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REVIEW ARTICLE

Estrogen for the prevention of recurrent urinary tract infections in postmenopausal women: a meta-analysis of randomized controlled trials

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Abstract

Introduction and hypothesis Recurrent urinary tract infections (rUTIs) are commonly encountered in postmenopausal women. Optimal non-antimicrobial prophylaxis for rUTIs is an important health issue. The aim of this study was to evaluate the use of estrogen in the prevention of rUTIs versus placebo.

Methods Eligible studies published up to December 2019 were retrieved through searches of MEDLINE, Embase, and Cochrane Central Register of Controlled Trials and Database of Systematic Reviews. We included randomized controlled trials of estrogen therapies versus placebo regarding the outcomes of preventing rUTIs. Changes in vaginal pH and estrogen-associated adverse events were also analyzed.

Results Eight studies including 4702 patients (2367 who received estrogen and 2335 who received placebo) were identified. Five studies including 1936 patients evaluated the use of vaginal estrogen, which resulted in a significant reduction in rUTIs (relative risk, 0.42; 95% CI, 0.30–0.59). Three studies including 2766 patients evaluated the outcomes of oral estrogen in the prevention of UTIs and showed no significant difference in the number of rUTIs compared to treatment with placebo (relative risk, 1.11; 95% CI, 0.92–1.35). Two studies reviewed changes in vaginal pH and showed a lower pH (mean difference, −1.81; 95% CI, −3.10–−0.52) after vaginal estrogen therapy. Adverse events associated with vaginal estrogen were reported, including vaginal discomfort, irritation, burning, and itching. There was no significance increase in the vaginal estrogen group (relative risk, 3.06; 95% CI, 0.79–11.90).

Conclusions Compared with placebo, vaginal estrogen treatment could reduce the number of rUTIs and lower the vaginal pH in postmenopausal women.

Keywords Estrogen · Post-menopause · Prevention · Recurrent urinary tract infection

Abbreviations

UTI urinary tract infection
rUTI recurrent UTI

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Introduction

Urinary tract infections (UTIs) are common in women, and appropriate antibiotics are the mainstay of treatment of acute infections. Recurrent UTIs (rUTIs) are defined as at least two episodes of UTIs within 6 months or three episodes within 1 year [1]. It is an important health issue for women after menopause. Continuous long-term low-dose antibiotic treatment has been reported to be an effective management strategy to prevent rUTIs; however, it can lead to an increase in drug-resistance rates to the causative microorganisms, thereby leading to another health problem [2]. As a result, the use of optimal non-antimicrobial prophylaxis for rUTIs has become increasingly important. The proposed non-antimicrobial treatments include estrogen, probiotics, and vitamins. However, evidence-based data on the use of these prophylaxis treatments are still required.

The prevalence of UTIs increases with age in women [3–5], and 10–15% of women > 60 years old have been reported to have rUTIs [3, 4] compared to > 20% of those > 65 years and 25–50% of those > 80 years old [5]. An important pathogenesis of rUTIs in these women is hormonal deficiency [2–6]. Estrogen deficiency inhibits the growth of vaginal Lactobacillus flora, which can maintain vaginal pH and prevent colonization by uropathogens such as *Escherichia coli* [7]. The presence of such uropathogens increases the risk of infection. A few randomized controlled trials have evaluated the efficacy of using estrogen to prevent rUTIs, and they have reported the significant efficacy of local estrogen applications compared to systemic estrogen [2–7]. A Cochrane systematic review by Perrotta in 2008 reported that vaginal estrogen treatment could reduce the number of rUTIs in postmenopausal women [7]. However, this finding was based on only two randomized controlled studies [3, 4], and their study was published > 10 years ago. In addition, the methods of estrogen application in the two studies were different, using either vaginal cream or ring. Therefore, the aim of this review was to evaluate current data and evidence to elucidate the efficacy of estrogen treatment as non-antimicrobial prophylaxis for rUTIs in postmenopausal women. Vaginal pH and hormone-associated adverse events were also analyzed to evaluate the safety of the treatment.

