

Safety of vaginal oestrogen in postmenopausal women

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The vaginal delivery of oestrogen has a number of benefits including enhancement of the efficacy of treatment of urogenital symptoms and avoidance of the need for daily dosage of systemic hormone replacement therapy (HRT). Despite the undoubted benefits of vaginal unopposed oestrogenic preparations there have been concerns regarding safety, particularly with regards to endometrial hyperplasia. These concerns arose mainly from the use of high-dose synthetic oestrogen preparations used in the past for local relief of urogenital atrophy. The newer estriol and estradiol-containing vaginal hormone therapies are safe for short-term use. However, the majority of these preparations are only licensed for 3–6 months of continual use in the UK. Although observational data exist suggesting safety for long-term use, randomised prospective studies are required to confirm this. The purpose of this article is to review the spectrum of vaginal oestrogen-releasing preparations used in postmenopausal women.

Introduction

The vagina has been identified as a drug absorption area since the early 1900s.¹ Vaginal administration of oestrogen is commonly used in postmenopausal women to improve the quality of the vaginal epithelium in atrophic vaginitis.² Fifteen percent of pre-menopausal women, 10–40% of postmenopausal women and 10–25% of women receiving systemic hormone therapy experience urogenital atrophy. The most common symptoms that are relieved by vaginal oestrogen are vaginal dryness, burning, pruritus, irritation and dyspareunia.³ Limited evidence exists to show that there may be protection against recurrent urinary tract infections.

This article reviews the spectrum of vaginal oestrogen-releasing preparations in postmenopausal women. Particular emphasis is placed on safety aspects in view of the concerns raised regarding endometrial hyperplasia and potential systemic absorption in individuals for whom oestrogen would otherwise be contraindicated.

Vaginal oestrogen preparations

Oestrogenic preparations administered vaginally have traditionally been oestrogen-based vaginal creams and pessaries containing estriol. More recently, a slow release, low-dose 17 β -estradiol tablet (Vagifem[®], Novo Nordisk, Crawley, West

Sussex; 25 μ g/day) has been developed to improve safety and convenience of use.⁴ Menopausal vaginal rings provide a further option for low-dose delivery of oestrogen to the vagina (Estring[®], Pharmacia, Walton-on-the-Hill, Surrey; 2 mg 17 β -estradiol, 7.5 μ g/24 hours). All these preparations work directly on the oestrogen-sensitive tissues of the lower genitourinary tract, relieving the symptoms of local urogenital atrophy. A higher dose vaginal ring for use in women who have had a hysterectomy is now available (Menoring[®], Galen, Craigavon, Northern Ireland; estradiol acetate, 50 μ g /24 hours) for systemic as well as local hormone replacement therapy (HRT).⁵ If the latter is used in women who have not had a hysterectomy it is advisable that progestogen opposition is added. A combined systemic ring is in development but is not yet licensed.

Vaginal oestrogen studies

Endometrial safety: reviews

Although it is commonly believed that low doses of vaginal oestrogen are without adverse effects on the endometrium, there is actually little long-term evidence to support this.² Pharmacokinetic studies have shown that lower doses are required vaginally to produce the same plasma concentrations as oral oestrogen due to the avoidance of first pass

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metabolism. This has led to concern that continuous use of low-dose vaginal oestrogen preparations could result in circulating oestrogen levels that can be sufficient to stimulate the endometrium in women with a uterus.

Systemic absorption of some local oestrogen preparations has been supported by the observation that breast tenderness occurs among some users of vaginal oestrogen. Data from four studies quoted in a 2003 review² have shown that small increases in serum estradiol were reported with various regimens of vaginal estriol or conjugated equine oestrogen cream, but not with vaginal estradiol tablets or low-dose oestrogen rings. However, the review stated that the results from seven clinical and epidemiological studies did not show an increase in relative risk for endometrial cancer or atypical endometrial hyperplasia. Endometrial hyperplasia (without atypia) was reported in some of the studies, but the findings were hampered by the fact that, in many cases, long-term treatment doses were used, rather than the maintenance doses usually used in clinical practice. It is, therefore, suggested that if vaginal oestrogen is to be used over a longer period of time, one should choose estradiol tablets or a low-dose oestrogen ring, as these are associated with endometrial safety data of the longest duration and do not lead to increased serum estradiol levels.

