A Controlled Trial of Intravaginal Estriol in Postmenopausal Women with Recurrent Urinary Tract Infections

Raul Raz, and Walter E. Stamm

ABSTRACT

Background Recurrent urinary tract infections are a problem for many postmenopausal women. Estrogen replacement restores atrophic mucosa, lowers vaginal pH, and may prevent urinary tract infections.

Methods We enrolled 93 postmenopausal women with a history of recurrent urinary tract infections in a randomized, double-blind, placebo-controlled trial of a topically applied intravaginal estriol cream. Midstream urine cultures were obtained at enrollment, monthly for eight months, and whenever urinary symptoms occurred. Vaginal cultures and pH measurements were obtained at entry and after one and eight months. The women were assigned to receive either estriol (n = 50) or placebo (n = 43), both administered intravaginally; 36 and 24, respectively, completed the eight months of follow-up.

Results The incidence of urinary tract infection in the group given estriol was significantly reduced as compared with that in the group given placebo (0.5 vs. 5.9 episodes per patient-year, P<0.001). Survival analysis showed that more of the women in the estriol group than in the placebo group remained free of urinary tract infection (P<0.001). Lactobacilli were absent in all vaginal cultures before treatment and reappeared after one month in 22 of 36 estriol-treated women (61 percent) but in none of the 24 placebo recipients (P<0.001). With estriol the mean vaginal pH declined from 5.5 to 3.8 (P<0.001), whereas there was no significant change with placebo. The rate of vaginal colonization with Enterobacteriaceae fell from 67 percent to 31 percent in estriol recipients but was virtually unchanged (from 67 to 63 percent) in the placebo recipients (P<0.005). Side effects were minor, but caused 10 estriol recipients (28 percent) and 4 placebo recipients (17 percent) to discontinue treatment.

Conclusions The intravaginal administration of estriol prevents recurrent urinary tract infections in postmenopausal women, probably by modifying the vaginal flora.

An estimated 10 to 15 percent of women over 60 years of age have frequent urinary tract infections[1]. Hormonally induced changes in the vaginal flora associated with menopause are thought to play an important part in the pathogenesis of urinary tract infections in older women. In premenopausal women, circulating estrogens encourage colonization of the

vagina by lactobacilli, which produce lactic acid from glycogen and maintain a low vaginal pH that inhibits the growth of many uropathogens[2,3]. After menopause, however, the vaginal pH increases, lactobacilli disappear from the vaginal flora, and the vagina is predominantly colonized by Enterobacteriaceae, especially Escherichia coli. Such colonization presumably accounts in part for the increased susceptibility of these women to urinary tract infections[4].

Previous studies by Parsons and Schmidt[5] and Brandberg et al.[6] suggested that estrogen replacement with either a topically applied vaginal cream or an orally administered agent restores the atrophic vaginal, urethral, and trigonal mucosa; lowers the vaginal pH; and may reduce the occurrence of urinary tract infections. However, the studies involved only a small number of women, they were not randomized or blinded, and neither had an untreated comparative group. We undertook this randomized, double-blind study to determine whether topically applied vaginal estriol cream was more effective than placebo cream in reducing the incidence of urinary tract infections in postmenopausal women with recurrent urinary tract infections and to ascertain the effects of topical estrogen on the vaginal flora.

Methods

Patient Population and Recruitment

Postmenopausal women who had been referred to the Infectious Disease Clinic at Central Emek Hospital, Afula, Israel, with a history of three or more microbiologically confirmed symptomatic episodes of urinary tract infection during the previous year were included in the study. Patients with thromboembolic disorders, severe liver disease, estrogen-dependent tumors, anatomical lesions in the urogenital area, an indwelling urinary catheter, or a history of long-term use of antimicrobial agents for the prevention of urinary tract infections or for other reasons were excluded from the study, as were women receiving oral estrogen therapy.

After providing informed consent, all patients were evaluated clinically and gynecologically, and each provided a urine specimen to exclude current infection. After a negative culture result was obtained, patients were randomly assigned to one of two regimens: one group received 0.5 mg of estriol in vaginal cream to be used once each night for two weeks followed by twice-weekly applications for eight months, and the other group received a placebo cream to be used in the same manner.

Follow-up Schedule and Outcome Measurements

At study entry, the women received a tube of their assigned cream, a vaginal applicator, and a diary in which to record their use of the cream, the occurrence of side effects, symptoms of urinary tract infection, and the use of antibiotics. They visited the outpatient clinic monthly throughout the study. At each visit, the diary was reviewed so that we could evaluate treatment compliance.

