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REVIEW - SYSTEMATIC

Evaluation of systemic estrogen for preventing urinary tract infections in postmenopausal women

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Abstract

Importance: Current guidelines for postmenopausal recurrent urinary tract infection (rUTI) prevention recommend the use of vaginal topical estrogen products but not systemic estrogens. Studies show that vaginal estrogen decreases the risk of rUTI, but evidence *against* use of systemic estrogen is less convincing.

Objective: We performed a comprehensive literature review to evaluate the effect of systemic estrogen on UTI occurrence among postmenopausal women.

Evidence Review: MEDLINE (PubMed), EMBASE, and CINAHL were searched for manuscripts published in English between January 1990 and July 2020. The search terms were ''urinary tract infection'' and ''estrogen.'' Inclusion criteria were studies of postmenopausal women who received systemic estrogen therapy (any regimen) that reported UTI frequency during any follow-up period. Case studies, commentaries, and reviews were excluded. A priori specifications of seven study criteria were set representing the ideal study for assessing efficacy of systemic estrogen for rUTI prevention and were used to evaluate each included study.

Findings: Searches identified 281 results, and after deduplication and review, 8 studies met inclusion criteria: 4 randomized controlled trials, 1 secondary analysis of a randomized controlled trial, 1 prospective cohort study, 1 case-control study, and 1 cross-sectional study. Of the eight included studies, only two enrolled postmenopausal women with a rUTI diagnosis, four had sufficient sample size to detect a clinically meaningful difference between systemic estrogen versus placebo, two used dosage regimens anticipated to achieve a therapeutic effect, and three assessed UTI rates for an adequate duration of 6 months or more (the standard minimum duration of time needed to make a diagnosis of rUTI). Overall, none of the studies met all predefined criteria for the ideal study to assess the efficacy of systemic estrogen for rUTI prevention.

Conclusions and Relevance: UTIs will continue to be a significant cause of morbidity and hospitalizations in postmenopausal women unless more research is done to better understand the role of estrogen on UTI rates. The evidence arguing use (or abandonment) of systemic estrogen for the prevention of rUTI is based on few studies with substantial methodologic limitations; there is significant room for improvement.

Key Words: Prevention – Recurrent urinary tract infection – Systemic estrogen treatment.

Urinary tract infections (UTIs) are the most common outpatient infections in the United States, totaling more than 8 million healthcare visits annually with an estimated cost of more than $2 billion.[1,2] The prevalence of UTIs appears to increase with age.[1] Postmenopausal women have a high risk of recurrent UTI (rUTI) defined as 2 or more infections in 6 months or 3 or more infections in 1 year.[3] It is estimated that up to 10% of postmenopausal women will experience at least one UTI in a given year and among those who experience a UTI, 5% will experience a recurrence within the year.[4,5] With our aging population, rUTI is increasingly important due to risks of serious complications from sepsis and reduced quality of life.[6,7]

The increased prevalence of rUTI among postmenopausal women may be explained by hormonal and microbial changes with aging. During menopause, local and circulating estrogen concentrations fall, vaginal pH rises, and the vaginal microbiota shifts away from a beneficial *Lactobacillus* species dominance.[8] This shift is inversely associated with vaginal colonization with *Escherichia coli* which may increase the risk for UTIs in postmenopausal women.[9] The use of exogenous estrogens has been proposed as a preventive strategy for

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rUTI in postmenopausal women, and various methods of estrogen administration have been tested including systemic (oral and transdermal) and local vaginal therapies (creams, tablets, and rings). Current guidelines for rUTI prevention from multiple professional urology-related societies recommend the use of vaginal topical estrogen products but not systemic estrogens.[3,10] Studies show that vaginal estrogen decreases the risk of rUTI,[11-13] but evidence *against* use of systemic estrogen is less convincing. Recommendations regarding systemic estrogen for UTIs are largely based on two randomized controlled trials of oral estrogen versus placebo.[14,15] Two additional studies are rarely cited and do not support the use of systemic estrogen,[16,17] but none of these four studies directly compare the efficacy of systemic versus vaginal administration of estrogen for prevention of rUTI. Two other studies which compare vaginal versus oral estrogen on the risk of UTI do not show benefit of vaginal estrogen over systemic estrogen, but these are rarely cited.[18,19]

