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

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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, cystocoele, 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 strategy
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 relative risk (RR) for dichotomous outcomes or mean difference (WMD) 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

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, cystocoele, 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 oestrogens 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 atrophia 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).

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 intervention

Oral oestrogens (with or without progestogens), or vaginal oestrogens (delivered by cream, vaginal ring, vaginal pessaries, vaginal tables 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 atrophia 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

See: Cochrane Renal Group methods used in reviews.

We searched the following electronic bibliographic databases (see Table 01 - *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.

METHODS OF THE REVIEW

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.
- Blinding of outcome assessor: Yes/no/not stated.
- Blinding of data analysis: 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.

4. 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 relative risk (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 (WMD) 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 I^2test (Higgins 2003).). I^2 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.

DESCRIPTION OF STUDIES

We identified 17 potential studies from the search strategy. We excluded eight studies (Ayton 1996; Brandberg 1987; Chompootaweep 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 2001; Cardozo 1998; Eriksen 1999; Kirkengen 1992; Kjaergaard 1990; Ouslander 2001; Raz 1993; Raz 2003; Xu 2001) (see table: *Characteristics of included studies*).

Interventions

- Oral oestrogens versus placebo (Brown 2001; Cardozo 1998; Kirkengen 1992; Ouslander 2001).
- 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 forth 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).

METHODOLOGICAL QUALITY

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 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; septicaemia; 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).

RESULTS

Oral oestrogens versus placebo (comparison 01)
Proportion of women with UTI at the end of the treatment period (analysis 01.01)
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 (4 studies, 2798 women: RR 1.08, 95% CI 0.88 to 1.33; I^2 = 0%).

Vaginal pH (analysis 01.02)
Two studies reported the change in vaginal pH (Kirkengen 1992; Ouslander 2001). There was a significant decrease in vaginal pH with the oral oestrogens (2 studies, 62 women: WMD -1.00, 95% CI -1.43 to -0.57; I^2 = 0%).

Proportion of women Lactobacillus positive (analysis 01.03)
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 (1 study, 32 women: RR 10.13, 95% CI 0.59 to 173.83).

All adverse events (analysis 01.04)
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 (2 studies, 104 women: RR 5.11, 95% CI 1.39 to 18.76; I^2 = 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 (comparison 02)
Proportion of infection at the end of the treatment period (analysis 02.01)
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 (analysis 02.02)
Raz 1993 reported a significant decrease in pH with vaginal oestrogens (93 women: WMD -2.50, 95% CI -3.16 to -1.84).

Proportion of women Lactobacillus positive (analysis 02.03)
Raz 1993 reported significantly more women were *Lactobacillus* positive in the vaginal oestrogen group (93 women: RR 38.82, 95% CI 2.42 to 621.60).

All adverse events (analysis 02.04)
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 (201 women: RR 4.72, 95% CI 0.67 to 33.53; I^2 = 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 (comparison 03)
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 (analysis 03.01)
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 (RR 1.30, 95% CI 1.01 to 1.68).
- Xu 2001 (42 women) reported significantly less UTIs in the oestrogen group compared the antibiotic group after three months (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 (RR 0.56, 95% CI 0.09 to 3.55).

Vaginal pH (analysis 03.02)
There was no statistical difference in vaginal pH between vaginal oestrogens and antibiotics ((2 studies, 213 women: WMD -1.69, 95% CI -4.24 to 0.85; I^2 = 99.3%), however there was very significant heterogeneity.

Proportion of women Lactobacillus positive (analysis 03.03)
There was no statistical difference in the number of women *Lactobacillus* positive between vaginal oestrogens and antibiotics (2 studies, 213 women: RR 4.02, 95% CI 0.25 to 65.06; I^2 = 75.1%). There was significant heterogeneity.

Adverse events (analysis 03.04)

- 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 oestriol) 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).