Materials and methods

We performed a detailed computerized data search in December 2019 of MEDLINE (1950–2019), EMBASE (1980–2019), and the Cochrane Central Register of

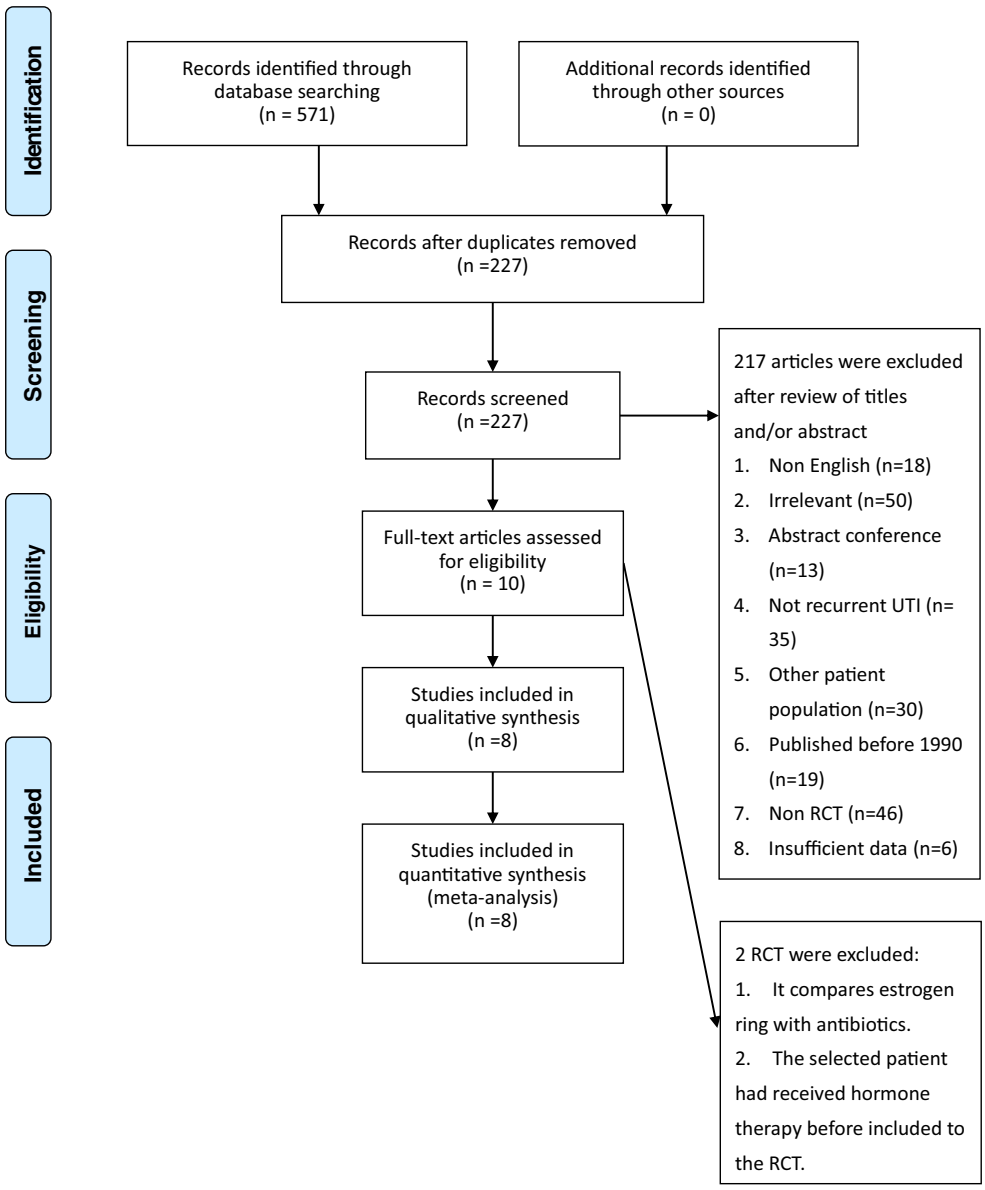

Fig. 1 Flow diagram of literature identification and inclusion and exclusion criteria

