Oestrogens for preventing recurrent urinary tract infection in postmenopausal women (Review)

Perrotta C, Aznar M, Mejia R, Albert X, Ng CW

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Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

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ABSTRACT

Background

Recurrent urinary tract infection (RUTI) is defined as three episodes of urinary tract infection (UTI) in the previous 12 months or two episodes in the last six months. The main factors associated with RUTI in postmenopausal women are vesical prolapse, cystocele, post-voidal residue and urinary incontinence, all associated with a decrease in oestrogen. The use of oestrogens to prevent RUTI has been proposed.

Objectives

To estimate the efficacy and safety of oral or vaginal oestrogens for preventing RUTI in postmenopausal women.

Search methods

We searched the Cochrane Renal Group’s specialised register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 1950), EMBASE (from 1980), reference lists of articles without language restriction.

Date of last search: February 2007.

Selection criteria

Randomised controlled trials (RCTs) in which postmenopausal women (more than 12 months since last menstrual period) diagnosed with RUTI received any type of oestrogen (oral, vaginal) versus placebo or any other intervention were included.

Data collection and analysis

Authors extracted data and assessed quality. Statistical analyses were performed using the random effects model and the results expressed as risk ratios (RR) for dichotomous outcomes or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Main results

Nine studies (3345 women) were included. Oral oestrogens did not reduce UTI compared to placebo (4 studies, 2798 women: RR 1.08, 95% CI 0.88 to 1.33). Vaginal oestrogens versus placebo reduced the number of women with UTIs in two small studies using different application methods. The RR for one was 0.25 (95% CI 0.13 to 0.50) and 0.64 (95% CI 0.47 to 0.86) in the second. Two studies compared oral antibiotics versus vaginal oestrogens (cream (1), pessaries (1)). There was very significant heterogeneity and the results could not be pooled. Vaginal cream reduced the proportion of UTIs compared to antibiotics in one study and in the second study antibiotics were superior to vaginal
pessaries. Adverse events for vaginal oestrogens were breast tenderness, vaginal bleeding or spotting, nonphysiologic discharge, vaginal irritation, burning and itching.

Authors' conclusions

Based on only two studies comparing vaginal oestrogens to placebo, vaginal oestrogens reduced the number of UTIs in postmenopausal women with RUTI, however this varied according to the type of oestrogen used and the treatment duration.

Plain Language Summary

Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Recurrent urinary tract infection (RUTI) is defined as three episodes of urinary tract infection (UTI) in the previous 12 months or two episodes in the last six months. In postmenopausal women the prevalence rate for having one episode of UTI in a given year varies from 8% to 10%. This increased risk is associated with a decrease in oestrogen levels. The use of oestrogens (orally or vaginally) has been proposed as a preventive strategy. This review identified nine studies (3345 women) treated with oestrogens versus placebo, no treatment or antibiotics. Vaginal oestrogens reduced the number of UTIs when compared to placebo. All studies reported adverse events for the oestrogen treatment groups. These included breast tenderness, vaginal bleeding or spotting, vaginal discharge, vaginal irritation, burning and itching.
BACKGROUND

Recurrent urinary tract infection (RUTI) is defined as three episodes of urinary tract infection (UTI) in the previous 12 months or two episodes in the last six months. In postmenopausal women the prevalence rate for having one episode of UTI in a given year varies from 8% to 10%. Of those women who have an episode, 5% will experience a recurrence within the year (Brown 1999; Foxman 2000).

In premenopausal women the main risk factors associated with RUTI are frequency of sexual intercourse, the use of spermicides, the age at first UTI (less than 15 years of age indicates a greater risk of RUTI) and a history of UTI in the mother. After menopause the main risk factors are vaginal prolapse, cystocele, post-voidal residue, changes in vaginal flora, and urinary incontinence (Foxman 2000; Raz 2000). Weaker associations have been found with non-secretor status and a history of UTI before menopause. The association of RUTI with sexual habits, such as frequency of sexual intercourse and the use of spermicides is not as positive as in younger women. No association were found in a study by Foxman 2001 and in another case controlled study, sexually active women had an odds ratio (OR) of 1.42 (95% CI 1.07 to 1.87) of having RUTIs over non-sexually active women (Hu 2004).

Several approaches have been proposed for the prevention of RUTI. A Cochrane systematic review showed that antibiotics are effective in reducing the number or recurrences. However, adverse events were common and compliance with treatment varied (Albert 2004). Cranberry juice or cranberry pills has some effect as a preventive strategy (Jepson 2004).

During the last few decades there has been an increasing interest in the treatment with local or oral oestrogens for the prevention of UTI and urinary symptoms in postmenopausal women. Basic research has demonstrated that oestrogen receptors are present in the vagina, urethra, the trigone of the bladder and pelvic floor musculature. It is believed that they play a crucial role in the continence mechanism (Iosif 1981; Robinson 2003).

Vaginal flora changes with the reduction of local and circulating estrogens during menopause. Vaginal pH rises after and vaginal Lactobacillus decrease, allowing gram negative bacteria to grow and act as uropathogen. A Cochrane systematic review (Suckling 2006) concluded that vaginal estrogens improve vaginal atrophy and increase vaginal Lactobacillus. A Cochrane systematic review by Moehrer 2004 reported that oestrogens are effective in the subjective impression of cure in women with urinary incontinence, and that increase as well the presence of Lactobacillus and vaginal pH decrease. Given this evidence oestrogens have been proposed as a strategy for the prevention of UTI in postmenopausal women. Several methods of administration have been tested: oral, vaginal cream, vaginal tablets, vaginal ring and vaginal pessaries. However some controversy surrounds the use of oestrogens in RUTI. While it appears that vaginal oestrogens decrease UTI occurrence, oral oestrogens apparently do not have this effect. In addition, there is concern in relation to its long term use and the adverse events associated with them. There is also some evidence suggesting oral antibiotics have a higher efficacy as a preventing strategy for RUTI than local oestrogen use (Raz 2001).

OBJECTIVES

To examine the efficacy of oestrogens (oral or vaginal) in decreasing the rate of RUTI in postmenopausal women and their safety (in terms of systemic or local adverse events such as allergic reactions or local irritation).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi randomised-RCTs (in which allocation to treatment was obtained by alternation, medical record numbers, date of birth or other predictable methods).