For a woman with rUTI who is currently taking systemic hormone therapy (or is planning to start), must she take both systemic and local estrogen to treat her menopausal symptoms and to decrease her risk of rUTI? Or, is systemic estrogen alone effective for her? Even after early publications from the Women's Health Initiative when systemic estrogen use was in decline, 1 in 20 American women older than 40 years were estimated to still be taking oral estrogen or estrogen-plus-progestin therapy in 2009 to 2010,[20] and systemic hormone therapy is still the preferred treatment for women with moderate to severe hot flashes.[21] Although many Medicare insurance plans cover the cost of systemic estrogens, the cost of vaginal estrogen formulations can range in retail price from \$240 to \$600 every 3 months even with a prescription drug plan.[22] This added cost for women with menopausal symptoms and rUTI is not inconsequential. The goal of this review is to critically examine the literature on systemic estrogens and rUTI prevention and to explain why studies to date might be inadequate to answer whether there is a beneficial effect.

Key points

Question/Objective: What is the effect of systemic estrogen on prevention of recurrent urinary tract infection (rUTI)?

Findings: Eight studies met inclusion criteria: four randomized controlled trials, one secondary analysis of a randomized controlled trial, one prospective cohort, one case-control, and one cross-sectional. Overall, none of the studies met all predefined criteria for the ideal study to assess the efficacy of systemic estrogen for rUTI prevention.

Meaning: The evidence arguing use (or abandonment) of systemic estrogen for rUTI prevention is based on few studies with substantial methodologic limitations; there is significant room for improvement.

METHODS

For this comprehensive review, MEDLINE (PubMed), EMBASE, and CINAHL were searched for manuscripts published between January 1990 and July 2020. The search terms were ''urinary tract infection'' and ''estrogen.'' Inclusion criteria were studies of postmenopausal women who received systemic estrogen therapy (any regimen) that reported UTI frequency during any follow-up period. References from a systematic review[23] and a meta-analysis[23,24] on estrogen for the prevention of rUTI in postmenopausal women and from all eligible manuscripts identified in searches were reviewed for potential inclusion. Non-English publications, case studies, commentaries, and reviews were excluded. Population, systemic estrogen regimen, methods for UTI ascertainment, and study results were abstracted for each included study into a standardized spreadsheet (K.A.F.) and reviewed for quality control (E.M.L.).

Seven criteria were established outlining the ''ideal'' study criteria to answer this clinical question and included (1) Population—women who were postmenopausal and had a rUTI diagnosis at or before enrollment, (2) Study Design—randomized trial, (3) Sample Size/Power—conservatively, 214 participants randomized 1:1 would have 80% power to detect a 33%—or one-third—reduction in recurrent UTI frequency from 60%[10] to 40% over 6 months between those using/not using systemic estrogen, allowing 10% lost-to-follow-up, a difference considered clinically meaningful by the authors, (4) Intervention and Comparators—a systemic estrogen dosed to provide the anticipated therapeutic effect and compared with either placebo or a vaginal estrogen preparation, (5) Study Duration—adequate time to treatment effect ($\geq$1 mo) and adequate time for UTI assessment ($\geq$6 mo), (6) Primary Outcome—UTI rate, and (7) UTI ascertainment—UTI diagnosed by culture with associated symptoms. We determined whether each included study met each criterion on a three-level scale (did not meet criteria, somewhat met criteria, met criteria).

RESULTS

The searches identified 281 results, and after deduplication and review, only eight met inclusion criteria (Fig. 1). Of these eight articles, four studies were randomized trials,[14-16,25] one was a secondary analysis of a randomized trial,[17] one was prospective cohort study,[19] one was a case-control study,[18] and one was a cross-sectional study[26] (Table 1). Just two of the eight studies enrolled postmenopausal women specifically with a rUTI diagnosis[14,15] and four of eight had sufficient sample size estimated to detect a clinically meaningful difference between systemic estrogen versus placebo (Table 2). Only two of the five studies with reported treatment regimens likely used dosages anticipated to achieve therapeutic effect,[16,17] and three of the eight studies assessed UTI rates for an adequate duration of 6 months or more.[15,17,19] Overall,