Table 1 Characteristics of the reviewed studies

Author	Year	Type of RCT	Number of participants	Study duration	Characteristics of participants	Interventions	Tools for evaluations	Outcomes
Ferrante [5]	2019	Multicenter, single-blind, randomized, placebo controlled trial	35 (9, 9, 17)	6 months	PMP symptoms > 1 year or age > 55 years old. Participants had documented rUTI (≥ 3 in 1 year or 2 in 6 months) by positive U/C	T1: Vaginal estradiol ring 2 mg every 3 months T2: conjugated estrogen. Cream 0.625 mg/g dosed at 0.5 g (0.312 mg) twice a week at night. C: Placebo cream	Non-UTI rate, FSFI, MESA I, MESA II, PFDI, PFIQ, EPI	Vaginal estrogen prevented UTIs in PMP women with rUTI
Dessole [10]	2004	Prospective, randomized, placebo controlled trial	88 (44, 44)	6 months	All participants presented symptoms and signs of USI, vaginal atrophy, and histories of rUTI. None had received estrogen treatment before the study	T: One intravaginal estriol ovule (1 mg) once daily for 2 weeks and then 2 ovules once weekly as maintenance therapy. C: Vaginal placebo in a similar regimen	Urinary incontinence, therapeutic efficacy, urogenital atrophic symptoms, vaginal atrophy, vaginal pH, significant bacteriuria, vaginal and urethral smears, and karyopyknotic index	Vaginal estrogen resulted in subjective improvements in incontinence, urogenital atrophy, vaginal dryness, dyspareunia, vaginal pH, and colposcopic parameters; increases in mean MUP and MUCP
Simunic [10]	2003	Multicenter, double-blind, randomized, placebo controlled trial	1612 (828, 784)	12 months	PMP women>1Y with urogenital symptoms. Participants had rUTI (≥ 2 in 1 year)	T: 25 μg of micronized 17 β-estradiol once a day over a period of 2 weeks, and then twice a week for the remaining 12 months. C: Placebo at same period	Full history questionnaire, micturition diary, gynecologic and cystometric examination, transvaginal ultrasound, and serum 17β estradiol level determination	Local administration of 25 μg of micronized 17β-estradiol is an effective and safe treatment option in the management of women with urogenital complaints and rUTI
Brown [11]	2001	Double-blind, randomized, controlled trial	2654 (1318, 1336)	4.1 years	PMP women < 80 years old with coronary heart disease and with an intact uterus	T: One oral tablet containing both conjugated estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) daily. C: One identical placebo tablet daily	Vaginal/genital symptoms, frequency of sexual activity, smoking habit, alcohol consumption, body weight, waist, hip circumference, body mass index, waist-to-hip ratio, fasting glucose measurements, urinary tract infections, stress incontinence, and urge incontinence	Oral hormone therapy did not reduce frequency of UTI
Eriksen [4]	1999	Randomized, open, parallel-group trial	108 (53, 55)	36 weeks	PMP women ≥ 2 years with ≥ 3 UTIs treated during the previous 12 months and had normal urine	T: A silicone vaginal ring of 2 mg micronized 17β-estradiol every 12 weeks. C: No treatment	Time to the first bacteriologically confirmed and symptomatic rUTI, improvement of PMP symptoms, urethral and vaginal mucosal maturation, vaginal pH	Estring is useful to prolong the time to next recurrence and to decrease the number of recurrences per year. It also alleviated other PMP urogenital symptoms
Cardozo [6]	1998	Double-blind, randomized, parallel group, placebo controlled trial	72 (36, 36)	12 months	At least 2 UTIs in the last 18 months; serum estradiol < 220 pmol/l; serum FSH > 40 IU/l; > 2 years since the last menstrual period; > 60 years of age; able to give informed consent	T: Oral estriol (3 mg) daily. C: Placebo tablets	Non-UTI rate, frequency, dysuria, hematuria, incontinence, and other LUTs	Oral estriol (3 mg per day) was not shown to be superior to placebo in the prevention of rUTI

Table 1 (continued)

Author	Year	Type of RCT	Number of participants	Study duration	Characteristics of participants	Interventions	Tools for evaluations	Outcomes
Raz [3]	1993	Double-blind, randomized, placebo. Controlled trial	93 (50, 43)	8 months	PMP women with rUTI (> 3 in the past year)	T: 0.5 mg of estriol in vaginal cream to be used daily for 2 weeks and twice a week for 8 months C: Placebo cream	UTI rate, vaginal lactobacilli, vaginal pH, and side effects	The intravaginal administration of estriol prevents rUTI in PMP women
Kirkengen [12]	1992	Double-blind, randomized, placebo controlled trial	40 (20, 20)	12 weeks	RUTI (≥ 1 episode within 2 weeks or ≥ 3 episodes during the previous year), vaginal pH, and treatment of current UTI with antibiotics	T: Oral estriol 3 mg daily for 4 weeks, followed by 1 mg daily for 8 weeks. C: Placebo for same periods	The number of bacteriologically verified UTI per week during the treatment period. Possible adverse effects	Estriol reduces rUTI in PMP women

