

## ABSTRACT

**Objective.** To determine the effect of extremely low-dose vaginal estrogen cream on the incidence of urinary tract infections (UTIs) in postmenopausal women. The extremely low-dose of cream is accomplished by a one to three times weekly fingertip application method.

**Methods.** This retrospective chart review was based on data collected from women cared for at Froedtert Medical Lutheran Hospital (FMLH) in Milwaukee, Wisconsin. We gathered data from patients charts who satisfied the following criteria: (a) women who were menopausal by history, (b) women who reported having three or more UTIs in a period of 12 months, (c) women who were instructed to apply (conjugated estrogen cream or estradiol cream) one to three times per week using a fingertip application method, (d) women whose compliance was confirmed at each follow-up office visit, and (e) women who had follow-up data recorded for greater than or equal to 12 months from the initiation of treatment. Exclusion criteria included: women who had previously been or were currently on prophylactic antibiotics, were currently taking other forms of estrogen (including oral estrogen, rings or tablets), were prescribed bolus doses of estrogen, or who had other urologic conditions causing UTI symptoms. Baseline data points, most importantly number of UTIs per year, were collected. Each UTI recorded in the follow-up time was based on a urine culture demonstrating bacterial growth of greater than or equal to 50,000 cfu/ml bacteria. Descriptive statistics with mean and standard deviation were calculated on data gathered. An interim analysis from 25 patients showed significant response and the study was terminated. A Poisson regression model was used to predict the UTI frequency (per year) after treatment for three baseline UTI frequency groups (3-4/year, 5-6/year, >5-6/year).

**Results.** The mean age of the women was 66.8 years ± 13.2 (standard deviation). The average age of menopause was 47.5 years ± 5.6. Most (96%) reported that their urinary tract infections were accompanied by one or more of the following symptoms: frequency (68%), urgency (60%), hematuria (28%), fever (4%), chills (24%), sweats (8%), dysuria (64%), and back pain (44%). The majority (76%) of the patient electronic medical records confirmed the baseline UTIs by urine culture results.

The baseline UTI frequency was 4.5 per year. The average follow-up time, starting from the date of treatment initiation, was 1036 days (median: 707 days). The overall rate of UTI per person-year following the vaginal cream fingertip application decreased by an exponent of 0.04, i.e. a 25-fold decrease from the baseline UTI frequency (p<0.0001; 95% confidence interval: 0.02-0.08; Table II). This corresponded to a post-treatment rate of 0.2 UTIs per person per year. The data was also stratified into three baseline UTI frequency groups: 3-4 per year (68%), 5-6 per year (16%), greater than 5-6 per year (16%). Analysis of these three groups revealed no difference in the UTI reduction rate among the groups.

**Conclusion.** The fingertip application method of using topical estrogen cream dramatically decreases the number of UTIs per year in postmenopausal women who experience recurrent UTIs. This application method is felt to provide a significantly lower dose than what has been previously shown to reduce UTI frequency: daily use of a full applicator of cream intravaginally. The fingertip application method potentially has better compliance than the use of the applicator and may be more cost-effective.

## INTRODUCTION

It is estimated that 10 to 15 percent of women over the age of 60 suffer from recurrent urinary tract infections (RUTIs). The vulvovaginal atrophy (VVA) related to menopause is believed to predispose a woman to RUTIs. Estrogen is needed in order to maintain the normal structure and function of the vaginal tract. Following menopause, the decreased stimulation of the vaginal epithelium by estrogen reduces the number of superficial epithelial cells. The decreased exfoliation of cells thereby reduces the amount glycogen released. The lowered glycogen content causes a shift in vaginal bacterial flora from a dominance of glycogen-dependent lactobacilli toward a dominance of fecal gram-negative bacteria thereby creating a potential reservoir for urinary tract infection. Although RUTIs have a huge impact on quality of life, only 20% to 25% of women who experience RUTIs seek treatment. This number is unacceptably low considering the safe and effective treatment options available, including vaginal estrogen therapy.