POTENTIAL CONFLICT OF INTEREST

None declared.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	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. Coronary heart disease and intact uterus.
Interventions	TREATMENT GROUP 0.625 mg of oral conjugated oestrogen plus 2.5 mg of medroxyprogesterone acetate. CONTROL GROUP

Characteristics of included studies (*Continued*)

	Placebo.
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).
Allocation concealment	A – Adequate

Study	**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	1. Percentage of women remaining infection-free (dichotomous). 2. Breast tenderness (dichotomous). 3. Vaginal bleeding (dichotomous).
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; septicaemia; cerebrovascular accident; left arm paresis; adverse experiences and general decline in health.
Allocation concealment	B – Unclear

Study	**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).

Characteristics of included studies (*Continued*)

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)".
Allocation concealment	B – Unclear

Study	**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).
Notes	Definition of RUTI: at least one episode with a repeat infection within two weeks or at least three episodes during the previous year.
Allocation concealment	B – Unclear

Study	**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	
Allocation concealment	B – Unclear

Study	**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

Characteristics of included studies (*Continued*)

	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). 6. Breast discomfort (dichotomous).
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)
Allocation concealment	B – Unclear

Study	**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
Allocation concealment	B – Unclear

Study	**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)
Allocation concealment	B – Unclear

Study	**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	
Allocation concealment	B – Unclear

Characteristics of excluded studies

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

ADDITIONAL TABLES

Table 01. Electronic search strategies

Database	Search terms
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 Estrogens 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. 13. ert.tw. 14. or/9-13 15. 8 and 14

ANALYSES

Comparison 01. Oral oestrogens versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 UTI at the end of the treatment period	4	2798	Relative Risk (Random) 95% CI	1.08 [0.88, 1.33]
02 Vaginal pH	2	62	Weighted Mean Difference (Random) 95% CI	-1.00 [-1.43, -0.57]
03 Lactobacillus positive			Relative Risk (Random) 95% CI	Totals not selected
04 All adverse events	2	104	Relative Risk (Random) 95% CI	5.11 [1.39, 18.76]

Comparison 02. Vaginal oestrogens versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 UTI at the end of the treatment period			Relative Risk (Random) 95% CI	Totals not selected
02 Vaginal pH			Weighted Mean Difference (Random) 95% CI	Totals not selected
03 Lactobacillus positive			Relative Risk (Random) 95% CI	Totals not selected
04 Any adverse events	2	201	Relative Risk (Random) 95% CI	4.72 [0.67, 33.53]

Comparison 03. Vaginal oestrogens versus antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 UTI			Relative Risk (Random) 95% CI	Totals not selected
02 Vaginal pH	2	213	Weighted Mean Difference (Random) 95% CI	-1.69 [-4.24, 0.85]
03 Lactobacillus positive	2	213	Relative Risk (Random) 95% CI	4.02 [0.25, 65.17]
04 Adverse events (burning, itching or vaginal bleeding)	2	216	Relative Risk (Random) 95% CI	12.86 [1.75, 94.29]

COVER SHEET

Title

Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Authors

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Contribution of author(s)

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.

Issue protocol first published

2005/1

Review first published

2008/2

Date of most recent amendment

05 February 2008

Date of most recent SUBSTANTIVE amendment

31 January 2008

What's New

Information not supplied by author

Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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Cochrane Library number	CD005131
Editorial group	Cochrane Renal Group
Editorial group code	HM-RENAL

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Oral oestrogens versus placebo, Outcome 01 UTI at the end of the treatment period

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 01 Oral oestrogens versus placebo

Outcome: 01 UTI at the end of the treatment period

Study	Oral oestrogens n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Brown 2001	132/1318	120/1336		74.3	1.12 [0.88, 1.41]
Cardozo 1998	19/36	18/36		20.3	1.06 [0.67, 1.65]
Kirkengen 1992	1/20	3/20		0.9	0.33 [0.04, 2.94]
Ouslander 2001	5/15	6/17		4.4	0.94 [0.36, 2.47]
Total (95% CI)	1389	1409		100.0	1.08 [0.88, 1.33]

Total events: 157 (Oral oestrogens), 147 (Placebo)

