in 2008.

## 6. Topical estrogens after breast cancer

Vaginal dryness is commonly reported in women receiving adjuvant endocrine and chemotherapy for breast cancer [17]. While topical estrogens are effective there are safety concerns in postmenopausal women taking adjuvant aromatase inhibitors because of systemic absorption [18]. Thus a study in 7 postmenopausal women using aromatase inhibitors and estradiol 25 mcg tablets found that serum estradiol levels rose from baseline levels  $\leq 5$  pmol/l consistent with aromatase inhibitor therapy to a mean 72 pmol/l at 2 weeks. By 4 weeks this had decreased to 35 pmol/l in the majority (median 16 pmol/l) although significant further rises were seen in two women [19]. Vaginal estriol and lower doses of estradiol (12.5 mcg) seem to result in lower serum levels [20]. Of note these studies were of short duration with

a limited sample size and no long-term safety data are currently available. Data with low dose oestrogen are scant. However, in view of these concerns, nonhormonal lubricants and moisturisers should be considered first line [21–24].

## 7. Topical estrogens and cervical cytology after the menopause

Taking cervical smears (Pap test) after the menopause may not only cause pain and discomfort but also lead to an unsatisfactory for assessment or result in a false-positive diagnosis of a cytological abnormality. This open labelled randomised controlled trial in 154 women examined (1) a regimen of one 25 mcg vaginal estradiol tablet inserted nightly for five nights before the Pap test, (2) a single 25 mcg vaginal estradiol tablet before the test, or (3) a control group with no previous oestrogen administration [25]. The odds of an atrophic smear were significantly lower in women who used the five-night oestrogen regimen than in women who did not use oestrogen. Using one tablet of oestrogen had no significant effect on the likelihood of an atrophic smear compared with using none. While not universal for all vaginal oestrogen preparations, in some countries one of the indications for topical estriol includes prior to taking cervical smears [26]. Topical estrogens may also be helpful before colposcopy [27]. However, data with low dose estrogens are scant.

## 8. Topical estrogens and surgery for prolapse

While topical estrogens are used in postmenopausal women before vaginal surgery for prolapse when there is epithelial atrophy [28], the data are limited. Thus a Cochrane systematic review found no evidence to show whether or not this is beneficial (e.g. by reducing tearing and bleeding during surgery, avoiding the need for blood transfusion, improving tissue healing and/or facilitating and hastening post-operative recovery) [29]. Another Cochrane systematic review found limited evidence that local oestrogen in conjunction with pelvic floor muscle training for three weeks before surgery may reduce the incidence of post-operative cystitis [30]. Rigorous randomised controlled trials are required with low dose oestrogen.

## 9. Conclusion

Since the 2006 Cochrane review lower dose vaginal preparations have been evaluated with the aim to reduce side effects but maintain efficacy. They have been studied in healthy postmenopausal women but not in breast cancer survivors. With regard to duration of use, recommendation vary between preparations, but vaginal atrophy is a chronic condition and will recur on cessation of treatment. Thus annual review would be prudent.

## 10. Summary

- Symptoms of urogenital atrophy are common and can adversely affect quality of life.
- Low dose vaginal estrogens are effective.
- There is no need for added progestogens for endometrial protection if topical estrogens are used in the recommended doses.
- There are safety concerns about topical estrogens in postmenopausal women taking adjuvant aromatase inhibitors because of systemic absorption and nonhormonal lubricants and moisturisers should be considered first line.
- Short term topical estrogens may help in assessing cervical cytology, but the data are limited and evidence with low dose preparations is required.

- Randomised controlled trials are required to assess use of topical estrogens before pelvic floor surgery for prolapse with low dose oestrogen.

## Provenance and peer review

EMAS clinical guide.

## Contributors

MR prepared the initial draft which was circulated to all EMAS board members for comment and approval, production was coordinated by MR, FRPL and FT.

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