Types of participants

All postmenopausal women (more than 12 months since last menstrual period) with RUTIs (defined as three UTI episodes in the last 12 months or two episodes in the last six months) where at least one UTI outcome was assessed. There were no exclusions based on other underlying disease or urinary tract abnormality.

Types of interventions

Oral oestrogens (with or without progestogens), or vaginal oestrogens (delivered by cream, vaginal ring, vaginal pessaries, vaginal tablets or any other formulation) given at any dose or any length of treatment used as a preventive strategy for the reduction of RUTI versus:

- Placebo.
- Another type of oestrogen delivery (e.g. oral versus local, cream versus vaginal ring, vaginal ring versus vaginal pessaries).
- Another preventive strategy (e.g. antibiotic, cranberry juice).
- No treatment.

We excluded those studies that only included assessment of vaginal atrophy as this has been covered in another Cochrane review (Suckling 2006).

Types of outcome measures

Primary outcomes

- Women with RUTIs at the end of active treatment period.
- UTIs at the end active treatment period.
- Time until recurrence.
- Number of urinary infections/person/year.
- Number of asymptomatic women at the end of the study.
- Number of relapsing after the end of the study.

Secondary outcomes

- Proportion of women Lactobacillus positive.
- Vaginal pH at the end of the active treatment period.

Adverse events

- Proportion of severe adverse events (resulting in the cessation of treatment).
- Proportion of referred adverse events.
• Endometrial thickness at the end of the active treatment period.
• Proportion of women with vaginal bleeding or spotting.
• Proportion of women with breast tenderness.

Search methods for identification of studies
We searched the following electronic bibliographic databases (Appendix 1 - Electronic search strategies):

• The Cochrane Renal Group's specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (issue 1, 2007). CENTRAL and the Renal Groups Specialised Register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2007). Therefore we did not specifically search conference proceedings.

• MEDLINE (1950 to February 2007) using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Coordinators.

• EMBASE (1980 to February 2007) using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy developed with input from the Cochrane Renal Group Trial Search Coordinators.

• Lilacs (1988 to February 2007).
• Reference list of retrieved articles.
• Communication with authors for clarification of results and/or methods. We contacted Kjaergaard 1990, but could not reach the investigators from Xu 2001.

Data collection and analysis

Study selection
Two authors (CP, CW) independently screened the initial search results of all the databases and references lists to identify citations relevant to our review. Once identified the abstracts were checked and full text articles obtained when inclusion criteria were met.

Quality assessment
Each RCT was evaluated by two authors (CW, MA) and a third author (CP) resolved discrepancies.

Allocation concealment
• Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study.
• Unclear (B): Randomisation stated but no information on method used is available.
• Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

Blinding
• Blinding of investigators: Yes/no/not stated.
• Blinding of participants: Yes/no/not stated.

The above are considered not blinded if the treatment group can be identified in > 20% of participants because of the side effects of treatment.

Intention-to-treat analysis
• Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
• Yes: Not stated but confirmed on study assessment.
• No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Women who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
• No: Stated but not confirmed upon study assessment.
• Not stated.

Completeness of follow-up
Number of participants with data/number of participants randomised, expressed as a percentage overall and in each intervention group.

We evaluated outcome definitions (how the authors defined clinical and microbiological recurrences) and the ways in which adverse events were recalled. Discrepancies in those definitions and assessments were taken into consideration while doing the analysis especially if heterogeneity was identified.

Data analysis
Data was extracted using a data extraction form (CW, MA) and then entered into RevMan. CP checked the original papers for discrepancies. Dichotomous outcomes were analysed as risk ratio (RR) and 95% confidence interval (CI). The time until recurrence was intended to be done using Kaplan-Meier method. However, because we could not contact the authors to obtain individual data from each of the studies, we have reported the results from each study individually. Continuous variables were analysed using mean differences (MD) and 95% CI. We used random effects model to assess overall treatment effects. Heterogeneity was analysed using a chi squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and the I² test (Higgins 2003). ). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity. When heterogeneity was found we did subgroup analysis according to the intervention, study design (RCT and quasi-RCTs) and blinding.

RESULTS

Description of studies
We identified 17 potential studies from the search strategy. We excluded eight studies (Ayton 1996; Brandberg 1987; Chompootawee 1998; Henriksson 1996; Marx 2004; Molander 1990; Notelovitz 1995; Orlander 1992) because they only reported on vaginal atrophy which has been covered by another Cochrane review (Suckling 2006) or the population did not have to have had a previous UTI. Nine studies (3345 women) met our inclusion criteria (Brown 2003; Cardozo 1998; Eriksen 1999; Kirkeneng 1992;
Interventions

- Vaginal oestrogens versus placebo (Kjaergaard 1990; Eriksen 1999; Raz 1993).
- Vaginal oestrogens versus antibiotics (Raz 2003; Xu 2001).

Reported outcomes

**Oral oestrogens versus placebo**

- Proportion of two or more UTIs during first, second, third and fourth year of treatment as reported by the participants answering the question: "During the past year, how many times has a doctor told you that you had a urinary tract infection?" (Brown 2001).
- The proportion of women who developed at least one UTI during the study period (Cardozo 1998).
- The percentage of vaginal superficial cells, vaginal pH, vaginal parabasal cells, bacteriuria and pyuria, and presence of Lactobacillus (Ouslander 2001).
- Proportion of women with two UTIs at the end of treatment period and vaginal pH (Kirkengen 1992).

**Vaginal oestrogens versus placebo**

- Women were evaluated once a month for five months to evaluate the number of positive cultures and patient satisfaction (Kjaergaard 1990).
- Proportion of women with RUTI and proportion of women remaining free of UTI, vaginal atrophy and vaginal pH (Eriksen 1999).
- Incidence of UTI, proportion of women remaining free of UTI and number of episodes of UTI/patient/year, presence of Lactobacillus and vaginal pH (Raz 1993).

**Vaginal oestrogens versus antibiotics**

- Number of UTI episodes/patient/year, the proportion of women who remained free of UTI, percentage of superficial cells and the presence of Lactobacillus (Raz 2003).
- Proportion of women with UTI at the end of the study period, adverse events and vaginal atrophy (Xu 2001).

Risk of bias in included studies

Overall, the quality of the included studies were good.

Allocation concealment

One study had adequate allocation concealment (Brown 2001) and the rest were unclear. In the study by Xu 2001 it was not clear why the two groups were unbalanced (oestriol group n = 30; antibiotic group n = 15).