Vaginal pH was measured and vaginal cultures were obtained at study entry and after one and eight months of treatment. Vaginal cultures were obtained by rolling a swab across the lateral vaginal wall just inside the introitus. The swab was promptly inoculated onto MacConkey agar to isolate aerobic gram-negative rods and onto fresh Rogosa agar to isolate lactobacilli. Midstream urine specimens were also obtained at study entry and at each monthly visit during the eight months of follow-up, or whenever symptoms of urinary tract infection appeared.

The diagnosis of symptomatic urinary tract infection was based on the presence of typical clinical symptoms (dysuria, frequency, urgency, and incontinence) in addition to laboratory evidence of pyuria (at least 8 leukocytes per cubic millimeter of unspun urine) and a midstream urine culture yielding $\geq 10^5$ colony-forming units (CFU) per milliliter. In symptomatic patients with a positive culture without pyuria, a second urine sample was obtained with an indwelling catheter. Asymptomatic bacteriuria was considered to be present if the midstream urine culture yielded $\geq 10^5$ CFU per milliliter without accompanying clinical symptoms. Women with asymptomatic bacteriuria were not treated with antibiotics unless symptoms developed. Symptomatic urinary tract infections were treated with a three-day regimen of either trimethoprim-sulfamethoxazole or ciprofloxacin.

Microbiologic Techniques

Midstream urine specimens were collected and cultured with the Uritest system (Hylab, Rehovot, Israel). All isolates were identified by standard procedures and tested for susceptibility to antimicrobial drugs by the Kirby-Bauer method. Lactobacillus was identified by the catalase reaction, beta-hemolysis on human bilayer Tween agar, and typical morphologic characteristics on Gram's staining. The vaginal pH was measured with pH indicator paper (Universal indicator, Merck Sharp & Dohme, West Point, Pa.) applied directly to the vaginal mucosa just inside the introitus.

Statistical Analysis

The chi-square test was used to compare dichotomous variables, and Student's t-test was used to compare continuous variables. The cumulative proportions of estrogen-treated women and placebo recipients who were free of bacteriuria in each month of the study were compared by Kaplan-Meier survival analysis and the log-rank test. The cumulative likelihood of remaining disease-free at four months and the 95 percent confidence intervals at four months were calculated with product-limit estimates. The annualized incidence rates in the two groups were compared by the Wilcoxon test.

Results

Comparison of the Study Groups

Ninety-three women participated in the study: 50 were randomly assigned to receive estriol cream, and 43 to receive placebo cream (Table 1). The mean ages of the estriol-treated women (64.7 years; range, 52 to 81) and the placebo recipients (65.4 years; range, 51 to 79)

were comparable, as was the number of urinary tract infections the women had had in the previous year (mean [±SE], 5.2 ±1.1 vs. 5.4 ±1.4). Thirty-six women given estriol and 24 women who received placebo completed the entire eight months of the study and were compliant with medication use. The following were reasons for early withdrawal from the study: side effects in 10 women in the estriol 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 estriol-treated patient; and failure to respond to topical prophylaxis necessitating systemic antimicrobial prophylaxis for recurrent infections in 10 women in the placebo groTable 1.

View this table: [in this window] [in a new window]	**Table 1.** Characteristics of the Women in the Estriol and Placebo Groups.

Rates of Infection in the Study Groups

The estrogen-treated women and the placebo recipients were followed for a total of 310 and 225 person-months, respectively (Table 2). The annualized median incidence of urinary tract infections in the group given estrogen was significantly lower than the rate in the group given placebo (0.5 vs. 5.9 per patient-year, $P<0.001$ by the Wilcoxon test). Kaplan-Meier analysis showed that the cumulative proportion of patients remaining free of urinary tract infection was significantly higher in the group given estriol than in the group given placebo ($P<0.001$ by the log-rank test) (Figure 1). After four months of treatment, the cumulative likelihood of remaining disease-free was 0.95 (95 percent confidence interval, 0.88 to 1.0) in the estrogen-treated women and 0.30 (95 percent confidence interval, 0.16 to 0.46) in the placebo recipients. The eight infected patients in the estriol group had 12 episodes of bacteriuria; 10 were symptomatic, and 2 were asymptomatic. The 27 infected patients in the placebo group had 111 episodes of bacteriuria; 103 were symptomatic, and 8 were asymptomatic (Table 2).