EPI, estimated percent improvement; FSFI, Female Sexual Functioning Index; FSH, follicle stimulating hormone; LUTs, lower urinary tract symptoms; MESA, Medical, Epidemiologic, and Social Aspects of Aging Questionnaire; MUP, maximum urethral pressure; MUCP, maximum urethral closure pressure; PFDI, Pelvic Floor Disability Index; PFIQ, Pelvic Floor Impact Questionnaire; PMP, postmenopausal; RCT, randomized controlled trial; UTI, urinary tract infection; rUTI, recurrent urinary tract infection; U/C, urine culture; USI, urinary stress incontinence

Controlled Trials and Database of Systematic Reviews (1991–2019). The search strategy was to use combinations of search terms related to population, intervention, comparison, and outcome as follows: "postmenopausal or menopausal," "recurrent urinary tract infection," "urinary tract infection," "dysuria," "lower urinary tract symptoms," "vaginal or systemic," "estrogen or hormonal therapy," "side effects," and "prophylaxis". The search was limited to human studies. We selected randomized controlled studies that reported on the effectiveness of preventing rUTIs after estrogen treatment versus placebo in postmenopausal women with a minimum of 12 weeks of follow-up. Studies including patients who received different estrogen applications (e.g., vaginal estrogen ring, pessary, tablets, cream, or oral estrogen) compared with placebo were included. Studies which were not in English, those that did not meet the criteria for rUTIs, and those in which the patients received antimicrobial treatments or other non-antimicrobial agents were excluded from the review. Data related to vaginal condition including vaginal pH and hormone-associated adverse events were also retrieved and analyzed.

Data were extracted from each study by two reviewers and confirmed by another reviewer. We assessed the risk of bias of studies using domain-based evaluations, which were produced by The Cochrane Collaboration in 2011 [8]. The risk of bias included generation of the allocation sequence, concealment of the allocation sequence, blinding, incomplete outcome data, selective outcome reporting, and other biases. The risk of bias was rated as "low," "high," or "unclear." In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to rate the quality of evidence [9]. Meta-analysis was used to estimate the risk ratio (RR) (for binary outcomes) or net change (for continuous outcomes) using RevMan Review Manager Version 5.0 [RevMan Review Manager (RevMan) computer program, version 5.0. 2008. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration].

Results

We identified 571 publications that evaluated the effect of estrogen preparations versus placebo for the prevention of rUTIs in postmenopausal women. The cited references in the primary articles or specialist reviews and publications were also searched. After removing duplicates, 227 publications were reviewed with regard to the inclusion and exclusion criteria. The flow diagram of the literature search and inclusion and exclusion criteria is shown in Fig. 1. A total of 188 articles were excluded, and 9 randomized controlled trials were eligible for initial assessment. Of these, one compared vaginal estrogen rings with antimicrobial agents and one included postmenopausal females who had already received oral hormone therapy before being randomized into the trial, and

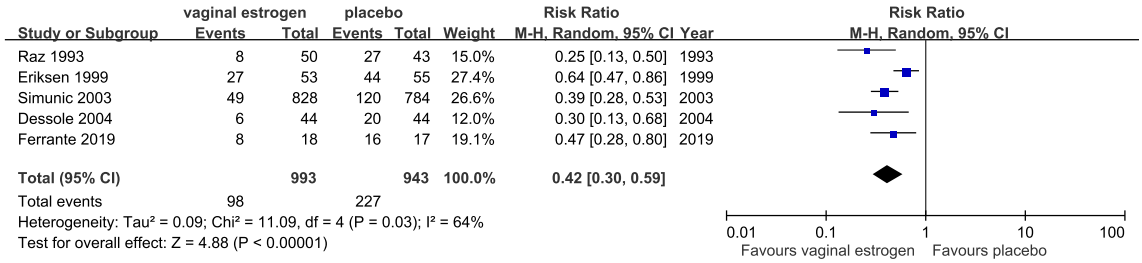

Fig. 2 Recurrent urinary tract infection between women undergoing local estrogen therapy and placebo

they were thus excluded from this review. The remaining eight articles were analyzed to assess the efficacy of estrogen as non-antimicrobial prophylaxis for rUTIs compared with placebo. Table 1 shows the characteristics of the studies included in the review. We reviewed the outcomes of different hormonal applications and compared vaginal and oral estrogen preparations versus placebo.