Test for heterogeneity chi-square=1.28 df=3 p=0.74 I^2 =0.0%

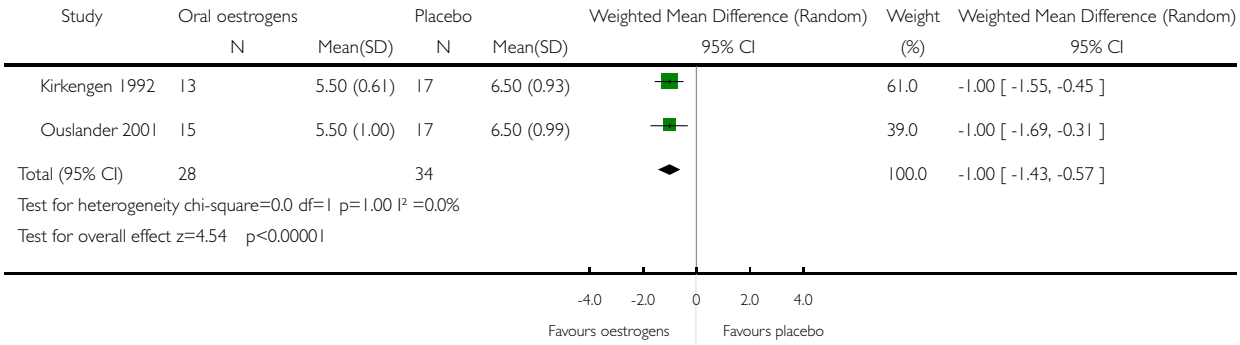
Test for overall effect z=0.77 p=0.4

Analysis 01.02. Comparison 01 Oral oestrogens versus placebo, Outcome 02 Vaginal pH

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 01 Oral oestrogens versus placebo

Outcome: 02 Vaginal pH

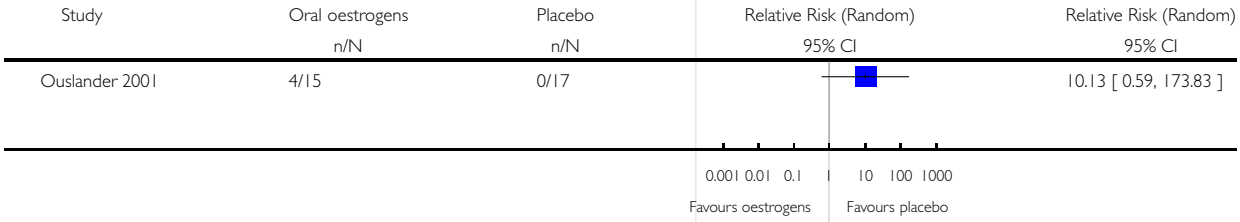


Analysis 01.03. Comparison 01 Oral oestrogens versus placebo, Outcome 03 Lactobacillus positive

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 01 Oral oestrogens versus placebo

Outcome: 03 Lactobacillus positive

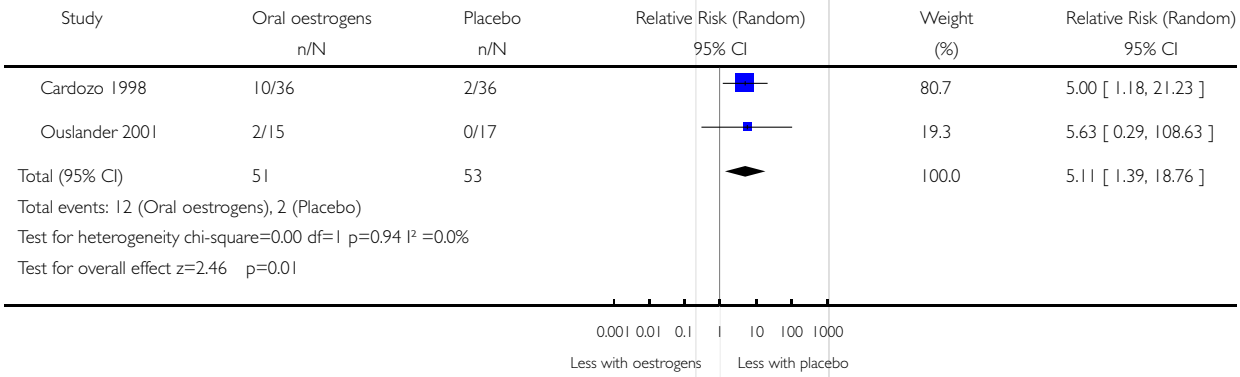


Analysis 01.04. Comparison 01 Oral oestrogens versus placebo, Outcome 04 All adverse events