## METHODS

This retrospective analysis was based on data collected from women cared for at Froedtert Medical Lutheran Hospital (FMLH) in Milwaukee, Wisconsin. Approval was sought and granted from the Medical College of Wisconsin/Froedtert Hospital Institutional Review Board. Froedtert Hospital's electronic medical record system (Epic) was utilized in order to generate a list of women whose charts contained the words 'vaginal estrogen,' 'estrace cream,' 'premarin cream' or 'estradiol cream' on their medication list or medical history. The earliest records accessed were from 1/1/2006.

Women with the following criteria were included: (a) those who were menopausal by history (b) women who reported having three or more UTIs in a period of 12 months (c) women who were instructed to apply the vaginal estrogen one to three times per week using a fingertip application method (d) women whose compliance was confirmed at each follow-up office visit, and (e) women who had follow-up data recorded for greater than or equal to 12 months from the initiation of treatment. Patients who met the following criteria were excluded: (a) those who had been currently on prophylactic antibiotics (b) women currently taking other forms of estrogen, including oral estrogen, rings or tablets (c) women who were prescribed bolus doses of estrogen, for example those patients who were instructed to take a higher or more frequent dose of estrogen for one week before decreasing to a maintenance dose (d) women who had other urologic conditions causing UTI symptoms. Vaginal atrophy was examined at the initial visit and re-examined at each follow-up visit to see if atrophy was improving. This helped to confirm again with the patient if the cream was being used properly and to confirm compliance. Each UTI recorded in the follow-up time was based on symptomatology along with a positive urine culture demonstrating bacterial growth of greater than or equal to 50,000 cfu/ml bacteria from clean-catch urine specimens.

The initial report generated a list of 4,392 patients charts from which 400 charts were screened. 25 charts met inclusion criteria. Poisson regression model was used to predict the UTI frequency (per year) after treatment for three baseline UTI frequency groups (3-4/year, 5-6/year, >5-6/year). UTI frequency after treatment versus baseline was compared by assuming the baseline UTI was 3.5, 5.5, and 7.5 for each group respectively. In addition, the estimated rate of UTI decrease with 95% CI was calculated based on the Poisson model. All data analyses were carried out using the SAS, version 9.3(SAS institute, Cary, NC, USA). P-values <0.05 were considered statistically significant.

## RESULTS

The mean age of the women was 66.8 years ± 13.2. The average age of menopause was 47.5 years ± 5.6. The baseline UTI frequency was 4.5 per year. The average follow-up time, starting from the date of treatment initiation, was 1036 days (median: 707 days). The overall rate of UTI per person-year following the vaginal cream fingertip application decreased by an exponent of 0.04, i.e. a 25-fold decrease from the baseline UTI frequency (p<0.0001; 95% confidence interval: 0.02-0.08; Table II). This corresponded to a post-treatment rate of 0.2 UTIs per person per year. The data was also stratified into three baseline UTI frequency groups: 3-4 per year (68%), 5-6 per year (16%), greater than 5-6 per year (16%). Analysis of these three groups revealed no difference in the UTI reduction rate among the groups.

## CONCLUSION

The fingertip application method of using topical estrogen cream dramatically decreases the number of UTIs per year in postmenopausal women who experience recurrent UTIs. The fingertip application method 1-3 times a week is felt to provide a significantly lower dose than daily use of a full applicator of cream intravaginally. This method may be more cost-effective and better tolerated than other methods of delivering topical vaginal estrogen.

**Table I. Change in UTI Frequency with fingertip application of vaginal estrogen 1-3 times a week**

Pre-treatment UTI frequency (per year)	Follow-up UTI frequency	P (CI)
3-4 / year (n=17)	0.2	<0.0001 (0.07-0.38)
5-6 / year (n=4)	0.2	0.0748 (0.04-1.17)
>5-6 / year (n=4)	0.3	0.1429 (0.05-1.56)
Overall 4.46 / year (n=20)	0.2	<0.001 (0.02-0.08)