Vaginal estrogen

The use of vaginal estrogen was evaluated in five trials involving 324 patients. Two studies used vaginal estradiol silicone rings and conjugated estrogen cream [4, 5], and three used estriol in vaginal inserts (cream, ovules) [3, 10, 11]. Four studies evaluated the reduction or recurrence of new episodes of UTIs as the treatment outcome, whereas one trial assessed the occurrence of bacteriuria. All preparations of vaginal estrogen decreased the number of UTIs compared with placebo or compared to baseline conditions (number of UTIs before starting the trial or baseline bacteriuria) (relative risk, 0.42; 95% confidence interval, 0.30–0.59) (Fig. 2).

Oral estrogen

Three studies evaluated the outcomes of oral estrogen in the prevention of UTIs, including a total of 2766 patients [6, 12, 13]. Two studies used the same type of estriol but in different doses (3 mg daily for the duration of the study or 3 mg daily for 4 weeks and then 1 mg daily for the duration of the study), and another used oral tablets containing both conjugated estrogens (0.625 mg) and medroxyprogesterone acetate [12]. None of the studies showed a significant reduction in the episodes of UTIs compared with placebo (relative risk, 1.11; 95% confidence interval, 0.92–1.35) (Fig. 3). One study reported no improvements in UTI rate in the first 4 weeks but significant improvements at 12 weeks [13], and two studies reported no improvements after systemic estrogen therapy [6, 12].

Vaginal pH

Two studies were reviewed for the change in vaginal pH [3, 11], one of which used vaginal ovules and the other used vaginal cream. Estrogen showed significant efficacy in decreasing vaginal pH (mean difference, −1.81; 95% confidence interval, −3.10—0.52) (Fig. 4).

Adverse events

The adverse events associated with vaginal estrogen therapy included vaginal discomfort, irritation, burning, and itching. Compared with placebo, there was no significance increase in adverse events (relative risk, 3.06; 95% confidence interval, 0.79–11.90) (Fig. 5). The adverse effects in the oral systemic estrogen group varied widely, so they were difficult to evaluate [6, 12, 13]. One study reported no adverse events related to hormone therapy [13], and one study reported that oral estrogen increased the risks of diabetes, vaginal symptoms, and urge incontinence [12]. Another study reported that three (8.3%) patients had vaginal bleeding and seven (19.4%) had breast pain in the oral estrogen group compared to one (2.8%) with vaginal bleeding and one (2.8%) with breast pain in the placebo group [6].

Risk of bias and GRADE quality of evidence evaluation

The risks of bias assessments for each study are summarized and presented graphically in Figs. 6 and 7. There was a high

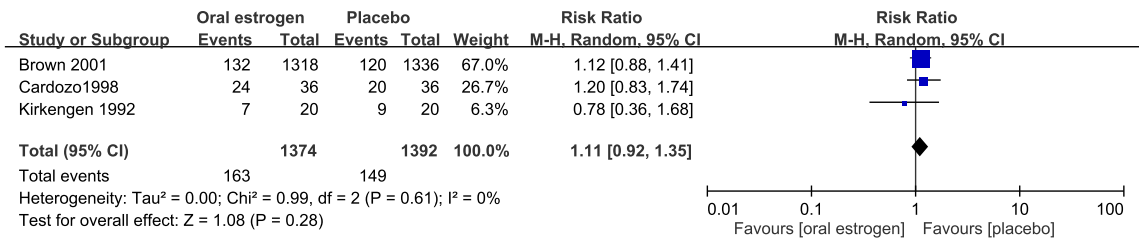

Fig. 3 Recurrent urinary tract infection between women undergoing systemic estrogen therapy and placebo