The 2003 Cochrane systematic review⁴ on local oestrogen treatment looked at 16 trials with 2129 women. The objective was to compare the effectiveness, safety and acceptability of oestrogenic preparations for women who suffer from vaginal atrophy. Fourteen trials compared safety. Four looked at hyperplasia, four looked at endometrial overstimulation and six looked at adverse effects. One trial showed significant adverse effects of cream (conjugated equine oestrogen) when compared with tablets (estradiol), which included uterine bleeding, breast pain and perineal pain (odds ratio [OR] 0.18, 95% CI 0.07–0.50). Two trials showed significant endometrial stimulation as evaluated by a positive progestogen challenge test in the cream (conjugated equine oestrogen) group when compared with the 17 β -estradiol ring (OR 0.29, 95% CI 0.11–0.78). In one study, a 4% incidence of hyperplasia (one simple, one complex) was detected in the Premarin[®] (Wyeth, Maidenhead, Berkshire) cream (conjugated equine oestrogen) group when compared with the estradiol vaginal tablet. The review concluded that vaginal creams, pessaries, tablets and the estradiol vaginal ring appeared to be equally effective for the symptomatic relief of vaginal atrophy but that the estradiol vaginal ring and tablets were the treatment of choice from a risk benefit point of view.

In a review of the low-dose vaginal oestrogen ring (Estring, 2 mg 17 β -estradiol), comparative clinical trials were said to have demonstrated no major adverse effects or endometrial proliferation during treatment. The sustained low-dose oestrogen therapy was found to improve the serum lipid profile in elderly women.⁶ One study⁷ compared the effects of the vaginal oestrogen ring plus an oral progestogen (medroxyprogesterone acetate) with an intrauterine device releasing levonorgestrel plus 50 μ g transdermal estradiol in 56 postmenopausal women with urogenital symptoms. The mean endometrial thickness before treatment was similar for both groups and was not significantly different from the endometrial thickness after treatment. Endometrial proliferation was not observed. The urogenital symptoms of all 56 women disappeared. After three months of treatment, vaginal bleeding patterns were similar in both groups.

Endometrial safety: clinical practice

In clinical practice, modern locally applied oestrogens for urogenital atrophy appear to be safe in the short term. In the UK, vaginal creams, tablets and pessaries are licensed for 3–6 months of continuous application and the low-dose oestrogen vaginal ring for two years. The problem is that the majority of women will have their symptoms return when therapy is discontinued; benefits only last as long as the treatment. Most menopause specialists will therefore continue unopposed local therapy indefinitely for their patients because it appears that long-term use is safe. However, a few may give a progestogen challenge at 6 or 12 months; for example, medroxyprogesterone acetate 5 mg twice daily for five days. If this is followed by a withdrawal bleed, treatment should be stopped and the bleeding should be investigated further.

Although observational data show that there does not appear to be a significant endometrial risk from long-term vaginal estradiol and estriol use, randomised prospective data are needed to confirm this. However, even if a small endometrial risk existed and progestogen opposition was contemplated, this would need to be balanced against the potential adverse effects⁸ and possible breast cancer risks of progestogens, implicated in the Women's Health Initiative and Million Women studies.^{9–10}

Breast cancer safety

A large cohort study¹¹ of 1472 Australian women estimated the risk of recurrence of breast cancer associated with the use of topical vaginal oestrogen therapy in the management of vaginal

atrophy in women previously treated for breast cancer. In 69 (4.7%) of these women vaginal symptoms were their only menopausal problem and, therefore, poorly absorbed vaginal oestrogen creams or tablets were used. The women who used a topical oestrogen alone for menopausal symptoms had an uncorrected hazard ratio of 0.30 (95% CI 0.11–0.80, $P = 0.02$) for breast cancer recurrence. The corrected hazard ratio was 0.57 (95% CI 0.20–1.58, $P = 0.28$). Although the numbers using topical oestrogen in the study were small, the authors concluded that topical oestrogen did not appear to be associated with an increased risk of recurrence of breast cancer.

It is also encouraging that the results of the 2004 unopposed oestrogen arm of the Women's Health Initiative study¹² did not demonstrate an excessive risk for breast cancer. By extrapolation, one would not expect the very low systemic levels of oestrogen produced by vaginal preparations to have a significant effect on breast cancer risk.