Blinding

Eight studies were ‘double blind’. Eriksen 1999 had a no treatment control group and the women and investigators were therefore not blinded.

Intention-to-treat

All studies analysed by intention-to-treat. Eriksen 1999 also analysed ‘per-protocol’.

Completeness of follow-up

- Cardozo 1998: Twenty-two women were unable to complete the study. Reasons for early discontinuation in the oestriol group (n = 13) were protocol violation (n = 4); hospital admission (n = 2); bleeding (n = 2); cerebrovascular accident (n = 2); poor compliance; adverse experiences; and depression. Early discontinuation reasons in the placebo group (n = 9) included femur fracture (n = 2); poor compliance; major protocol violation; septicemia; cerebrovascular accident; left arm paresis; adverse experiences and general decline in health.
- Eriksen 1999: Five subjects (9%) withdrew from the ring group and 1 subject (2%) withdrew from the control group before completion of the 36-week study period or before first recurrence (control group).
- Ouslander 2001: Three (9%) dropped out before the 3-month examination (two active, one placebo), leaving 29 subjects who had 3-month measures (13 active and 16 placebo; 91% of those enrolled). An additional eight (25%) dropped out before the 6-month examination (four active, four placebo), leaving 21 subjects who had 6-month measures (nine active and 12 placebo; 66% of those enrolled). Reasons for dropping out were primarily various acute illnesses (which resulted in two deaths).
- Raz 1993: reasons for early withdrawal from the study: side effects in 10 women in the oestriol group and 4 in the placebo group; lack of compliance with follow-up in 3 and 5 women, respectively; death due to myocardial infarction in 1 oestriol-treated patient; and failure to respond to topical prophylaxis necessitating systemic antimicrobial prophylaxis for recurrent infections in 10 women in the placebo group.
- Raz 2001: Twenty-seven women in the oestriol group and 23 in the NM group dropped out. Reasons for dropout included adverse events (9 women in the oestriol group and 14 in the NM group), lack of compliance with the treatment regimen (13 and 6, respectively), and intermittent illness (3 and 2, respectively).

Effects of interventions

**Oral oestrogens versus placebo**

**Proportion of women with UTI at the end of the treatment period**

Four studies assessed this outcome (Brown 2001; Cardozo 1998; Kirkengen 1992; Ouslander 2001). There was no significant difference in the number of women with UTI at the end of the treatment period between oral oestrogens and placebo (Analysis 1.1 (4 studies, 2798 women): RR 1.08, 95% CI 0.88 to 1.33; I² = 0%).

**Vaginal pH**

Two studies reported the change in vaginal pH (Kirkengen 1992; Ouslander 2001). There was a significant decrease in vaginal pH with the oral oestrogens (Analysis 1.2 (2 studies, 62 women): MD -1.00, 95% CI -1.43 to -0.57; I² = 0%).

**Proportion of women Lactobacillus positive**

One study (Ouslander 2001) reported this outcome. There was no significant difference between the two groups in the number of
women who were *Lactobacillus* positive (Analysis 1.3 (1 study, 32 women): RR 10.13, 95% CI 0.59 to 173.83).

**All adverse events**

Two studies reported adverse events that occurred during the treatment period. Cardozo 1998 reported breast tenderness and mild vaginal bleeding, and Ouslander 2001 reported vaginal spotting and mild breast discomfort (present in minority, however number not reported). There were significantly less adverse events in the placebo group (Analysis 1.4 (2 studies, 104 women): RR 5.11, 95% CI 1.39 to 18.76; I² = 0%).

**Other outcomes reported**

Cardozo 1998 reported 34% women free of infection in the oestriol group at the end of the study period (12 months) versus 44% in the placebo group. The results were not statistical significant.

**Vaginal oestrogens versus placebo**

**Proportion of infection at the end of the treatment period**

Analysis 2.1

Two studies (Eriksen 1999; Raz 1993) reported this outcome. We did not pool these studies as there was significant heterogeneity. The heterogeneity could be explained by the type of application method used. Raz 1993 compared topically applied intravaginal oestriol cream oestrogens to placebo cream while Eriksen 1999 compared releasing silicone vaginal ring (Estring) (2 mg oestriol) with no treatment control group. The RR for Raz 1993, was 0.25 (95% CI 0.13 to 0.50) and in Eriksen 1999, the RR was 0.64 (95% CI 0.47 to 0.86).

**Vaginal pH**

Raz 1993 reported a significant decrease in pH with vaginal oestrogens (Analysis 2.2 (93 women): MD -2.50, 95% CI -3.16 to -1.84).

**Proportion of women *Lactobacillus* positive**

Raz 1993 reported significantly more women were *Lactobacillus* positive in the vaginal oestrogen group (Analysis 2.3 (93 women): RR 38.82, 95% CI 2.42 to 621.60).

**All adverse events**

The adverse events included vaginal bleeding and nonphysiologic discharge (Eriksen 1999), and vaginal irritation, burning, or itching (Raz 1993). There was no significant difference in adverse events between the two groups (Analysis 2.4 (201 women): RR 4.72, 95% CI 0.67 to 33.53; I² = 67.5%), however there was moderate heterogeneity. The control group in Eriksen 1999 received no treatment and the control group in Raz 1993 received a placebo cream.

**Other outcomes**

- Eriksen 1999 reported that after 9 months the 45% of participants were free of UTIs in the oestrogen group and approximately 20% in the control group (P < 0.008). In Raz 1993, the intervention group had a cumulative likelihood of remaining disease free of 0.95 and the placebo group 0.30 (P < 0.001 log rank test).
- Raz 1993 reported the mean number of days of antibiotic use. The oestrogen group received antibiotics for 6.9 days (± 1.1 SD) and the placebo group 32.0 days (± 7.8) (P < 0.001).
- Kjaergaard 1990 reported a median of 1.5 UTIs in the oestrogen group and 1 in the control group (range 0 to 5 for both groups). There were no differences in patient satisfaction.
- Eriksen 1999 reported 34 women (67%) in the Estring group and one (2%) in the control group were free of vaginal mucosal atrophy at the end of the treatment period.

**Vaginal oestrogens versus antibiotics**

Two studies used different mode of administration. Raz 2003 used a vaginal pessary and Xu 2001 used vaginal cream.