View this table: [in this window] [in a new window]	**Table 2.** Episodes of Infection in the Two Groups.

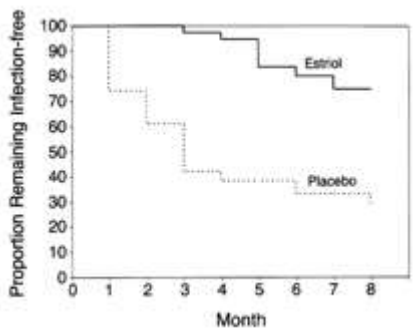

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Figure 1. Kaplan-Meier Analysis Showing the Cumulative Proportions of Women Remaining Free of Urinary Tract Infections in the Estriol and Placebo Groups (P<0.001 by the Log-Rank Test).

The estrogen-treated patients used significantly fewer antibiotics for the treatment of urinary tract infections during the study. Thus, among the women followed for the entire eight months, the mean number of days of antibiotic use per patient was considerably lower in the women who received estrogen than in those who received placebo (6.9 ±1.1 vs. 32.0 ±7.8, P<0.001).

Alterations in Vaginal pH and Flora

At the beginning of the study, none of the women in either group had vaginal cultures that were positive for lactobacilli (Table 3). In contrast, after one and eight months, lactobacilli were detected in the vaginas of 22 and 21, respectively, of the 36 estriol-treated patients who were seen at both visits but in none of the placebo recipients (P<0.001 for the comparison between groups at each time). On the other hand, the number of estriol-treated women with vaginal cultures positive for Enterobacteriaceae fell from 24 (67 percent) before therapy to 11 (31 percent) after one month of treatment and to 10 (28 percent) after eight months of treatment, whereas there were no substantial changes in the rate of colonization with Enterobacteriaceae among the placebo recipients throughout the study (P<0.005 for the comparison between groups at one and eight months) (Table 3).

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Table 3. Alterations in Vaginal Flora and pH in the Two Groups.

The mean vaginal pH fell from 5.5 ±0.7 at base line to 3.8 ±0.8 after one month and to 3.6 ±1.0 after eight months in the estriol-treated patients, whereas it changed little, from 5.8 ±1.2 to 6.2 ±1.2 and 6.1 ±2.0, in the placebo recipients (P<0.001 for the comparison between groups at one and eight months) (Table 3).

Despite the small numbers of patients enrolled, there appeared to be a relation between vaginal-colonization status and the risk of infection. Thus, urinary tract infections developed in 3 of the 23 estriol-treated women who were colonized with lactobacillus at one or eight months as compared with 7 of the 13 who were not colonized with lactobacillus. Of the 28 women with vaginal colonization with Enterobacteriaceae at either the one- or the eight-month visit, 7 of 10 in the estriol group and 14 of 18 in the placebo group had urinary tract infections.

Adverse Reactions

Localized adverse reactions consisted of vaginal irritation, burning, or itching and were observed in 10 of the estriol-treated women and 4 of the placebo recipients (Table 1). These reactions were mild and self-limited but caused the women to withdraw from the study. No systemic adverse reactions were observed.

Discussion

Urinary tract infections represent an important health problem for postmenopausal women[1]. Although the majority of such infections in these patients remain asymptomatic, some women have recurrent episodes of symptomatic infection. Our objectives in this study were to ascertain whether estrogen replacement would reduce the susceptibility of such women to recurrent urinary tract infection and, if so, whether the reduction was associated with alterations in vaginal colonization with lactobacilli. Using a randomized, double-blind, placebo-controlled design and an eight-month observation period, we found that topical estrogen treatment had a dramatic effect on the incidence of recurrent urinary tract infection. The considerable reduction in the frequency of symptomatic episodes of urinary tract infection in patients treated with estrogen also greatly reduced their use of antibiotics.