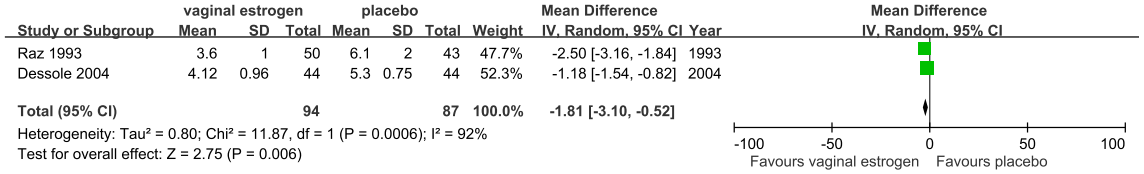

Fig. 4 Vaginal pH between women undergoing local estrogen therapy and placebo

risk of bias in 50% (4/8) of the trials due to incomplete outcome data. Other biases included blinding of outcome assessment (2/8, 25%), and blinding of the participants (1/8, 12.5%). The GRADE quality of evidence evaluation is summarized in Table 2.

Discussion

The results showed that vaginal estrogen could reduce the number of rUTIs in postmenopausal women compared with placebo (five studies, 1936 women: RR 0.42; 95% CI, 0.30–0.59), but that oral estrogen did not (three studies, 2766 women: RR 1.11; 95% CI, 0.92–1.35). Vaginal estrogen treatment significantly lowered vaginal pH (two studies, 211 women: mean difference, −1.81; 95% CI, −3.10—0.52) and was not associated with adverse events, including vaginal discomfort, irritation, burning, or itching (four studies, 324 women: RR 3.06; 95% CI, 0.79–11.90).

Several physiologic changes increase the risk of rUTIs in postmenopausal women, one of which is urogenital atrophy. Thinning of the vaginal or urethral mucosa and relaxation of pelvic floor muscles may cause the development of urinary or fecal incontinence and pelvic organ prolapse. These pelvic floor disorders can then cause an increase in post-voiding residual urine volume and incontinence causing poor hygiene, which are predisposing factors for UTIs. Another physiologic change is the change in vaginal microflora. Estrogen deficiency is not beneficial to lactobacilli-dominated vaginal microflora, which can maintain vaginal pH and prevent colonization by uropathogens [14]. In a prospective study, Meister et al. enrolled 70 postmenopausal women to evaluate changes in the urine inflammatory profile after vaginal estrogen therapy, and they proposed that hormone treatment could help to prevent rUTIs and reduce the symptoms of infection [15]. They also reported that vaginal estrogen could reduce levels of urine interleukin 6 and reduce urine inflammatory scores, indicating the genitourinary inflammatory response and suppression of associated symptoms with local estrogen treatment [15].

Although vaginal estrogen treatment appears to be a promising choice for postmenopausal women, there are concerns over the efficacy and safety of its long-term use. Because estradiol absorption is dose dependent and may be influenced by the delivery system, various formulations and positioning in the vagina have been suggested [16]. A Cochrane systematic review reported that vaginal estrogen cream may be associated with an increase in endometrial thickness compared to estrogen rings because of the higher doses of cream used [7]. Besides endometrial thickness, other estrogen-associated adverse events included breast tenderness, vaginal bleeding or spotting, non-physiologic discharge, vaginal irritation, burning, and itching [7]. Currently, the recommendations for local estrogen dosage and administration for vulvovaginal atrophy are to avoid a significant increase in serum estradiol [17]. The preparations of vaginal estrogen therapy can be classified as low-, intermediate-, and high-dosage preparations [18]. Low-dose vaginal estrogen is defined as around 7.5 μg for vaginal rings and 10 μg for tablets. Long-term low-dose vaginal estrogen administration has been reported to possibly increase plasma estradiol levels, but not above the normal range of ≤ 20 pg/ml [18], suggesting that low-dose estrogen therapy does not increase the rate of adverse events associated with systemic hormone therapy. An intermediate dose is defined as 25 μg estradiol or 0.3 mg conjugated equine estrogen, and a high dose is defined as 50–2000 μg estradiol or 0.625–2.5 mg conjugated equine estrogen. These doses may result in plasma estradiol levels approaching or exceeding 20 pg/ml [18]. In our review, all vaginal estrogen preparations used higher doses; however, no serious adverse events were reported. Although the meta-analysis revealed non-significant side effects, the longest use of vaginal estrogen therapy was only 36 weeks [4]. Therefore, further studies regarding the safety of long-term vaginal estrogen preparations are warranted. In addition, further studies to evaluate the efficacy of low-dose