Venous thromboembolic safety

There is an absence of specific data concerning local vaginal oestrogen preparations and venous thromboembolic risk. A case control study¹³ has suggested that non-oral systemic oestrogen is safer than oral oestrogen. These data need confirmation but if proven to be correct they suggest that the very low systemic oestrogen levels generated by vaginal oestrogen preparations should be safe from the point of view of venous thromboembolic risk. Thus, local preparations could safely provide an option for treating urogenital atrophy even in women with a personal or family history of venous thromboembolism. Caution should, of course, be exercised and the pros and cons carefully weighed up in the absence of better data.

Comparative studies of vaginal oestrogen

Vaginal ring versus tibolone

A comparative study¹⁴ of an estradiol vaginal ring versus tibolone in 72 postmenopausal women evaluated the endometrial blood flow characteristics of treatments using transvaginal colour Doppler ultrasound examinations and plasma estradiol levels. The data observed suggested that both the oestrogen vaginal ring and tibolone modify normal postmenopausal endometrial perfusion. Tibolone had a weaker oestrogenic effect on endometrial blood flow resistance and vaginal ring treatment enhanced endometrial blood perfusion.

Vaginal cream versus Replens

The effects of Replens® (Lil' Drug Store Products, Inc., Cedar Rapids, IA), a non-hormonal moisturising vaginal gel, was evaluated on symptoms of vaginal atrophy in postmenopausal women, in comparison with Dienoestrol, a synthetic oestrogenic vaginal cream which has now been withdrawn.¹⁵ No adverse events in relation to the two drugs were found. All symptoms such as itching, irritation and dyspareunia significantly decreased or disappeared without any significant difference between the two treatments. This study suggests that in women wishing to avoid hormonal therapy entirely, Replens is a reasonable alternative for local symptom relief.

Combination vaginal regimens

Systemic oestrogen and progesterone ring

Two small studies evaluated the effects of two variants of combined vaginal rings on the endometrium and vasomotor symptoms. One study¹⁶ compared a ring that delivered systemic estradiol 160 µg/day and progesterone 20 mg/day with a ring that delivered the same dosage of estradiol but only half the progesterone (10 mg/day). Ultrasound monitoring of the endometrium constantly revealed a thickness of less than 3 mm for both variants throughout use for 16 weeks. Three of the 20 women enrolled discontinued the treatment due to ring expulsion. Climacteric symptoms decreased significantly and vaginal bleeding and spotting were confined to the first six weeks.

Further work¹⁷ compared two rings that delivered approximately 150 µg/day of 17β-estradiol and approximately 5 mg/day or 9 mg/day of progesterone. The results showed that endometrial proliferation was prevented by both progesterone dosages. The incidence of vasomotor symptoms decreased quickly and significantly, as did the incidence of bleeding.

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Box 1. Vaginal oestrogen preparations currently available

- 0.01% estriol cream and pessaries: Ortho-Gynest® (Janssen Cilag, High Wycombe, Bucks)
- 0.1% estriol cream: Ovestin® (Organon, Cambridge, Cambs)
- 25 µg/24 hours estradiol vaginal tablets: Vagifem
- 7.5 µg/24 hours low-dose estradiol ring: Estring
- 50 µg/24 hours estradiol-releasing silicone ring: Menoring
- Conjugated equine oestrogen cream: Premarin

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Systemic estradiol vaginal ring with vaginal progesterone

The effects of a systemic estradiol-releasing ring combined with a cyclical 100 mg progesterone suppository were compared with the effects of 50 µg transdermal estradiol with a levonorgestrel-releasing intrauterine device in 56 postmenopausal women.¹⁸ Endometrial proliferation was not observed in either group. This suggests that a low-dose progesterone pessary could provide adequate endometrial protection; this is a useful alternative in progestogen-intolerant women. Both treatment regimens effectively relieved climacteric symptoms.

Conclusions

The vaginal route of administration of oestrogen has the advantage of delivering hormone therapy directly to the affected tissues in postmenopausal women with symptoms caused by urogenital atrophy. It is becoming increasingly clear that even in women who are oestrogen replete systemically, there may still be intractable local symptoms that will only respond to local application. Local application of systemic HRT also avoids first pass metabolic effects, allowing a lower dosage to be used with the same effect. Patient choice, and therefore likelihood of continuation of therapy, has been improved with the advent of vaginal rings and vaginal tablets.