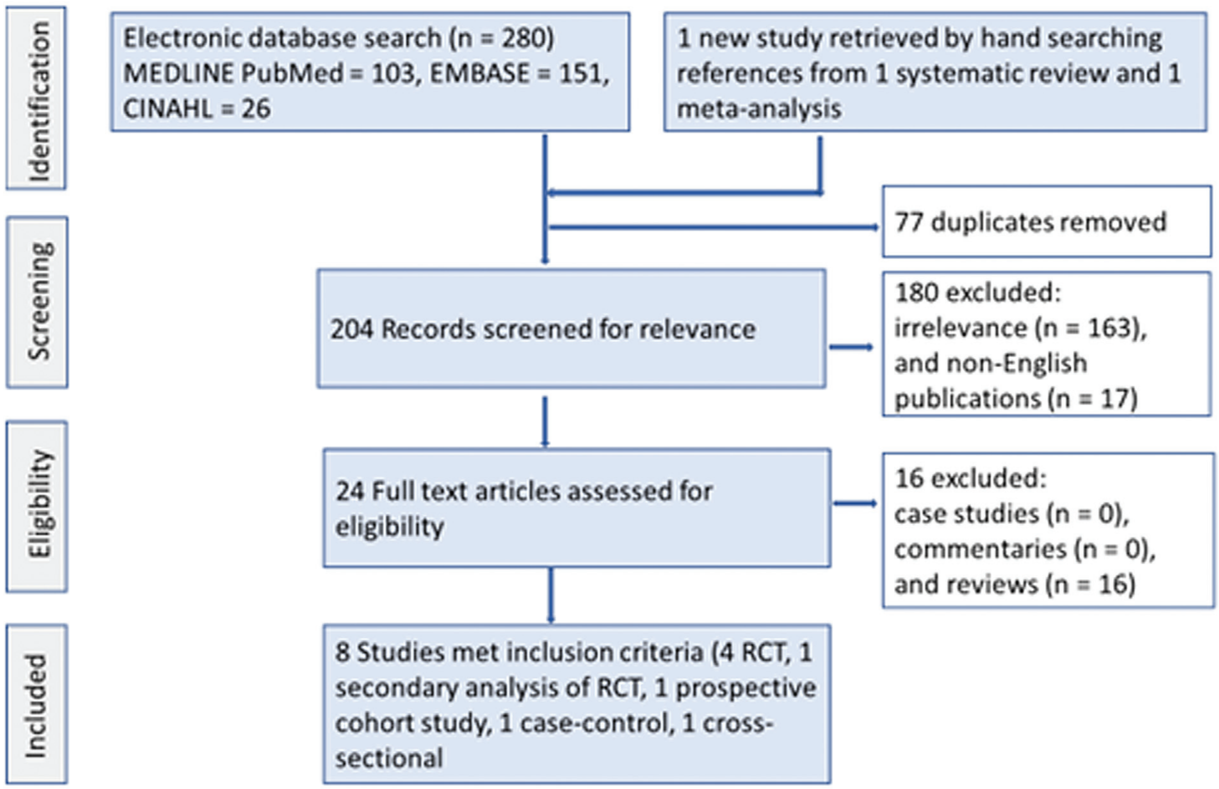

FIG. 1. PRISMA style flow diagram with identification, screening, eligibility, and inclusion of studies. RCT, randomized controlled trial.

none of the eight included studies met all of the predefined criteria for the ideal study to assess the efficacy of systemic estrogen versus placebo or vaginal estrogen to prevent rUTI.

Randomized controlled trials

Only two studies enrolled postmenopausal women with a ''history of rUTI''; both were double-blind, randomized trials assessing oral estriol versus placebo with UTI frequency as a primary outcome.[14,15] Kirkengen et al defined rUTI as ''at least one UTI episode with a recurrence within 2 weeks or at least three episodes during the previous year'' and Cardozo et al defined rUTI as a ''history of at least two documented UTIs in the last 18 months.'' Although multiple definitions for rUTI exist,[27] current guidelines endorse the two most commonly used definitions of two or more episodes of acute bacterial cystitis within 6 months or three or more infections within 1 year.[3,10] Neither study's rUTI definition for enrollment matches the current standard.