**Proportion of women with UTIs at the end of the treatment period**

The pooled results went in different directions and had significant heterogeneity. We have shown these results without the summary estimate.

- Raz 2003 (171 participants) reported significantly less UTIs in the antibiotic group compared to the oestrogen group (Analysis 3.1.1: RR 1.30, 95% CI 1.01 to 1.68).
- Xu 2001 (42 women) reported significantly less UTIs in the oestrogen group compared to the antibiotic group after three months (Analysis 3.1.2: RR 0.09, 95% CI 0.02 to 0.36). Two months after stopping treatment there was no significant difference in the number women with RUTIs (Analysis 3.1.2: RR 0.56, 95% CI 0.09 to 3.55).

**Vaginal pH**

There was no statistical difference in vaginal pH between vaginal oestrogens and antibiotics (Analysis 3.2 (2 studies, 213 women: MD -1.69, 95% CI -4.24 to 0.85; I² = 99.3%), however there was very significant heterogeneity.

**Proportion of women *Lactobacillus* positive**

There was no statistical difference in the number of women *Lactobacillus* positive between vaginal oestrogens and antibiotics (Analysis 3.3 (2 studies, 213 women): RR 4.02, 95% CI 0.25 to 65.06; I² = 75.1%). There was significant heterogeneity.

**Adverse events**

Analysis 3.4

- Xu 2001 reported that in the oestrogen group five reported burning, two reported itching. Doses were decreased and three dropped out of the study. There were no reported side effects for the antibiotic group.
- In Raz 2003 the adverse events were more frequent in the vaginal estrogens group, 36% for all adverse events and 16% for drug-related adverse events. In those women receiving oestriol the adverse events were itching, burning, vaginal discharge and metrorrhagia.

**DISCUSSION**

**Oral oestrogens versus placebo**

Oral oestrogens did not reduce the occurrence of RUTI or the number of postmenopausal women who were *Lactobacillus*
positives. There was a significant decrease in vagina pH and significantly more women reported adverse events (breast tenderness, mild vaginal bleeding and spotting) in the group treated with oral oestrogens.

Vaginal oestrogens versus placebo

There was a reduction on the number of UTIs in the vaginal oestrogens group in two studies. The two studies used different type of application method (Raz 1993 used topical vaginal cream and Eriksen 1999 used releasing silicone vaginal ring (Estring) (2 mg oestril) that it is likely to explain the heterogeneity in the pool analysis. Both trials have a reduction in the proportion of UTIs. The RR for Raz 1993, was 0.25 (95% CI 0.13 to 0.50) and in Eriksen 1999, the RR was 0.64 (95% CI 0.47 to 0.86).

Vaginal oestrogens versus antibiotics

When pooling the results from the two studies that compared antibiotics and vaginal oestrogens, the differences in magnitude and direction of effects and the subsequent heterogeneity while pooling these two studies should be noted. One possible explanation is the use different types of vaginal oestrogens, Raz 2003 used a vaginal pessary and Xu 2001 vaginal cream. Raz 2003 discussed in his paper the small effect of oestrogens compared to nitrofurantoin and the paper suggest that the use of vaginal pessaries could have been less effective than the use of cream. It is seems that the oestrogens administration form may have had an impact on its effect on the vaginal mucosa. It is of notice the high number of infections under the antibiotics arm in the Xu 2001 study. It is unclear the reason for this high number of infections in this group.

Evidence from two small studies shows that in postmenopausal women with RUTI, vaginal oestrogens reduce the number of UTIs. However the true magnitude of the effect is difficult to assess as the two studies used different type of vaginal oestrogens and different type of comparators. The significant heterogeneity seen in this comparison means it is not appropriate to pool these data.

The type of vaginal oestrogens to use is unclear; while cream seems more effective than vaginal ring, vaginal cream could be more difficult to apply for certain women and acceptability is lower compared to vaginal ring as it has to be applied every day to maintain the effect (Suckling 2006). Vaginal ring on the other hand is more expensive and requires a trained doctor to place correctly. The role for vaginal pessaries is unclear. In the study by Raz 2003 they were not effective in reducing the pH no increasing the presence of Lactobacillus or decreasing UTIs. Vaginal creams are possibly more suitable for outpatients and vaginal rings or pessaries could be used in nursing homes residents. Adverse events did occur more frequently in women receiving oestrogens comparing to placebo, no treatment or antibiotic. This issue must be discussed and anticipated with any potential patient as it may affect adherence to treatment. The effect of vaginal oestrogens on the reduction of UTIs could take at least 12 weeks (evaluating the time until recurrence or the time taken for the vaginal pH to decrease Eriksen 1999) and women should also be advised about this to avoid discontinuation of the treatment.

AUTHORS' CONCLUSIONS

Implications for practice

- In postmenopausal women with RUTI associated with a lack of oestrogens and signs and significant symptoms of vaginal atrophy, vaginal oestrogens are a potentially valid intervention. However, women should be advised that the evidence is based on only a few small studies.
- The type of oestrogens to use is less clear. Vaginal rings need to be changed periodically and have to be placed by an experienced doctor, however they could be an option in women who have difficulties in applying a cream or used in nursing home residents.
- Vaginal creams are a cheaper and possibly a more efficient option but women should be advised about adverse events (itching and burning, occasionally spotting).
- The studies comparing vaginal oestrogens to antibiotics were inconclusive due to the significant heterogeneity between the two studies.

Implications for research

- Future research should focus first in confirm the results of these small studies. They will need to evaluate which type of vaginal delivery is the best option and the outcomes should include cost, patient satisfaction and duration of treatment.
- Is not clear how long treatment should be given, what is the best treatment schedule and what would be the long-term adverse consequences of sustaining this intervention for more than 8 months.
- Studies comparing antibiotics plus vaginal oestrogens and vaginal oestrogens and cranberry juice should be encouraged in addition to studies in different populations (e.g. outpatients and nursing home residents or geriatric population).