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 01 Oral oestrogens versus placebo

Outcome: 04 All adverse events

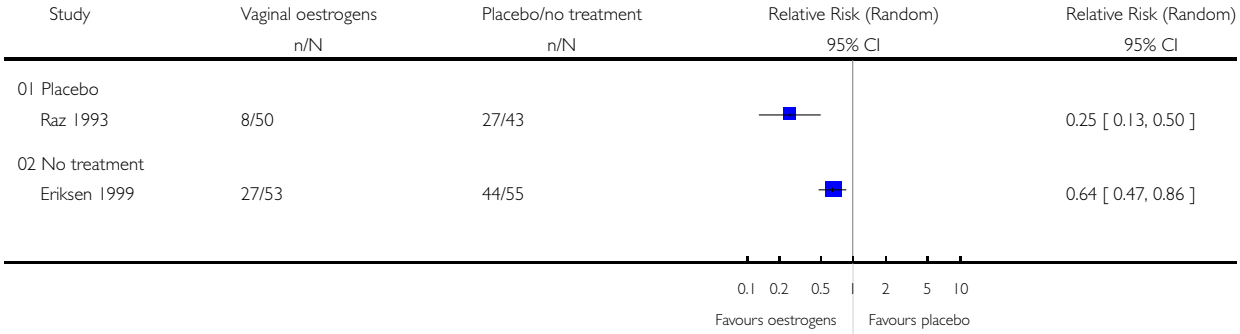


Analysis 02.01. Comparison 02 Vaginal oestrogens versus placebo/no treatment, Outcome 01 UTI at the end of the treatment period

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 02 Vaginal oestrogens versus placebo/no treatment

Outcome: 01 UTI at the end of the treatment period

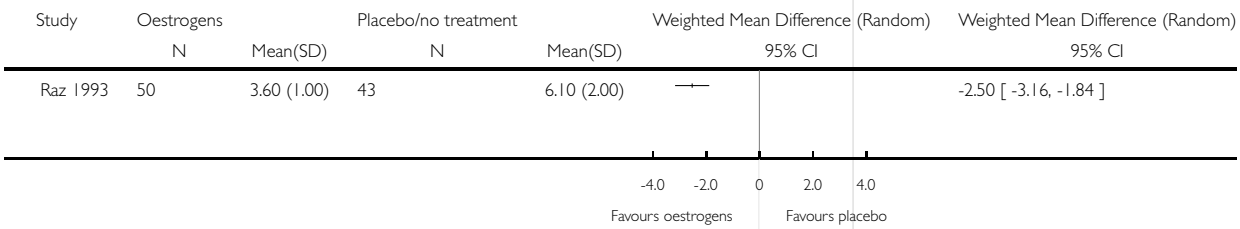


Analysis 02.02. Comparison 02 Vaginal oestrogens versus placebo/no treatment, Outcome 02 Vaginal pH

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 02 Vaginal oestrogens versus placebo/no treatment

Outcome: 02 Vaginal pH

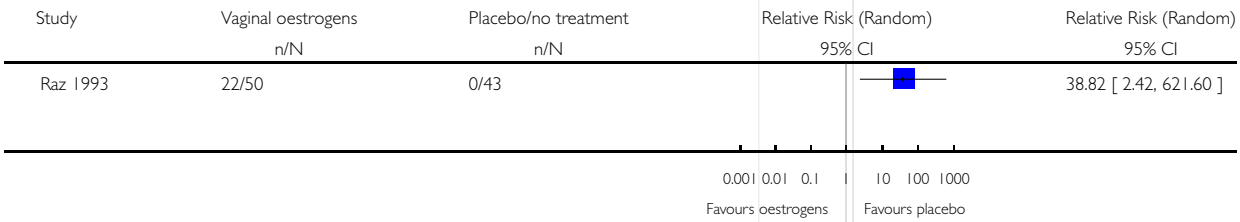


Analysis 02.03. Comparison 02 Vaginal oestrogens versus placebo/no treatment, Outcome 03 Lactobacillus positive