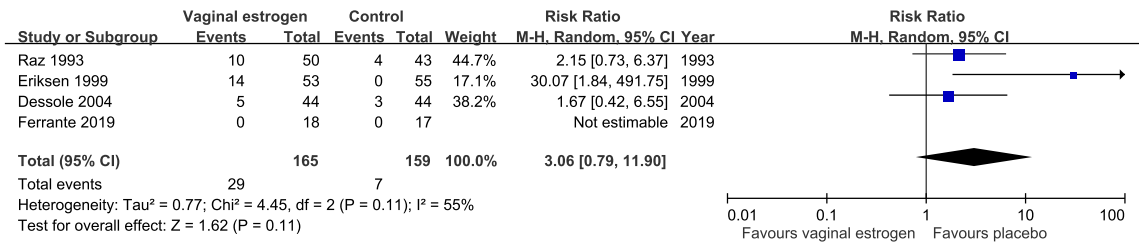

Fig. 5 Adverse events between women undergoing local estrogen therapy and placebo

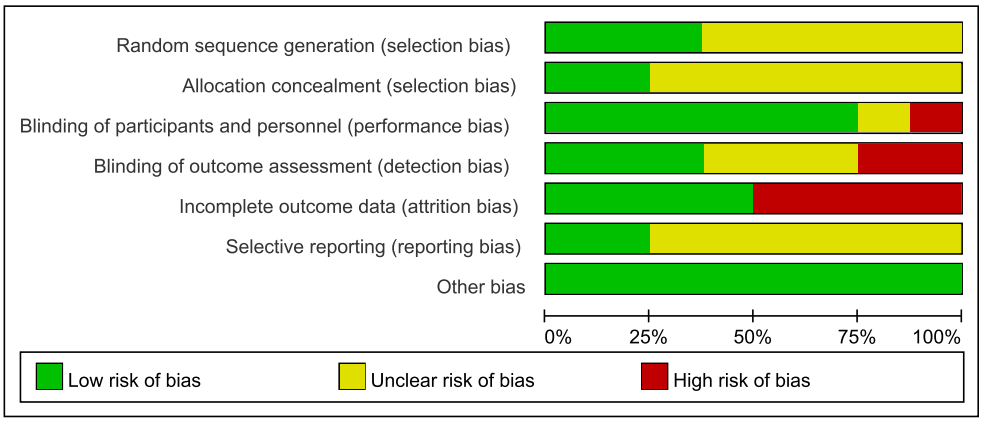

Fig. 6 Risk of bias graph

vaginal estrogen for preventing rUTIs are also warranted, because low-dose regimens may be preferred clinically to high-dose regimens in women, particularly for those who are concerned about the side effects of chronic estrogen therapy.

Although none of the studies reported direct outcomes with regard to the growth of lactobacilli flora, the meta-analysis showed that vaginal estrogen could lower vaginal pH in postmenopausal women. It is worth noting that vaginal estradiol absorption is acute with peaks at about 8 h that return to baseline at 12 h [19], indicating that the absorption of estradiol decreases shortly after the start of treatment. This means that vaginal mucosa and acidity may recover from an atrophic state if treatment with estrogen preparations is not continued. In this review, we included one study that used oral conjugated estrogens and medroxyprogesterone acetate; however, there were still insufficient data to compare their use with progestins for rUTIs in postmenopausal women. In addition to estrogen receptors, progesterone receptors are expressed in the bladder, trigone, and vagina, but their role is still not clear [18].

There are several limitations to this review. We limited the searches to English language, which may have missed potentially relevant studies. In addition, the number of patients, vaginal estrogen applications, and follow-up periods varied between the studies. Most of the studies had a limited follow-up period of ≤ 6 months, so the long-term outcomes were unclear. One study involved the use of oral conjugated estrogens and medroxyprogesterone acetate. Although there were insufficient data to evaluate the relationship between progestin and rUTIs, this combination of hormone therapy may have caused bias. We also acknowledge that some bias was unavoidable when performing the meta-analysis, especially with regard to the variations in intra-vaginal estrogen methods and formulations. There were too many inherent variables related to individual characteristics, patients' compliance, application skill, and different delivery systems. For example, an estrogen-containing vaginal pessary inside the vagina can provide a steady and continuous delivery of estrogen, unlike vaginal estrogen cream which requires regular use to achieve an optimal functional estrogenization effect. Therefore, the results should be interpreted with caution because of potential bias.