ACKNOWLEDGEMENTS

Dr Shijun Zhou from the UCD School of Public Health and Cheen Werne Ng translated the Chinese paper.
References to studies included in this review

Brown 2001 {published data only}


Cardozo 1998 {published data only}


Eriksen 1999 {published data only}


Kirkengen 1999 {published data only}


Kjaergaard 1999 {published data only}


Ouslander 2001 {published data only}


Raz 1993 {published data only}


Raz 2003 {published data only}


Xu 2001 {published data only}


References to studies excluded from this review

Ayton 1996 {published data only}


Brandberg 1987 {published data only}


Chompoataweep 1998 {published data only}


Henriksson 1996 {published data only}


Marx 2004 {published data only}


Molander 1990 {published data only}


Notelovitz 1995 {published data only}


Orlander 1992 {published data only}

Additional references

Albert 2004

Brown 1999

Dickersin 1994

Foxman 2000

Foxman 2001

Higgins 2003

Hu 2004

Iosif 1981

Jepson 2004

Lefebvre 1996

Master List 2007

Moehrer 2004

Raz 2000

Raz 2001
Raz R. Hormone replacement therapy or prophylaxis in postmenopausal women with recurrent urinary tract infection. Journal of Infectious Diseases 2001;183 Suppl(1):74-6. [MEDLINE: 11171020]

Robinson 2003

Suckling 2006

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brown 2001

Methods
Randomised, double-blinded controlled trial. 20 clinical centres in the US. Jan 1993 and Sep 1994. Follow-up: Mean of 4.1 years.

Participants
Number: 2763 postmenopausal women. Age: < 80 years old.
Cochrane Database of Systematic Reviews

Brown 2001 (Continued)

Coronary heart disease and intact uterus.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>TREATMENT GROUP 0.625 mg of oral conjugated oestrogen plus 2.5 mg of medroxyprogesterone acetate.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROL GROUP Placebo.</td>
</tr>
</tbody>
</table>

Outcomes

| 1. Proportion with 2 or more UTIs during the 1st, 2nd, 3rd and 4th year of treatment (dichotomous). |

Notes

| Definition of RUTI: two or more UTIs. Logistic regression to examine the predictors of UTIs. Data not collected for this outcome (secondary analysis). |

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Cardozo 1998

Methods

| Double-blind, randomised, parallel group, placebo-controlled trial. Randomisation, blinding OK, allocation seems to follow randomisation. King's College Hospital, St Pancras Hospital and Dulwich Hospital, London (UK). |

Participants

| Recurrent UTI. Number: 72 postmenopausal women. Age: > 60 years (mean 73.2 years). |

Interventions

| TREATMENT GROUP Oral oestriol (3 mg/d) for 6 months, followed for a further 6 months after treatment. |
| CONTROL GROUP Placebo. |

Outcomes


Notes

| Definition of RUTI: at least UTI. Twenty-two women were unable to complete the trial. Reasons for early discontinuation in the oestriol group (n = 13) were major protocol violation (n = 4); hospital admission (n = 2); bleeding (n = 2); cerebrovascular accident (n = 2); poor compliance; adverse experiences; and depression. Early discontinuation reasons in the placebo group (n = 9) included femur fracture (n = 2); poor compliance; major protocol violation; sepsis; cerebrovascular accident; left arm paresis; adverse experiences and general decline in health. |

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
**Eriksen 1999**

**Methods**
Multi-centred (15), randomised, open, parallel group study.  
Country: Norway.  
Time frame: 15 October 1993 to 5 June 1996.  
Not blinded.

**Participants**
Number: 108 women.  
Age: ≥ 2 years after spontaneous or surgical menopause.  
UTIs: ≥ 3 treated during previous 12 months and had normal urine.

**Interventions**
**TREATMENT GROUP**
Estradiol-releasing silicone vaginal ring (Estring) (2 mg oestriol) was carried vaginally for 12 weeks.  
**CONTROL GROUP**
Untreated controlled group.

Duration of treatment: 36 weeks for Estring group, and until first recurrence for the control group.

**Outcomes**
1. Proportion of women with recurrent UTI (dichotomous).  
2. Proportion of women remaining free of UTI (dichotomous).  
3. Vaginal mucosal atrophy (dichotomous).  
4. Vaginal pH (continuous).  
5. Vaginal bleeding (dichotomous).

**Notes**
Quality is lower than the others.  
"Fourteen of the 108 subjects (9 subjects treated with the vaginal ring and 5 with no oestrogen treatment) were excluded from the per-protocol analysis of time to first recurrence. In addition, 3 subjects, all from the Estring group, were excluded from the per-protocol analysis for secondary variables. Five subjects (9%) withdrew from the ring group and 1 subject (2%) withdrew from the control group before completion of the 36-week study period or before first recurrence (control group). The reason for withdrawal was "local discomfort" (3 subjects in the Estring group) or "subject's own wish" (2 subjects in the Estring group and 1 subject in the control group)."

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

**Kirkengen 1992**

**Methods**
Randomised, double-blind, group-comparative, placebo-controlled trial.  
Block randomisation.  
In-patients at the Red Cross Clinic and patients being treated by general practitioners in Oslo.

**Participants**
Number: 40 postmenopausal women.  
Age: median 78 years (66-91).

**Interventions**
**TREATMENT GROUP**
Single daily 3 mg oral oestriol every morning during the first 4 weeks and 1 mg/d during the last 8 weeks of the treatment period.  
**CONTROL GROUP**
Placebo in the same schedule as treatment group.

**Outcomes**
1. Proportion of women with recurrent UTI (dichotomous).  
2. Vaginal pH (continuous).
Kirkengen 1992 (Continued)

Notes  Definition of RUTI: at least one episode with a repeat infection within two weeks or at least three episodes during the previous year.

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Kjaergaard 1990

Methods  Randomised double-blind, control trial.

Participants  Number: 21 postmenopausal women.

Interventions  TREATMENT GROUP
Vaginal estradiol.

CONTROL GROUP
Placebo.

Outcomes  1. Median of UTI at the end of the study period.
2. Patient satisfaction.

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Ouslander 2001

Methods  Randomised placebo-controlled trial.
5 community nursing homes in USA.
Allocation concealment adequate.

Participants  Number: 32 incontinent female residents.
Age: average 88 years.

Interventions  TREATMENT GROUP
Oral oestrogen (0.625 mg/d) combined with progesterone (2.5 mg/d) for 6 months.

CONTROL GROUP
Placebo for 6 months.

Outcomes  1. Percentage of vaginal superficial cells (dichotomous).
2. Vaginal parabasal cells (continuous).
3. Vaginal pH (continuous).
4. Bacteriuria and pyuria (dichotomous).
5. Presence of lactobacillus (dichotomous).