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 02 Vaginal oestrogens versus placebo/no treatment

Outcome: 03 Lactobacillus positive

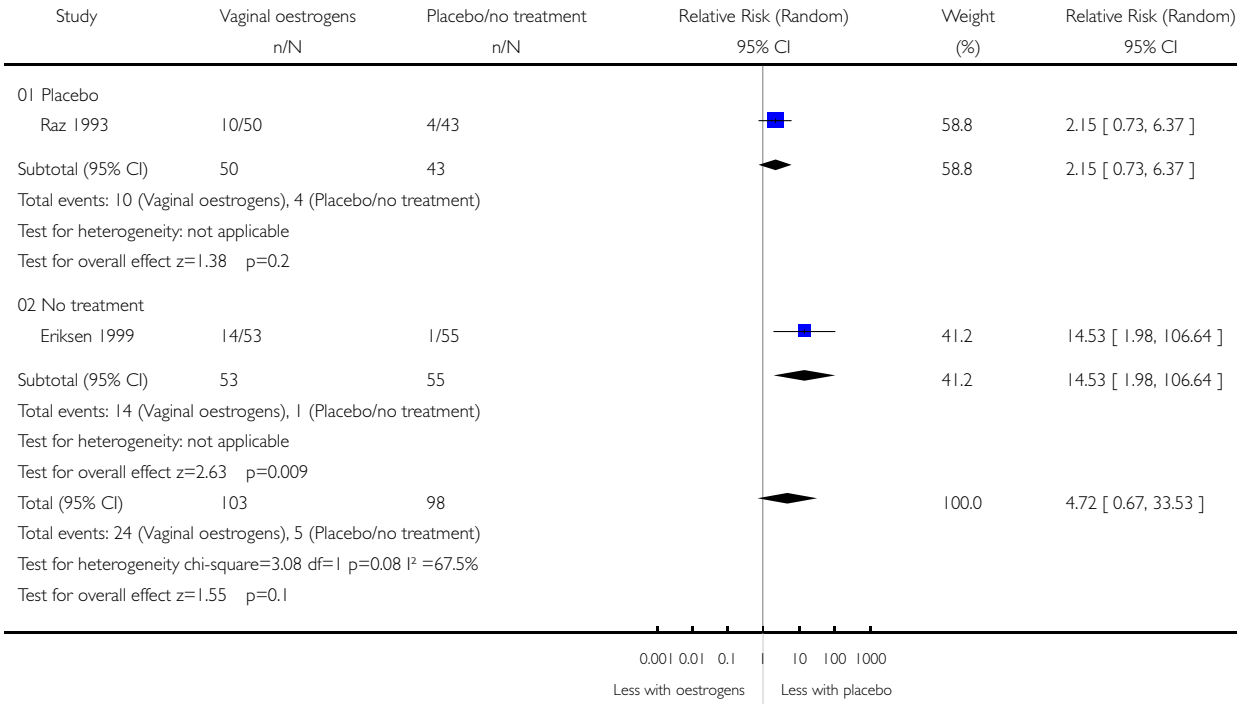


Analysis 02.04. Comparison 02 Vaginal oestrogens versus placebo/no treatment, Outcome 04 Any adverse events

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 02 Vaginal oestrogens versus placebo/no treatment

