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[Intervention Review]

Local oestrogen for vaginal atrophy in postmenopausal women

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ABSTRACT

Background

Vaginal atrophy is a frequent complaint of postmenopausal women; symptoms include vaginal dryness, itching, discomfort and painful intercourse. Systemic treatment for these symptoms in the form of oral hormone replacement therapy is not always necessary. An alternative choice is oestrogenic preparations administered vaginally (in the form of creams, pessaries, tablets and the oestradiol-releasing ring). This is an update of a Chochrane systematic review; the original version was first published in October 2006.

Objectives

The objective of this review was to compare the efficacy and safety of intra-vaginal oestrogenic preparations in relieving the symptoms of vaginal atrophy in postmenopausal women.

Search methods

We searched the following databases and trials registers to April 2016: Cochrane Gynaecology and Fertility Group Register of trials, The Cochrane Central Register of Controlled Trials (CENTRAL; 2016 issue 4), MEDLINE, Embase, PsycINFO, DARE, the Web of Knowledge, OpenGrey, LILACS, PubMed and reference lists of articles. We also contacted experts and researchers in the field.

Selection criteria

The inclusion criteria were randomised comparisons of oestrogenic preparations administered intravaginally in postmenopausal women for at least 12 weeks for the treatment of symptoms resulting from vaginal atrophy or vaginitis.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and extracted the data. The primary review outcomes were improvement in symptoms (participant-assessed), and the adverse event endometrial thickness. Secondary outcomes were improvement in symptoms (clinician-assessed), other adverse events (breast disorders e.g. breast pain, enlargement or engorgement, total adverse events, excluding breast disorders) and adherence to treatment. We combined data to calculate pooled risk ratios (RRs) (dichotomous outcomes) and mean differences (MDs) (continuous outcomes) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic. We assessed the overall quality of the evidence for the main comparisons using GRADE methods.

Main results

We included 30 RCTs (6235 women) comparing different intra-vaginal oestrogenic preparations with each other and with placebo. The evidence was low to moderate quality; limitations were poor reporting of study methods and serious imprecision (effect estimates with wide confidence intervals)

1**. Oestrogen ring versus other regimens**

Other regimens included oestrogen cream, oestrogen tablets and placebo. There was no evidence of a difference in improvement in symptoms (participant assessment) either between oestrogen ring and oestrogen cream (odds ratio (OR) 1.33, 95% CI 0.80 to 2.19, two RCTs, n = 341, I^2 = 0%, low-quality evidence) or between oestrogen ring and oestrogen tablets (OR 0.78, 95% CI 0.53 to 1.15, three RCTs, n = 567, I^2 = 0%, low-quality evidence). However, a higher proportion of women reported improvement in symptoms following treatment with oestrogen ring compared with placebo (OR 12.67, 95% CI 3.23 to 49.66, one RCT, n = 67). With respect to endometrial thickness, a higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring (OR 0.36, 95% CI 0.14 to 0.94, two RCTs, n = 273; I^2 = 0%, low-quality evidence). This may have been due to the higher doses of cream used.

2. Oestrogen tablets versus other regimens

Other regimens in this comparison included oestrogen cream, and placebo. There was no evidence of a difference in the proportions of women who reported improvement in symptoms between oestrogen tablets and oestrogen cream (OR 1.06, 95% CI 0.55 to 2.01, two RCTs, n = 208, I^2 = 0% low-quality evidence). A higher proportion of women who were treated with oestrogen tablets reported improvement in symptoms compared to those who received placebo using a fixed-effect model (OR 12.47, 95% CI 9.81 to 15.84, two RCTs, n = 1638, I^2 = 83%, low-quality evidence); however, using a random-effect model did not demonstrate any evidence of a difference in the proportions of women who reported improvement between the two treatment groups (OR 5.80, 95% CI 0.88 to 38.29). There was no evidence of a difference in the proportions of women with increase in endometrial thickness between oestrogen tablets and oestrogen cream (OR 0.31, 95% CI 0.06 to 1.60, two RCTs, n = 151, I^2 = 0%, low-quality evidence).

3. **Oestrogen cream versus other regimens**

Other regimens identified in this comparison included isoflavone gel and placebo. There was no evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and isoflavone gel (OR 2.08, 95% CI 0.08 to 53.76, one RCT, n = 50, low-quality evidence). However, there was evidence of a difference in the proportions of women with improvement in symptoms between oestrogen cream and placebo with more women who received oestrogen cream reporting improvement in symptoms compared to those who were treated with placebo (OR 4.10, 95% CI 1.88 to 8.93, two RCTs, n = 198, I^2 = 50%, low-quality evidence). None of the included studies in this comparison reported data on endometrial thickness.

Authors' conclusions

There was no evidence of a difference in efficacy between the various intravaginal oestrogenic preparations when compared with each other. However, there was low-quality evidence that intra-vaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo. There was low-quality evidence that oestrogen cream may be associated with an increase in endometrial thickness compared to oestrogen ring; this may have been due to the higher doses of cream used. However there was no evidence of a difference in the overall body of evidence in adverse events between the various oestrogenic preparations compared with each other or with placebo.

PLAIN LANGUAGE SUMMARY

Use by postmenopausal women of creams, pessaries or a vaginal ring to apply oestrogen vaginally for symptoms of vaginal dryness

Review question

Cochrane researchers reviewed the evidence about the efficacy and safety of intravaginal oestrogenic preparations compared with each other or placebo (inactive or sham treatment) in women undergoing treatment for the symptoms of vaginal atrophy.

Background

Vaginal atrophy is a common condition in women after menopause. It causes vaginal dryness and itching and can make intercourse painful. The female hormone oestrogen is a treatment option for vaginal atrophy, but can cause adverse effects such as increased thickness in the lining of the womb (endometrium) which could be due to endometrial hyperplasia or cancer (resulting in vaginal bleeding) and breast tenderness. Oestrogen is available as an oral tablet, skin patch or implant under the skin. Alternatively, women can apply the hormone locally using creams, pessaries (tablets placed in the vagina) or a hormone-releasing ring placed in the vagina. There is, therefore, the need to evaluate the efficacy and safety of these locally-administered oestrogenic preparations.

Study characteristics

We found 30 randomised controlled trials comparing intravaginal oestrogenic preparations with one another or with placebo in a total of 6235 postmenopausal women undergoing treatment for the symptoms of vaginal atrophy. The evidence is current to April 2016.

Key results

There was no evidence of a difference in the proportions of women who reported improvement in symptoms of vaginal atrophy between the following treatment comparisons: oestrogen ring and oestrogen cream, oestrogen ring and oestrogen tablets, oestrogen tablets and oestrogen cream, oestrogen cream and isoflavone gel. However, a higher proportion of women reported improvement in symptoms in the following active treatments compared with placebo: oestrogen ring versus placebo, oestrogen tablets versus placebo and oestrogen cream versus placebo. In the case of oestrogen tablets versus placebo and using a random-effect model for analysis of the data because of substantial heterogeneity, there was no longer evidence of a difference in effect on improvement in symptoms.

With respect to safety, a higher proportion of women who received oestrogen cream showed evidence of increase in endometrial thickness compared to those who were treated with oestrogen ring, which may have been due to the higher doses of cream used. However, there was no evidence of a difference in the proportions of women with increase in thickness of the lining of the womb between oestrogen tablets and oestrogen cream.

Quality of the evidence:

The evidence was of low quality for both improvement in symptoms as reported by women and increase in endometrial thickness. The main limitations of the evidence were poor reporting of study methods, and lack of precision (i.e. effect estimates with wide confidence intervals) in the findings for both outcomes.