Oestrogens for preventing recurrent urinary tract infection in postmenopausal women (Review)
Ouslander 2001  (Continued)

Notes
Definition of RUTI: prevalence of bacteriuria.
Three (9%) dropped out before the 3-month examination (two active, one placebo), leaving 29 subjects who had 3-month measures (13 active and 16 placebo; 91% of those enrolled). An additional eight (25%) dropped out before the 6-month examination (four active, four placebo), leaving 21 subjects who had 6-month measures (nine active and 12 placebo; 66% of those enrolled). Reasons for dropping out were primarily various acute illnesses (which resulted in two deaths)

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Raz 1993

Methods
Randomised, double-blind, placebo-controlled trial.
Infectious Diseases Clinic, Central Emek Hospital, Afula, Israel.

Participants
Number: 93 postmenopausal women.
History of 3 or more microbiologically confirmed symptomatic episodes or UTI during the previous year.

Interventions
TREATMENT GROUP
Topically applied intravaginal oestriol cream of 0.5 mg each night for 2 weeks followed by twice-weekly applications for 8 months.

CONTROL GROUP
Placebo applied in a same manner as treatment.

Outcomes
1. Incidence of UTI (dichotomous).
2. Proportion of patients remaining free of UTI (dichotomous).
3. Presence of lactobacillus (dichotomous).
4. Vaginal pH (continuous).
5. Number of episodes of UTI/patient/year) (continuous).

Notes
Reasons for early withdrawal from the study: side effects in 10 women in the oestriol group and 4 in the placebo group; lack of compliance with follow-up in 3 and 5 women, respectively; death due to myocardial infarction in 1 oestriol-treated patient; and failure to respond to topical prophylaxis necessitating systemic antimicrobial prophylaxis for recurrent infections in 10 women in the placebo group

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Raz 2003

Methods
Double-blind, double dummy, randomised trial.
Outpatient clinics (3) in northern Israel.

Participants
Number: 171 postmenopausal women.
History of recurrent UTI.
Interventions

TREATMENT GROUP
Oestriol-containing vaginal pessary.
Daily for 2 weeks, and then once every 2 weeks for 9 months together with oral placebo capsules each night during the same period.

CONTROL GROUP
Nitrofurantoin macrocrystal (NM).
A capsule of NM nightly for 9 months together with a placebo vaginal pessary daily for 2 weeks.

Outcomes

1. Number of UTI episodes/patient/(continuous).
2. Proportion of women who remained free of UTI (dichotomous).
3. Percentage of superficial cells (dichotomous).
4. Lactobacillus colonisation (dichotomous).

Notes

Twenty-seven patients in the oestriol group and 23 in the NM group dropped out.
Reasons for dropout included adverse events (9 patients in the oestriol group and 14 in the NM group), lack of compliance with the treatment regimen (13 and 6, respectively), and intermittent illness (3 and 2, respectively).

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Xu 2001

Methods
Randomised control trial.
Gynaecological units.

Participants
Number: 45 postmenopausal women.
History of recurrent UTI.

Interventions
TREATMENT GROUP
Vaginal estrogens (intravaginal premarin cream) for 3 months.
Number: 30.

CONTROL GROUP
Oral ofloxacin 600 mg/d for 3 months.
Number: 15.

Outcomes

1. UTI.
2. Adverse events.
3. Vaginal pH.
4. UTI two months after finishing the study.

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayton 1996</td>
<td>Outcomes for urogenital atrophy in postmenopausal women, not about the treatment for recurrent UTI in postmenopausal women.</td>
</tr>
<tr>
<td>Brandberg 1987</td>
<td>The quality of this clinical trial was low. The primary outcomes were not reported.</td>
</tr>
<tr>
<td>Chompootaweeep 1998</td>
<td>Outcomes for vaginal atrophy.</td>
</tr>
<tr>
<td>Henriksson 1996</td>
<td>The primary outcomes were not reported.</td>
</tr>
<tr>
<td>Marx 2004</td>
<td>Main outcomes were vaginal atrophy. Participants did not meet inclusion criteria for this systematic review (no previous history of UTI).</td>
</tr>
<tr>
<td>Molander 1990</td>
<td>Main outcomes were related to vaginal atrophy.</td>
</tr>
<tr>
<td>Notelovitz 1995</td>
<td>Participants did not meet the inclusion criteria for this review.</td>
</tr>
<tr>
<td>Orlander 1992</td>
<td>Not an RCT.</td>
</tr>
</tbody>
</table>

DATA AND ANALYSES

Comparison 1. Oral oestrogens versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 UTI at the end of the treatment period</td>
<td>4</td>
<td>2798</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.08 [0.88, 1.33]</td>
</tr>
<tr>
<td>2 Vaginal pH</td>
<td>2</td>
<td>62</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.0 [-1.43, -0.57]</td>
</tr>
<tr>
<td>3 Lactobacillus positive</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 All adverse events</td>
<td>2</td>
<td>104</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>5.11 [1.39, 18.76]</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison 1 Oral oestrogens versus placebo, Outcome 1 UTI at the end of the treatment period.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral oestrogens</th>
<th>Placebo</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 2001</td>
<td>132/1318</td>
<td>120/1336</td>
<td>74.35%</td>
<td>1.12[0.88,1.41]</td>
<td></td>
</tr>
<tr>
<td>Cardozo 1998</td>
<td>19/36</td>
<td>18/36</td>
<td>20.34%</td>
<td>1.06[0.67,1.65]</td>
<td></td>
</tr>
<tr>
<td>Kirkengen 1992</td>
<td>1/20</td>
<td>3/20</td>
<td>0.87%</td>
<td>0.33[0.04,2.94]</td>
<td></td>
</tr>
<tr>
<td>Ouslander 2001</td>
<td>5/15</td>
<td>6/17</td>
<td>4.44%</td>
<td>0.94[0.36,2.47]</td>
<td></td>
</tr>
</tbody>
</table>