Outcome: 04 Any adverse events

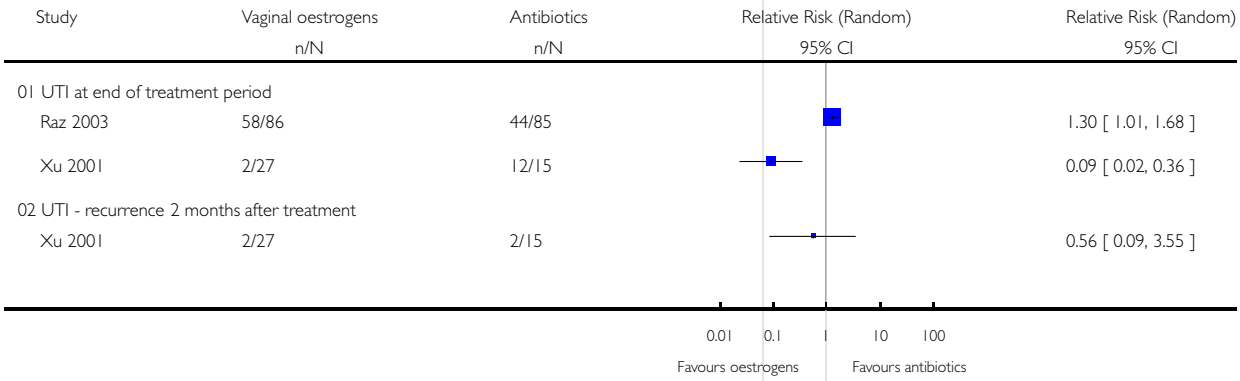


Analysis 03.01. Comparison 03 Vaginal oestrogens versus antibiotics, Outcome 01 UTI

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 03 Vaginal oestrogens versus antibiotics

Outcome: 01 UTI



Analysis 03.02. Comparison 03 Vaginal oestrogens versus antibiotics, Outcome 02 Vaginal pH

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

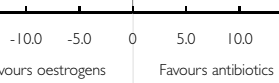
Comparison: 03 Vaginal oestrogens versus antibiotics

Outcome: 02 Vaginal pH

Study	Vaginal oestrogens N	Mean(SD)	Antibiotics N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Raz 2003	86	5.30 (0.60)	85	5.70 (0.70)		50.2	-0.40 [-0.60, -0.20]
Xu 2001	27	4.50 (0.30)	15	7.50 (0.70)		49.8	-3.00 [-3.37, -2.63]
Total (95% CI)	113		100			100.0	-1.69 [-4.24, 0.85]

Test for heterogeneity chi-square=147.11 df=1 p=<0.0001 I^2 =99.3%

Test for overall effect z=1.30 p=0.2



Analysis 03.03. Comparison 03 Vaginal oestrogens versus antibiotics, Outcome 03 Lactobacillus positive

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 03 Vaginal oestrogens versus antibiotics

Outcome: 03 Lactobacillus positive

Study	Vaginal oestrogens n/N	Antibiotics n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Raz 2003	15/86	10/85		60.7	1.48 [0.71, 3.11]
Xu 2001	16/27	0/15		39.3	18.86 [1.21, 293.69]
Total (95% CI)	113	100		100.0	4.02 [0.25, 65.17]

Total events: 31 (Vaginal oestrogens), 10 (Antibiotics)

Test for heterogeneity chi-square=4.02 df=1 p=0.04 I^2 =75.1%

Test for overall effect z=0.98 p=0.3

Analysis 03.04. Comparison 03 Vaginal oestrogens versus antibiotics, Outcome 04 Adverse events (burning, itching or vaginal bleeding)

Review: Oestrogens for preventing recurrent urinary tract infection in postmenopausal women

Comparison: 03 Vaginal oestrogens versus antibiotics

Outcome: 04 Adverse events (burning, itching or vaginal bleeding)

Study	Vaginal oestrogens n/N	Antibiotics n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Raz 2003	14/86	0/85		50.5	28.67 [1.74, 473.02]
Xu 2001	5/30	0/15		49.5	5.68 [0.33, 96.35]
Total (95% CI)	116	100		100.0	12.86 [1.75, 94.29]

Total events: 19 (Vaginal oestrogens), 0 (Antibiotics)

Test for heterogeneity chi-square=0.67 df=1 p=0.41 I^2 =0.0%

Test for overall effect z=2.51 p=0.01