The use of topical estrogen was associated with a significant decrease in vaginal pH, an increase in the rate of vaginal colonization with lactobacilli, and a decrease in the rate of vaginal colonization with Enterobacteriaceae. These changes in colonizing microorganisms undoubtedly have a critical role in altering the susceptibility of postmenopausal women to urinary tract infections. In normal, fertile women, lactobacillus species are the predominant microorganisms in the vaginal flora and maintain the normally acidic vaginal pH through their metabolic activity (the generation of lactic acid from carbohydrates)[6,7]. Lactobacilli may protect the vagina against colonization by potential uropathogens through several mechanisms[7,8,9,10]. First, the maintenance of a low pH may itself be of direct importance. Stamey et al. observed that colonization of the vaginal introitus with E. coli is rarely noted at a vaginal pH below 4.5, but is significantly more common among women with recurrent urinary tract infections, many of whom have a vaginal pH above 4.5[9]. Furthermore, E. coli strains from serogroups commonly associated with urinary tract infections survive better at a lower pH than serogroups not associated with urinary tract infections[9]. Second, some lactobacillus strains produce hydrogen peroxide, which may prevent vaginal colonization with uropathogens[7,8]. Finally, fragments of lactobacillus cell walls have been shown to prevent the attachment of E. coli to epithelial cells, perhaps by steric hindrance or by blocking potential sites of attachment[10]. Thus, through one or more of these mechanisms,

the loss of lactobacillus colonization and the associated atrophy of the vaginal mucosa that normally occurs after menopause may increase the likelihood of recurrent urinary infections.

The use of a diaphragm with a spermicide by premenopausal women who had an increased susceptibility to recurrent urinary tract infections was associated with an increased vaginal pH, decreased colonization with lactobacilli, and increased introital colonization with Enterobacteriaceae[11,12]. These alterations in the vaginal flora may result from the fact that nonoxynol 9, at concentrations achieved in the vagina, is readily microbicidal to lactobacilli but not to E. coli or other uropathogens, which are highly resistant[13]. Thus, at least two factors that influence colonization with lactobacilli and other components of the normal vaginal flora -- the use of a diaphragm with a spermicide and the lack of estrogen -- appear to predispose women to recurrent urinary tract infections.

We studied topically applied estriol rather than the orally administered drug, since the former should be safer and should not produce systemic effects. Although estriol is absorbed after vaginal administration, according to its pharmacokinetic profile, the risk of persistently elevated serum levels with the topical dose used in this study is negligible. Mattsson and Cullberg,[14] for example, showed that when a vaginal preparation of 0.5 mg of estriol was given to healthy postmenopausal women, no unconjugated estrogen could be measured in the serum after 24 hours. Furthermore, vaginal application of estriol leads to the normalization of the cervicovaginal mucosa, whereas the endometrium remains unaffected, suggesting the absence of any systemic estrogenic effect[15]. We observed no evidence of systemic toxicity in women using topical estrogen, and the side effects were limited to localized pruritus or burning. Although generally mild, these symptoms were irritating enough in 10 women to result in the cessation of treatment.

Our results support the hypothesis that estrogen deficiency is a major contributor to the pathogenesis of recurrent urinary tract infections in postmenopausal women and show that prolonged estrogen replacement with a topically applied vaginal cream safely and effectively prevents urinary tract infections in these patients. This preventive approach can be considered an alternative to the use of long-term low-dose antibiotics such as nitrofurantoin, co-trimoxazole, trimethoprim, cephalexin, or more recently, the fluoroquinolones. These regimens are effective[16,17,18,19,20]; however, topical estrogen may be particularly useful in patients in whom the prolonged use of antibiotics induces side effects, allergic reactions, drug interactions, or the emergence of multidrug-resistant microorganisms. The results of two previous open studies and one small controlled trial also suggest that orally administered estriol may prevent recurrent urinary infections in postmenopausal women[6,21,22]. However, in a case-control study of more than 23,000 older women attending general practice clinics in England, Orlander and associates found that estrogen use was associated with a twofold increase in the risk of a first episode of urinary tract infection[23]. Thus, the effects of oral estrogen use on initial and recurrent episodes of urinary tract infection in postmenopausal women require further evaluation.

Supported by a grant from Organon B.V. International, the Netherlands, and by a grant (DK-40045) from the National Institutes of Health.

Source Information

From the Infectious Disease Unit, Central Emek Hospital, and the Technion Faculty of Medicine, Haifa, Israel (R.R.), and the Department of Medicine, University of Washington, Seattle (W.E.S.).

Address reprint requests to Dr. Raz at the Infectious Disease Unit, Central Emek Hospital, Afula, 18101 Israel.