In the Norwegian study by Kirkengen et al,[14] 40 postmenopausal women were randomized to oral estriol 3 mg daily for 4 weeks followed by 1 mg daily for 8 weeks versus placebo. Urine samples were collected weekly during the 12-week total treatment period. At the end of the treatment period, 75% (15/20) of women in the estriol group versus 40% (8/20) of women in the placebo group had fewer UTIs than in the 4-week pretreatment period ($P = 0.05$). In Cardozo et al's[15] trial, 72 postmenopausal women from the United Kingdom were randomized to estriol 3 mg daily for 6 months versus placebo and were followed a total of 12 months. Urine samples were collected at 1, 3, 6, and at 12 months. The cumulative proportions of women with UTI during the 6-month treatment period did not differ by treatment group (57% estriol vs 51% placebo, log-rank $P = 0.65$). Notably, 30.5% (22/72) of participants were lost to follow-up, and the study was underpowered to detect a 20% difference between groups as initially intended.

Three other randomized controlled trials evaluated oral estrogen with UTI frequency as a secondary outcome.[16,17,25] Marx et al[25] recruited 71 healthy postmenopausal women and reported on the effect of placebo versus oral conjugated synthetic esterified estrogen (0.3 mg) on self-report of UTI over 16 weeks. The cumulative proportions of women with UTI in the oral estrogen treatment group was lower than that in the placebo group (0% vs 17.6%, $P = 0.009$). Ouslander et al[16] randomized 32 incontinent nursing home residents to oral conjugated esterified estrogen (0.625 mg) + medroxyprogesterone acetate (2.5 mg) or placebo. At 6 months, the prevalence of bacteriuria and pyuria was similar in the oral estrogen (36% for both diagnoses) and placebo groups (37%-38% for both diagnoses). Neither of these randomized trials enrolled women with rUTI and both had several methodologic limitations that prevent the assessment of the effect of systemic estrogen on UTI rates. Lastly, the Heart and Estrogen/Progestin Replacement Study (HERS) was a randomized, double-blinded controlled trial designed to evaluate oral conjugated equine estrogen (CEE; 0.625 mg) + medroxyprogesterone acetate

TABLE 1. *Individual study details*

Author, year	Sample size (exposed, unexposed)	Study design (quality of evidence)	Setting	Population	Intervention	UTI diagnosis method and frequency	Results	Oral estrogen prevents UTI?
Kirkengen, 1992[14]	40 (20, 20)	Randomized, double-blind, group-comparative, placebo-controlled trial (1.b)	Oslo, Norway	Postmenopausal women with rUTI ($\geq$1 UTI with a recurrence within 2 wk or $\geq$3 episodes during prior year); median age 78 y (range 66-91)	4-wk pretreatment period followed by 3 mg/d po estriol for 4 wk then 1 mg/d for 8 wk vs placebo	Bacteriologically verified UTI assessed weekly	75% (15/20) in the estriol group and 40% (8/20) in the placebo group reported fewer UTIs during weeks 5-12 of treatment period compared to pretreatment period ($P = 0.05$)	Low-dose oral estriol may reduce UTI frequency
Cardozo, 1998[15]	72 (36, 36)	Double-blind, randomized, parallel group, placebo-controlled trial (1.b)	United Kingdom	Postmenopausal women with rUTI defined as a history of $\geq$2 documented UTIs in the last 18 mo; mean age 73.2 y	3 mg/d estriol po for 6 mo vs placebo	Symptoms and bacteriuria assessed at 1, 3, 6, and 12 mo	Cumulative proportions of women without UTI did not differ by treatment group at end of 12-mo study period (log rank $p = 0.65$)	No effect of low-dose oral estriol on cumulative UTI
Ouslander, 2001[16]	32 (15, 17)	Randomized placebo-controlled trial (1.b)	Atlanta, GA	Incontinent female nursing home residents; mean age 88 y	0.625 mg/d CEE plus 2.5 mg/d MPA po for 6 mo vs placebo	Bacteriuria or pyuria assessed at baseline, 3 and 6 mo	Prevalence of bacteriuria and pyuria similar in oral EPT (36% both diagnoses) and placebo groups (37%-38% both diagnoses) at 6 mo	No effect of standard dose EPT on UTI prevalence
Marx, 2004[25]	71 (37, 34)	Randomized placebo-controlled trial (1.b)	5 Clinical research sites across United States	Healthy postmenopausal females; mean 59 y	0.3 mg/d synthetic CE po vs placebo for 16 wk; women with uterus used 14 d progesterone at study completion	Monthly self-reported UTI	Lower cumulative proportions of women with UTI in the treatment group compared to placebo (0% vs 17.6%, $P = 0.009$)	Lower cumulative proportions of women with UTI on oral low-dose estrogen
Brown, 2001[17]	2,763	Secondary analysis of HERS randomized control trial (1.b/2.0)	20 Clinical centers in the United States	Postmenopausal women with established coronary heart disease; mean age 67 y	0.625 mg/d CEE, 2.5 mg/d MPA po for 4 y vs placebo	Self-reported physician diagnosed UTI assessed by questionnaire at baseline and at annual visits for 4 y	10% EPT vs 9% placebo reported $\geq$2 UTI averaged over 4-y study period, $P = 0.3$	No effect of oral standard dose EPT on UTI prevalence
Jackson, 2004[19]	1,017	Population-based prospective cohort (2.0)	Seattle, WA	Postmenopausal women enrolled in an HMO aged 55-75	Exposure: Oral estrogen CEE (85% 0.625 mg, 15% other) Or Vaginal estrogen (majority 1/4 applicator $\geq$once per week) vs unexposed	Midstream urine specimen at baseline, 12 and 24 mo; monthly review of clinical records for diagnosis codes indicating acute cystitis	Oral estrogen: In last month: aHR 0.8 (95% CI 0.5-1.2) In last year: aHR 0.7 (95% CI 0.5-1.1) Estrogen cream; In last month: aHR 1.8 (95% CI 1.0-3.4) In last year: aHR 1.8 (95% CI 1.0-3.0)	No effect of oral estrogen on UTI but possible increased risk of UTI with estrogen cream