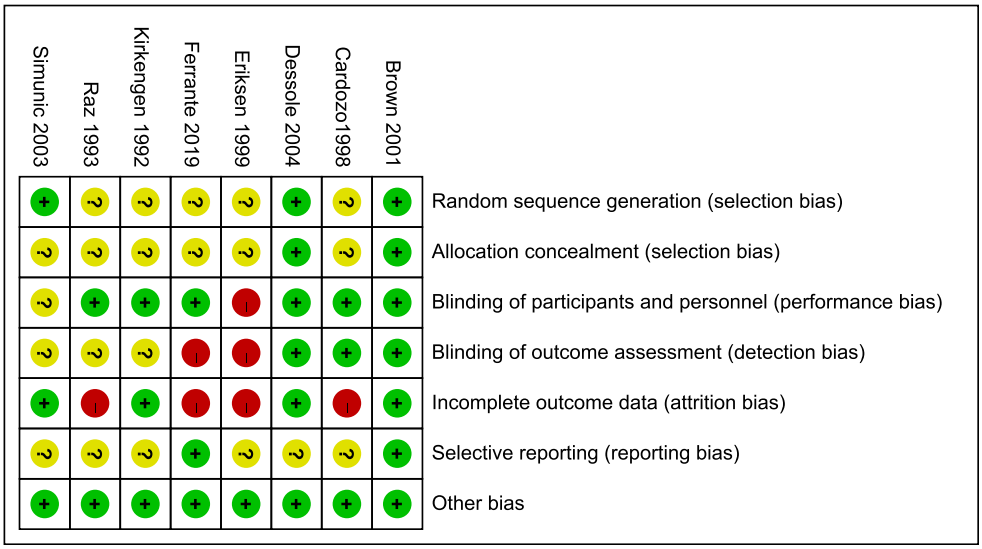

Fig. 7 Risk of bias summary

Table 2 GRADE quality of evidence evaluation

Quality assessment								Summary of findings			
Outcomes	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Estrogen (number of patients)	Placebo (number of patients)	RR (95% CI)	Quality
rUTI in local estrogen vs. placebo	5	RCT	Serous limitations (because of incomplete data)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	165	159	0.42 (0.30–0.59)	Moderate □□□□
rUTI in systemic estrogen vs. placebo	3	RCT	Serous limitations (because of incomplete data)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	1374	1392	1.11 (0.92–1.35)	Moderate □□□□
pH in local estrogen vs. placebo	2	RCT	Serous limitations (because of incomplete data)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	94	87	−1.81 (−3.1–-0.52)	Moderate □□□□
Adverse events in local estrogen vs. placebo	4	RCT	Serous limitations (because of incomplete data)	No serious inconsistency	No serious indirectness	Serious imprecision (wide 95% CI)	Undetected	165	159	3.06 (0.79–11.9)	Moderate □□□□

rUTI, recurrent urinary tract infection; RCT, randomized controlled trial; CI: confidence interval; RR, risk ratio

There are also several strengths to this review. All of the recruited studies had similar characteristics, and all of the patients were postmenopausal and were diagnosed with rUTIs. To the best of our knowledge, this is the most complete, up-to-date, and relevant review regarding the efficacy of using systemic or local estrogen versus placebo in the prevention of rUTIs. Vaginal estrogen therapy may be an effective prophylaxis for rUTIs in postmenopausal women. Nevertheless, further studies are needed to survey the long-term effectiveness and safety of vaginal estrogen preparations and the lowest efficacious dosage as prophylaxis for rUTIs.

Each author's participation in the manuscript Ying-Yu Chen: Protocol/project development, Data Collection and management, Data Analysis, Manuscript writing.

TH Su: Protocol/project development, Data collection and management.

HH Lau: Protocol/project development, Manuscript writing and editing.

Compliance with ethical standards

Financial disclaimer/conflict of interest None.

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