References

1. Romano JM, Kaye D. UTI in the elderly: common yet atypical. Geriatrics 1981;36:113-115.

2. Molander U, Milsom I, Ekelund P, Mellstrom D, Eriksson O. Effect of oral oestriol on vaginal flora and cytology and urogenital symptoms in the post-menopause. Maturitas 1990;12:113-120. [Medline]

3. Lang WR. Vaginal acidity and pH: a review. Obstet Gynecol Surv 1955;10:546-560. [Medline]

4. Stamey TA, Sexton CC. The role of vaginal colonization with enterobacteriaceae in recurrent urinary infections. J Urol 1975;113:214-217. [Medline]

5. Parsons CL, Schmidt JD. Control of recurrent lower urinary tract infection in the postmenopausal woman. J Urol 1982;128:1224-1226. [Medline]

6. Brandberg A, Mellstrom D, Samside G. Low dose oral estriol treatment in elderly women with urogenital infections. Acta Obstet Gynecol Scand Suppl 1987;140:33-38. [Medline]

7. Eschenbach DA, Davick PR, Williams BL, et al. Prevalence of hydrogen peroxide-producing Lactobacillus species in normal women and women with bacterial vaginosis. J Clin Microbiol 1989;27:251-256. [Free Full Text]

8. Klebanoff SJ, Hillier SL, Eschenbach DA, Waltersdorph AM. Control of the microbial flora of the vagina by H_2O_2-generating lactobacilli. J Infect Dis 1991;164:94-100. [Medline]

9. Stamey TA, Timothy M, Millar M, Mihara G. Recurrent urinary infections in adult women: the role of introital enterobacteria. Calif Med 1971;115:1-19.

10. Chan RC, Reid G, Irvin RT, Bruce AW, Costerton JW. Competitive exclusion of uropathogens from human uroepithelial cells by Lactobacillus whole cells and cell wall fragments. Infect Immun 1985;47:84-89. [Free Full Text]

11. Hooton TM, Hillier S, Johnson C, Roberts PL, Stamm WE. Escherichia coli bacteriuria and contraceptive method. JAMA 1991;265:64-69. [Free Full Text]

12. Hooton TM, Fihn SD, Johnson C, Roberts PL, Stamm WE. Association between bacterial vaginosis and acute cystitis in women using diaphragms. Arch Intern Med 1989;149:1932-1936. [Free Full Text]

13. Hooton TM, Fennell CL, Clark AM, Stamm WE. Nonoxynol-9: differential antibacterial activity and enhancement of bacterial adherence to vaginal epithelial cells. J Infect Dis 1991;164:1216-1219. [Medline]

14. Mattsson LA, Cullberg G. Vaginal absorption of two estriol preparations: a comparative study in postmenopausal women. Acta Obstet Gynecol Scand 1983;62:393-396. [Medline]

15. Trevoux R, van der Velden WH, Popovic D. Ovestin vaginal cream and suppositories for the treatment of menopausal vaginal atrophy. Reproduction 1982;6:101-6.

16. Raz R, Boger S. Long-term prophylaxis with norfloxacin versus nitrofurantoin in women with recurrent urinary tract infection. Antimicrob Agents Chemother 1991;35:1241-1242. [Free Full Text]

17. Stamm WE, Counts GW, Wagner KF, et al. Antimicrobial prophylaxis of recurrent urinary tract infections: a double-blind placebo-controlled trial. Ann Intern Med 1980;92:770-775.

18. Stamm WE, McKevitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. Rev Infect Dis 1991;13:77-84. [Medline]

19. Nicolle LE, Harding GK, Thomson M, Kennedy J, Urias B, Ronald AR. Efficacy of five years of continuous, low-dose trimethoprim-sulfamethoxazole prophylaxis for urinary tract infection. J Infect Dis 1988;157:1239-1242. [Medline]

20. Harding GKM, Ronald AR. A controlled study of antimicrobial prophylaxis of recurrent urinary infection in women. N Engl J Med 1974;291:597-601.

21. Kirkengen AL, Andersen P, Gjersoe E, Johannessen GR, Johnsen N, Bodd E. Oestriol in the prophylactic treatment of recurrent urinary tract infections in postmenopausal women. Scand J Prim Health Care 1992;10:139-142. [Medline]

22. Privette M, Cade R, Peterson J, Mars D. Prevention of recurrent urinary tract infections in postmenopausal women. Nephron 1988;50:24-27. [Medline]

23. Orlander JD, Jick SS, Dean AD, Jick H. Urinary tract infections and estrogen use in older women. J Am Geriatr Soc 1992;40:817-820. [Medline]