Favours oestrogens 0.02 0.1 1 10 50 10 50 10 50 Favours placebo
### Analysis 1.2. Comparison 1 Oral oestrogens versus placebo, Outcome 2 Vaginal pH.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral oestrogens</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N, Mean(SD)</td>
<td>N, Mean(SD)</td>
<td>Random, 95% CI</td>
<td></td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Kirkengen 1992</td>
<td>13, 5.5 (0.6)</td>
<td>17, 6.5 (0.9)</td>
<td>-1 [-1.55, -0.45]</td>
<td>61%</td>
<td>-1 [-1.55, -0.45]</td>
</tr>
<tr>
<td>Ouslander 2001</td>
<td>15, 5.5 (1)</td>
<td>17, 6.5 (1)</td>
<td>-1 [-1.69, -0.31]</td>
<td>39%</td>
<td>-1 [-1.69, -0.31]</td>
</tr>
<tr>
<td>Total **</td>
<td>28, 5.5 (0.6)</td>
<td>34, 6.5 (0.9)</td>
<td>-1 [-1.43, -0.57]</td>
<td>100%</td>
<td>-1 [-1.43, -0.57]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=0; Chi²=0.12; df=1; I²=0%
Test for overall effect: Z=4.54(P <0.0001)

### Analysis 1.3. Comparison 1 Oral oestrogens versus placebo, Outcome 3 Lactobacillus positive.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral oestrogens</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Ouslander 2001</td>
<td>4/15</td>
<td>0/17</td>
<td>10.13 [0.59, 173.83]</td>
<td>61%</td>
<td>10.13 [0.59, 173.83]</td>
</tr>
</tbody>
</table>

Total **

Heterogeneity: Tau²=0; Chi²=0.12; df=1; I²=0%
Test for overall effect: Z=4.54(P <0.0001)

### Analysis 1.4. Comparison 1 Oral oestrogens versus placebo, Outcome 4 All adverse events.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral oestrogens</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Cardozo 1998</td>
<td>10/36</td>
<td>2/36</td>
<td>80.74%</td>
<td>80.74%</td>
<td>51.18 [18.21, 23]</td>
</tr>
<tr>
<td>Ouslander 2001</td>
<td>2/15</td>
<td>0/17</td>
<td>19.26%</td>
<td>19.26%</td>
<td>5.63 [0.29, 108.63]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>51</td>
<td>53</td>
<td></td>
<td>100%</td>
<td>51 [1.39, 18.76]</td>
</tr>
</tbody>
</table>

Total events: 12 (Oral oestrogens), 2 (Placebo)
Heterogeneity: Tau²=0; Chi²=0.12; df=1; I²=0%
Test for overall effect: Z=2.46(P=0.01)

Less with oestrogens 0.001 0.1 1 10 1000 Less with placebo
### Comparison 2. Vaginal oestrogens versus placebo/no treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 UTI at the end of the treatment period</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.1 Placebo</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>1.2 No treatment</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>2 Vaginal pH</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 Lactobacillus positive</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>4 Any adverse events</td>
<td>2</td>
<td>201</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>4.72 [0.67, 33.53]</td>
</tr>
<tr>
<td>4.1 Placebo</td>
<td>1</td>
<td>93</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>2.15 [0.73, 6.37]</td>
</tr>
<tr>
<td>4.2 No treatment</td>
<td>1</td>
<td>108</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>14.53 [1.98, 106.64]</td>
</tr>
</tbody>
</table>

#### Analysis 2.1. Comparison 2 Vaginal oestrogens versus placebo/no treatment, Outcome 1 UTI at the end of the treatment period.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raz 1993</td>
<td>n/N: 8/50</td>
<td>n/N: 27/43</td>
<td>Risk Ratio: 0.25 [0.13, 0.5]</td>
</tr>
<tr>
<td>2.1.2 No treatment</td>
<td>Eriksen 1999</td>
<td>n/N: 27/53</td>
<td>Risk Ratio: 0.64 [0.47, 0.86]</td>
</tr>
</tbody>
</table>

#### Analysis 2.2. Comparison 2 Vaginal oestrogens versus placebo/no treatment, Outcome 2 Vaginal pH.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oestrogens N Mean(SD)</th>
<th>Placebo/no treatment N Mean(SD)</th>
<th>Mean Difference Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raz 1993</td>
<td>50 3.6 (1)</td>
<td>43 6.1 (2)</td>
<td>-2.5 [-3.16, -1.84]</td>
</tr>
</tbody>
</table>

#### Analysis 2.3. Comparison 2 Vaginal oestrogens versus placebo/no treatment, Outcome 3 Lactobacillus positive.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens n/N</th>
<th>Placebo/no treatment n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raz 1993</td>
<td>22/50</td>
<td>0/43</td>
<td>Risk Ratio: 38.82 [2.42, 621.6]</td>
</tr>
</tbody>
</table>
## Analysis 2.4. Comparison 2 Vaginal oestrogens versus placebo/no treatment, Outcome 4 Any adverse events.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.4.1 Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raz 1993</td>
<td>10/50</td>
<td>4/43</td>
<td></td>
<td>58.81%</td>
<td>2.15 [0.73, 6.37]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>50</td>
<td>43</td>
<td></td>
<td>58.81%</td>
<td>2.15 [0.73, 6.37]</td>
</tr>
<tr>
<td></td>
<td>Total events: 10 (Vaginal oestrogens), 4 (Placebo/no treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z=1.38 (P=0.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4.2 No treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriksen 1999</td>
<td>14/53</td>
<td>1/55</td>
<td></td>
<td>41.19%</td>
<td>14.53 [1.98, 106.64]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>53</td>
<td>55</td>
<td></td>
<td>41.19%</td>
<td>14.53 [1.98, 106.64]</td>
</tr>
<tr>
<td></td>
<td>Total events: 14 (Vaginal oestrogens), 1 (Placebo/no treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z=2.63 (P=0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100%</td>
<td>4.72 [0.67, 33.53]</td>
</tr>
<tr>
<td></td>
<td>Total events: 24 (Vaginal oestrogens), 5 (Placebo/no treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau^2=1.39; Chi^2=3.08, df=1 (P=0.08); I^2=67.52%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z=1.55 (P=0.12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Comparison 3. Vaginal oestrogens versus antibiotics