Despite the undoubted benefits of vaginal preparations, concerns have been raised

regarding safety, particularly endometrial hyperplasia. However, we have come a long way from the days when only high-dose synthetic oestrogen was available for urogenital atrophy. The well founded concerns regarding safety to the endometrium contributed to the withdrawal of one of these preparations from the market. The newer estriol creams, estradiol tablets and estradiol rings have already been proven much safer to the endometrium. These preparations could potentially reduce systemic effects on breast tissue and the coagulation cascade.

It is unfortunate that in the UK most of the local oestrogen preparations are only licensed for 3–6 months, with the exception of the low-dose oestrogen ring. It is a well recognised fact that most women's symptoms return when treatment is discontinued. Work should, therefore, now focus on providing evidence that the unopposed local application of low-dose oestrogen is safe in the long term, both on the endometrium and with regards to systemic effects on the breast and the cardiovascular system. This will encourage clinicians to be more positive in how they counsel women about vaginal oestrogen and increase patient confidence in using these preparations. In turn, it is hoped that this will increase the long-term use of vaginal oestrogen as a therapeutic option in the management of women who have contraindications to, or who prefer not to use, systemic HRT and in those with intractable urogenital symptoms despite systemic therapy. ■

References

1. Ballagh, SA. Vaginal ring hormone delivery systems in contraception and menopause. *Clin Obstet Gynecol* 2001;**44**:106–13.
2. Cameron S. Best practice with vaginal (unopposed) oestrogens. *Trends in Urology, Gynaecology & Sexual Health* 2003;**8**. [www.escriber.com/TrendsInUGSH/Features.asp?ID=151&Action=View].
3. Willhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment. *Pharmacotherapy* 2001;**21**:464–80.
4. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2003;**4**:CD001500.
5. Dezarnaulds G, Fraser IS. Vaginal ring delivery of hormone replacement therapy—a review. *Expert Opin Pharmacother* 2003;**4**:201–12.
6. Sarkar NN. Low-dose intravaginal estradiol delivery using a Silastic vaginal ring for estrogen replacement therapy in postmenopausal women: a review. *Eur J Contracept Reprod Health Care* 2003;**8**:217–24.
7. Kalogirou D, Antoniou G, Karakitsos P, Kalogirou O, Antoniou D, Giannikos L. A comparative study of the effects of an estradiol-releasing vaginal ring combined with an oral gestagen versus transdermal estrogen combined with a levonorgestrel-releasing IUD: clinical findings and endometrial response. *Int J Fertil Menopausal Stud* 1996;**41**:522–7.
8. Panay N, Studd J. Progestogen intolerance and compliance with hormone replacement therapy in menopausal women. *Hum Reprod Update* 1997;**3**:159–71.
9. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.
10. Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;**362**:419–27.
11. Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric* 2003;**6**:45–52.
12. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;**291**:1701–12.
13. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;**362**:428–32.
14. Botsis D, Kassanos D, Kalogirou D, Antoniou G, Karakitsos P, Zourlas PA. A comparative study of an estradiol-releasing vaginal ring versus tibolone in postmenopausal women: a transvaginal color Doppler study. *Maturitas* 1997;**27**:77–83.
15. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas* 1996;**23**:259–63.
16. Hamada AL, Maruo T, Samoto T, Yoshida S, Nash H, Spitz IM, et al. Estradiol/progesterone-releasing vaginal rings for hormone replacement therapy in postmenopausal women. *Gynecol Endocrinol* 2003;**17**:247–54.
17. Maruo T, Mishell DR, Ben-Chetrit A, Hochner-Celnikier D, Hamada AL, Nash HA. Vaginal rings delivering progesterone and estradiol may be a new method of hormone replacement therapy. *Fertil Steril* 2002;**78**:1010–6.
18. Antoniou G, Kalogirou D, Karakitsos P, Antoniou D, Kalogirou O, Giannikos L. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints versus estradiol-releasing vaginal ring with a vaginal progesterone suppository: clinical and endometrial responses. *Maturitas* 1997;**26**:103–11.