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TABLE 1 *(Continued)*

Author, year	Sample size (exposed, unexposed)	Study design (quality of evidence)	Setting	Population	Intervention	UTI diagnosis method and frequency	Results	Oral estrogen prevents UTI?
Orlander, 1992[18]	3,616 cases, 19,162 controls	Case-control study (3.0)	United Kingdom	Women with 1st recorded UTI between 1989-1990 and age matched controls (50-69 years)	Exposure: Long-term estrogen users (prescription within 7-90 days and $\geq$1 year prior to index diagnosis) including oral, transdermal patch, and vaginal creams Vs Unexposed	Diagnosis codes reflecting bacterial infection of the bladder or upper urinary tract	With uterus: Oral estrogen increases risk of UTI (OR 2.1, 95% CI 1.6-2.7); No effect of patch (OR 1.0, 95% CI 0.3-3.3) or cream (aOR 1.8, 95% CI 0.9-3.7)[a] Without uterus: No effect of oral (OR 1.0, 95% CI 0.7-1.5); patch (OR 1.2, 95% CI 0.6-2.4); or cream (aOR 1.5, 95% CI 0.5-5.0)[a]	Oral estrogen increased risk of UTI in women with a uterus, but not in women without a uterus No effect of estrogen patch or vaginal cream on UTI frequency in women with or without uterus
Hunjak, 2012[26]	245 (143 on HT, 77 systemic, 66 vaginal; 102 not on HT)	Cross-sectional study (4.0)	Zagreb, Croatia	Postmenopausal women with urinary symptoms who visited gynecological practices, mean 57 y for HT users; mean 56 y for non-HT users	Systemic HT users (77) vs local vaginal ET users (66) vs non-HT users (102)	Microbiologically confirmed UTI by urinalysis and urethral swabs of symptomatic patients	61% Prevalence of UTI in systemic HT users and 30% in vaginal ET vs 76% in nonusers ($P = 0.049$ and < 0.001, respectively).	Lower prevalence of UTI with systemic HT and with vaginal estrogen

aHR, adjusted hazard ratio; CE, conjugated estrogen; CEE, conjugated equine estrogen; EPT, estrogen plus progestin; ET, estrogen therapy; HERS, Heart and Estrogen/Progestin Replacement[28]; HMO, Health Maintenance Organization; HT, hormone therapy; MPA, medroxyprogesterone acetate; OR, odds ratio; rUTI recurrent urinary tract infection; UTI, urinary tract infection.
[a]Adjusted OR, controlled for atrophic vaginitis, neurologic deficit, diabetes, incontinence, and age. All other OR are crude as the adjusted models did not significantly change and are not reported.