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 UTI</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>1.1 UTI at end of treatment period</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>1.2 UTI - recurrence 2 months after treatment</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>2 Vaginal pH</td>
<td>2</td>
<td>213</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.69 [-4.24, 0.85]</td>
</tr>
<tr>
<td>3 Lactobacillus positive</td>
<td>2</td>
<td>213</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>4.02 [0.25, 65.17]</td>
</tr>
<tr>
<td>4 Adverse events (burning, itching or vaginal bleeding)</td>
<td>2</td>
<td>216</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>12.86 [1.75, 94.29]</td>
</tr>
</tbody>
</table>
### Analysis 3.1. Comparison 3 Vaginal oestrogens versus antibiotics, Outcome 1 UTI.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Antibiotics</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td><strong>3.1.1 UTI at end of treatment period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raz 2003</td>
<td>58/86</td>
<td>44/85</td>
<td>1.3[1.01,1.68]</td>
<td></td>
</tr>
<tr>
<td>Xu 2001</td>
<td>2/27</td>
<td>12/15</td>
<td>0.09[0.02,0.36]</td>
<td></td>
</tr>
<tr>
<td><strong>3.1.2 UTI - recurrence 2 months after treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu 2001</td>
<td>2/27</td>
<td>2/15</td>
<td>0.56[0.09,3.55]</td>
<td></td>
</tr>
</tbody>
</table>

Favours oestrogens 0.02 0.1 1 10 50 Favours antibiotics

### Analysis 3.2. Comparison 3 Vaginal oestrogens versus antibiotics, Outcome 2 Vaginal pH.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Antibiotics</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>Random, 95% CI</td>
<td></td>
<td>Random, 95% CI</td>
</tr>
<tr>
<td>Raz 2003</td>
<td>86 5.3 (0.6)</td>
<td>85 5.7 (0.7)</td>
<td>50.19%</td>
<td>-0.4[-0.6,-0.2]</td>
<td></td>
</tr>
<tr>
<td>Xu 2001</td>
<td>27 4.5 (0.3)</td>
<td>15 7.5 (0.7)</td>
<td>49.81%</td>
<td>-3[-3.37,-2.63]</td>
<td></td>
</tr>
<tr>
<td>**Total *****</td>
<td>113 100</td>
<td></td>
<td>100%</td>
<td>-1.69[-4.24,0.85]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=3.36; Chi²=147.11, df=1(P=0.001); i²=99.32%
Test for overall effect: Z=1.3(P=0.19)

Favours oestrogens 4 -2 0 2 4 Favours antibiotics

### Analysis 3.3. Comparison 3 Vaginal oestrogens versus antibiotics, Outcome 3 Lactobacillus positive.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Antibiotics</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Raz 2003</td>
<td>15/86</td>
<td>10/85</td>
<td>60.74%</td>
<td>1.48[0.71,3.11]</td>
<td></td>
</tr>
<tr>
<td>Xu 2001</td>
<td>16/27</td>
<td>0/15</td>
<td>39.26%</td>
<td>18.86[1.21,293.69]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>113 100</td>
<td></td>
<td>100%</td>
<td>4.02[0.25,65.17]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 31 (Vaginal oestrogens), 10 (Antibiotics)
Heterogeneity: Tau²=3.18; Chi²=4.02, df=1(P=0.04); i²=75.13%
Test for overall effect: Z=0.98(P=0.33)

Favours oestrogens 0.000 0.1 1 10 1000 Favours antibiotics

### Analysis 3.4. Comparison 3 Vaginal oestrogens versus antibiotics, Outcome 4 Adverse events (burning, itching or vaginal bleeding).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Antibiotics</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Raz 2003</td>
<td>14/86</td>
<td>0/85</td>
<td>50.5%</td>
<td>28.67[1.74,473.02]</td>
<td></td>
</tr>
<tr>
<td>Xu 2001</td>
<td>5/30</td>
<td>0/15</td>
<td>49.5%</td>
<td>5.68[0.33,96.35]</td>
<td></td>
</tr>
</tbody>
</table>

Favours oestrogens 0.000 0.1 1 10 1000 Favours antibiotics
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vaginal oestrogens</th>
<th>Antibiotics</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>116</td>
<td>100</td>
<td>100%</td>
<td>12.86(1.75,94.29)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 19 (Vaginal oestrogens), 0 (Antibiotics)
Heterogeneity: Tau²=0; Chi²=0.67, df=1(P=0.41); I²=0%
Test for overall effect: Z=2.51(P=0.01)

Favours oestrogens  0.001  0.1  1  10  1000  Favours antibiotics

APPENDICES

Appendix 1. Electronic search strategies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
</table>
| CENTRAL  | #1 MeSH descriptor Urinary Tract Infections explode all trees in MeSH products
#2 urin* near infect* in All Fields in all products
#3 uti or utis in All Fields in all products
#4 bacteriuria in All Fields in all products
#5 pyuria in All Fields in all products
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Estrogen explode all trees in MeSH products
#8 MeSH descriptor Estrogen Replacement Therapy, this term only in MeSH products
#9 estrogen* in All Fields in all products
#10 oestrogen* in All Fields in all products
#11 ERT in All Fields in all products
#12 (#7 OR #8 OR #9 OR #10 OR #11)
#13 (#6 AND #12) |
| MEDLINE   | 1. exp urinary tract infections/
2. (urin$ adj3 infection$).tw.
3. uti$.tw.
4. bacteriuria$.tw.
5. pyuria.tw.
6. or/1-5
7. exp Estrogens/
8. Estrogen Replacement Therapy/
9. estrogen$.tw.
10. oestrogen$.tw.
11. ert.tw.
12. or/7-11 |
| EMBASE    | 1. exp Urinary Tract Infection/
2. (urin$ adj3 infection$).tw.
3. uti$.tw.
4. exp BACTERIURIA/
5. bacteriuria$.tw.
6. exp PYURIA/
7. pyuria.tw.
8. or/1-7
9. Estrogen/
10. Estrogen Therapy/
11. estrogen$.tw.
12. oestrogen$.tw.
WHAT'S NEW

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 May 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

CP - Screen search results, select studies, assess quality, data extraction, data analysis and writing the final version of the review.
CWN - Search and retrieve relevant articles, did data extraction and entered into RevMan.
MA - Data extraction and quality assessments and collaborated in the final version of the review.
RM - Collaborated preparing the discussion and revising the review.
XA - Prepared the protocol and revised the final version of the review.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources
- Health Research Board, Ireland.
- Iberoamerican Cochrane Center, Barcelona, Spain.
- UCD School of Public Health and Population Sciences, Ireland.

External sources
- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)
*Postmenopause; Administration, Intravaginal; Administration, Oral; Anti-Infective Agents, Urinary [therapeutic use]; Estrogens [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Secondary Prevention; Urinary Tract Infections [*prevention & control]

MeSH check words
Female; Humans