TABLE 2. *Mapping of the eight included studies to the seven criteria of the ideal study population and study design*

	Population	Study Design					
Included Study	Postmenopausal Women with rUTI	Oxford Evidence Rating	Sufficient Sample Size [a]	Appropriate Dosing and Duration of Treatment	Adequate Time for UTI Assessment (≥6 months)	UTI Rate as Primary Outcome	UTI Measured by Culture and Symptoms
Kirkengen 1992[14]	Postmenopausal women with rUTI (non-standard rUTI definition)	RCT	40	3mg/d oestriol for 4 weeks then 1 mg/d for 8 weeks	12-weeks during treatment	Number of incident UTIs	Bacteriologically verified UTI assessed weekly
Cardozo 1998[15]	Postmenopausal women with rUTI (non-standard rUTI definition)	RCT	72 [b]	3 mg/d oestriol for 6 months	1 year	≥ 1 incident UTI	Symptoms and bacteriuria assessed at 1, 3, 6 and 12 months
Ouslander 2001[16]	Incontinent female nursing home residents	RCT	32 [b]	0.625mg/d conjugated equine estrogens plus 2.5 mg/d MPA for 6 months	6 months during treatment	UTI prevalence at each visit	Bacteriuria and pyuria assessed at baseline, 3 and 6 months
Marx 2004[25]	Healthy postmenopausal women	RCT	71 [b]	0.3mg/d synthetic conjugated estrogens for 16 weeks	16-weeks during treatment	Any UTI	Self-reported infection at monthly visits
Brown 2001[17]	Postmenopausal women with coronary heart disease	Secondary analysis of HERS RCT	2763	0.625 mg/d conjugated equine estrogens plus 2.5mg/d medroxyprogesterone acetate for variable years	Mean 4.1 years	0, 1, or 2+ incident UTI identified between each annual visit (UTI frequency)	Self-reported, physician diagnosed UTI at baseline and on questionnaire at annual visits
Jackson 2004[19]	Postmenopausal women	Prospective cohort	1017	Not reported	2 years	Number of incident UTIs	Midstream urine specimen at baseline, 12 and 24 months; monthly review of clinical records for diagnosis codes indicating acute cystitis–related clinic visit or lab result
Orlander 1992[18]	Postmenopausal women with a 1st recorded UTI	Case-control	3,616 cases, 19,162 controls	Dosing not reported. Included long-term estrogen users (prescription within 7-90 days and > 1 year prior to UTI diagnosis)	N/A	1st UTI diagnosis	Diagnosis in chart of bacterial infection of the bladder or upper urinary tract
Hunjak 2012[26]	Postmenopausal women with urinary symptoms who visited gynecological practices	Cross-sectional	245	Not reported	None	UTI prevalence	Bacteriuria in urethral swabs of symptomatic patients

White: meets criteria.
Medium gray: somewhat meets criteria.
Dark gray: does not meet criteria.
Dark gray: not reported or not applicable (N/A).
HERS, Heart and Estrogen/Progestin Replacement; MPA, medroxyprogesterone acetate; RCT, randomized controlled trial; rUTI recurrent urinary tract infection; UTI, urinary tract infection.
[a]Sample size/power—conservatively, 214 participants randomized 1:1 would have 80% power to detect a 33%—or one-third—reduction in recurrent UTI frequency from 60%[10] to 40% over 6 months between those using/not using systemic estrogen, allowing 10% lost-to-follow-up, a difference considered clinically meaningful by the authors.
[b]Loss to follow-up >10%.

(2.5 mg) on the risk of recurrent coronary heart disease events among 2,762 postmenopausal women with established coronary heart disease.[28] In a secondary analysis of HERS study data, Brown et al[17] found no association between oral estrogen and UTI frequency as defined by two or more physician-diagnosed UTIs annually over the course of the 4-year study period (10% for estrogen vs 9% for placebo, $P = 0.3$).

Observational studies

Three non-randomized observational studies were also included.[18,19,26] In a population-based cohort study of 1,017 postmenopausal women from a health maintenance organization in Washington state, women were defined as taking estrogen or not based on pharmacy records of oral estrogen and vaginal estrogen cream and were followed for cystitis for up to 2 years.[19] Episodes of acute cystitis were documented from annual midstream urine specimens in addition to monthly review of clinical records for related diagnosis codes. There was no significant difference in risk of cystitis among oral estrogen users compared to nonestrogen users (adjusted hazard ratio 0.7, 95% CI 0.5-1.2), and women who used vaginal estrogen cream in the prior month may have had a higher frequency of cystitis than women not taking vaginal estrogen (adjusted hazard ratio 1.8, 95% CI 1.0-3.4). In a case-control study using UK claims data, 3,616 women ages 50 to 69 years with a first recorded UTI were matched by age and practice with 19,162 controls.[18] Exposures were oral, transdermal, and vaginal estrogen. Models evaluating vaginal estrogen cream were adjusted for atrophic vaginitis, neurologic deficit, diabetes, incontinence, and age. None of the other odds ratios (ORs) in models evaluating oral tablets or patches changed when adjusting for potential confounding. In women with a uterus, the risk of first UTI was *increased* among those who used oral estrogen for 1 year or more (OR 2.1, 95% CI 1.6-2.7), but not among women using the patch (OR 1.0, 95% CI 0.3-3.3). Vaginal estrogen cream did not decrease the risk (adjusted OR 1.8, 95% CI 0.9-3.7). In hysterectomized women, the three estrogen delivery methods showed no overall effect on UTI risk (OR 1.1, 95% CI 0.8-1.5), with little difference by method of delivery: oral (OR 1.0, 95% CI 0.7-1.5); patch (OR 1.2, 95% CI 0.6-2.4); or cream (adjusted OR 1.5, 95% CI 0.5-5.0). Lastly, in a cross-sectional study of postmenopausal women with urinary symptoms visiting gynecologic clinics in Croatia, the prevalence of UTI was statistically significantly lower in women taking oral estrogen than those not taking estrogen (61% vs 75.5%, $P = 0.049$) and in women taking vaginal estrogen therapy versus nonusers (30% vs 75.5%, $P < 0.001$).[26]

DISCUSSION

Both systemic and vaginal estrogen are prescribed to treat genitourinary syndrome of menopause since estrogen is known to alter the vaginal mucosa and modulate the mucosal barrier to infection.[29] When compared directly, both routes appear to improve vaginal dryness, dyspareunia, and urinary complaints of dysuria, urgency, frequency, and nocturia, but data on UTI frequency are less clear.[30] Current guidelines specifically discourage use of systemic estrogen for rUTI prevention: ''systemic estrogen should not be recommended for treatment of rUTI,''[3] and ''Oral estrogen has not been shown to be effective and should not be used for rUTI prevention.''[10] We argue and this review would support that there is too little evidence to determine whether there is benefit or not to using systemic estrogen therapy for rUTI. All studies had methodologic limitations, and this question remains unanswered; lack of evidence does not prove lack of benefit. Others have suggested that the efficacy discrepancy between vaginal and systemic estrogen may reflect (1) a requirement for a higher estrogen dose locally at the vaginal and periurethral mucosal surfaces (best achieved with local estrogen application); (2) differential effects of systemic versus vaginal estrogen delivery on bladder or upper urinary tract mucosal responses; or (3) activation of an adverse systemic immune response by systemic estrogen doses.[31,32]

From our review, clear limitations to the data purported to assess this question include (1) evaluating postmenopausal women without a history of rUTI; (2) insufficient sample sizes to detect a clinically meaningful difference between groups; (3) potentially insufficient systemic estrogen dosing; (4) inadequate treatment duration to achieve desired tissue effects; and (5) inadequate outcome ascertainment. Specifically, although two of the randomized controlled trials often cited as the reason not to prescribe systemic estrogen for rUTI did enroll women with rUTI at baseline, inclusion criteria for both of these studies did not match the current definition of rUTI.[3,10,14,15] More importantly, neither trial was powered to detect a significant difference between systemic estrogen versus placebo. In addition, the dosing regimens, oral estriol 3 mg daily for 4 weeks then 1 mg daily for 8 weeks[14] and 3 mg estriol daily for 6 months[15] may not have delivered sufficient estrogen to the vaginal tissues to achieve a beneficial change in the genitourinary mucosa. It is estimated that approximately 10 mg oral estriol achieves the same effect on vaginal tissues as 1 mg vaginal estriol[33] and at least 0.625 mg oral CEE may be needed to achieve an effect similar to 0.625 mg vaginal CEE.[34-36] In addition, one of these studies likely had a confounded outcome measurement, that is, weekly bacterial UTI cultures that could not distinguish between a persistent infection versus a recurrence.[14] We found that the two other randomized trials[16,25] and the secondary analysis of the HERS trial,[17] included in this review evaluated postmenopausal women without rUTI so do not definitively answer whether systemic estrogen is efficacious for the prevention of rUTI. In addition, there were other limitations to these studies, including low-dose estrogen therapy for an inadequate duration[25] and small sample sizes.[16,25]

We suggest that to assess the effect of systemic estrogen on UTI rates, UTIs should be tracked for at least 6 months on treatment, but after an initial 4 weeks of therapy to provide sufficient time for mucosal epithelial remodeling before initiation of outcome evaluation. Two of the four randomized controlled trials tracked UTI rates for less than 6 months.[14,25] The ideal outcome assessment would capture two separate symptomatic culture-proven episodes of acute bacterial cystitis within 6 months or three symptomatic culture-proven episodes within 1 year.[3,10] This method of UTI ascertainment is consistent with studies of vaginal estrogen for rUTI prevention.[11,12] None of the randomized controlled trials met this standard. Two studies also had limited UTI outcome measurement: self-report of a physician-reported UTI at baseline and by questionnaire annually that the investigators suggest is accurate 60% to 80% of the time[17] and self-report of infections at monthly visits.[25] Both methods are subject to ascertainment bias, specifically an underascertainment of UTIs experienced between assessments. Lastly, in the HERS trial secondary analysis, annual prevalence of UTI reported for both the intervention and control groups (9% and 7.7%)[17] was lower than expected in a postmenopausal population with mean age 67 years (10%-20%).[5]

Observational studies, subject to confounding and selection bias, are suboptimal to answer the question at hand, but some of the methods from the studies we reviewed could be applied to future studies. Although the large cohort study at a health maintenance organization in Washington State did not require participants to have had a history of rUTI, outcome assessments were strong.[19] In addition to performing midstream urine testing at baseline and at 1 and 2 years of follow-up, they performed a monthly review of clinical records to identify acute cystitis by visit or laboratory results, an effective way to capture infections between study visits. This prospective cohort study[19] and the UK case-control study[18] were the only studies we could find that compared both vaginal estrogen and systemic estrogen to placebo. Findings from these two observational studies were, however, conflicting with regard to vaginal and systemic estrogen use for UTI prevention in postmenopausal women.

CONCLUSIONS

Vaginal estrogen should be the preferred treatment for rUTI risk reduction in women without systemic menopausal symptoms. In women already taking systemic estrogen for menopausal symptoms, this review did not definitively answer whether they would achieve additional benefit from vaginal estrogen for rUTI prevention. No randomized controlled trial has adequately examined the role of systemic estrogen in reducing rUTI. Ideally, there will emerge a trial that enrolls only postmenopausal women with rUTI with a sufficient number of participants to detect a significant difference between systemic and placebo (or vaginal estrogen) groups; administer sufficient systemic estrogen expected to provide adequate therapeutic vaginal tissue levels and adequate time for tissue remodeling to occur; and monitor for infections for at least 6 months duration. Frequency of UTI may increase with age and disproportionally affects postmenopausal women who are susceptible to serious complications.[6,7] UTIs will continue to be a significant cause of morbidity and hospitalizations in patients of advanced age unless more research can be done to better understand the role of estrogen on UTI rates. The evidence arguing use (or abandonment) of systemic estrogen for the prevention of rUTI is based on few studies with substantial methodologic limitations; there is significant room for improvement.

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